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SEZIONE EMILIA ROMAGNA

UNIVERSITÀ DI PARMA

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DEI CHIMICI E DEI FISICI
DI PARMA E PIACENZA

XVIII GIORNATA DELLA CHIMICA DELL'EMILIA ROMAGNA

2018, il Chimico entra nelle professioni sanitarie: prospettive e impegni futuri

Parma - 17/12/2018
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UNIVERSITÀ DI PARMA

Società Chimica Italiana
Sezione Emilia Romagna

XVIII Giornata della Chimica dell'Emilia Romagna

2018, il Chimico entra nelle professioni sanitarie: prospettive e impegni futuri

Parma, 17 dicembre 2018

9:00-10:00	**Registrazione, allestimento poster e caffè di benvenuto**
10:00-10:15	**Apertura dei lavori e saluto delle autorità**
	I Sessione
10:15-11:35	**Comunicazioni Orali dei Dottorandi**
10:15-10:35	**O1** - *Margherita Bazzoni (UniPr)*: "Efficient active-template synthesis of calix[6]arene-based oriented rotaxanes and pseudorotaxanes"
10:35-10:55	**O2** - *Tatiana Chenet (UniFe):* "Study of the adsorption of the amino acid L-lysine onto microporous materials"
10:55-11:15	**O3** - *Lidia Lancellotti (UniMoRe):* "Electron transfer and catalytic properties of redox proteins immobilized on functionalized electrodes"
11:15-11:35	**O4** - *Chiara Parise (UniBo):* "Structure, morphology and magnetic properties of Au/Fe_3O_4 nanocomposites fabricated by a soft aqueous route"
11:35-12:45	***Comunicazioni flash dei Dottorandi***
	F1 - *Greta Bagnolini (UniBo):* "Design and synthesis of BRCA2-RAD51 disruptors to induce synthetic lethality in cancer treatment"
	F2 - *Brunella Bardi (UniPr)*: "Multistimuli-responsive materials from benzothiadiazole-based charge-transfer chromophores: interdependence of optical properties and aggregation"
	F3 - *Arianna Brandolese (UniFe):* "Aerobic oxidation of biomass-derived 5-(hydroxymethyl)furfural through heterogeneous NHC-catalysis"
	F4 - *Mirko Buffagni (UniMoRe):* "Synthesis and characterisation of thiophene based acceptor-donor-acceptor small molecules"
	F5 - *Lucia Casali (UniBo):* "Smart Urea Ionic Co-crystals with Enhanced Urease Inhibition Activity for Improved Nitrogen Cycle Management"

F6 - *Maria Laura Ligabue (UniMoRe):* "Recycle of thermal treated cement-asbestos as secondary raw material in ceramic tiles"

F7 - *Emanuele Maccaferri (UniBo):* "NYLON 66/graphene electrospun NANOFIBERS as nano^2 materials: morphological, thermal and mechanical characterization"

F8 - *Asha Pankajakshan (UniPr):* "MOFs as SPME coatings for the analysis of environmental pollutants"

F9 - *Cecilia Poderi (UniBo):* "Synthesis and EPR study of a [2]-rotaxane BASED on a persistent paramagnetic Macrocycle acting as molecular machine"

F10 - *Mara Russo (UniFe):* "Different setups of ascorbic acid a-cellular assay for measuring oxidative stress potential of airborne particulate"

12:45-14:30	**Buffet lunch - Sessione poster**

II Sessione

"*2018, il Chimico entra nelle professioni sanitarie: prospettive e impegni futuri*"

14:30-15:00	Dott.ssa Nausicaa Orlandi (Presidente della Federazione Nazionale dei Chimici e dei Fisici) "*La tradizione e l'innovazione: a 90 anni dalla istituzione della professione il Chimico entra nelle professioni sanitarie*"
15:00-15:30	Dott. Matteo Biagetti (Lead Optimisation Unit Head – R&D. Chiesi Farmaceutici S.p.A.) "*L'unicità e la molteplicità del chimico nell'industria farmaceutica*"
15:30-16:00	Prof.ssa Rosangela Marchelli (Esperto scientifico di EFSA) "*Il ruolo del chimico all'European Food Safety Authority (EFSA)*"
16:00-16:30	**Premiazioni e chiusura dei lavori**

PRESENTAZIONI ORALI

O	1	Bazzoni	Margherita
O	2	Chenet	Tatiana
O	3	Lancellotti	Lidia
O	4	Parise	Davide

PRESENTAZIONI FLASH

F	1	Bagnolini	Greta
F	2	Bardi	Brunella
F	3	Brandolese	Arianna
F	4	Buffagni	Mirko
F	5	Casali	Lucia
F	6	Ligabue	Maria Laura
F	7	Maccaferri	Emanuele
F	8	Pankajakshan	Asha
F	9	Poderi	Cecilia
F	10	Russo	Mara

ELENCO POSTER

P	1	Albanese	Valentina
P	2	Albertini	Claudia
P	3	Andreo	Jacopo
P	4	Annunziata	Alexia
P	5	Balestri	Davide
P	6	Bartoli	Jennifer
P	7	Basagni	Filippo
P	8	Becconi	Maila
P	9	Bellotti	Denise
P	10	Bertuzzi	Giulio
P	11	Bugatti	Kelly
P	12	Caciolla	Jessica
P	13	Carraro	Claudia
P	14	Casnati	Alessandra
P	15	Cavallini	Nicola
P	16	Cecchini	Chiara
P	17	Chinaglia	Nicola
P	18	Cogliati	Beatrice
P	19	Corti	Vasco

P	20	Di Filippo	Maria Francesca
P	21	Durante	Joseph
P	22	Fantini	Adriana
P	23	Faroldi	Federica
P	24	Favero	Alessia
P	25	Felletti	Simona
P	26	Fornaia	Gianmaria
P	27	Fornasari	Luca
P	28	Gino	Maria Elena
P	29	Giordani	Martina
P	30	Giuri	Demetra
P	31	Gonçalves	Ana Elisa
P	32	Guernelli	Moreno
P	33	Gullo	Maria Chiara
P	34	Hallan	Supandeep Singh
P	35	Illuminati	Davide
P	36	Introvigne	Maria Luisa
P	37	Isopi	Jacopo
P	38	Lanthier	Caroline
P	39	Maceratesi	Vittorio
P	40	Magini	Andrea
P	41	Marangon	Vittorio
P	42	Marasca	Camilla
P	43	Marchegiani	Elisa
P	44	Marchetti	Lucia
P	45	Marchini	Edoardo
P	46	Mariani	Federica
P	47	Marinelli	Martina
P	48	Marzaroli	Vittoria
P	49	Menichetti	Arianna
P	50	Morselli	Giacomo
P	51	Mugnaini	Luca
P	52	Musella	Elisa
P	53	Neri	Martina
P	54	Nicolini	Alessio
P	55	Ocello	Riccardo
P	56	Orsoni	Nicolò
P	57	Pagnotta	Giorgia
P	58	Parisi	Mariafederica
P	59	Pecorari	Daniel
P	60	Rebeccani	Sara
P	61	Rossi	Michele
P	62	Rozzi	Andrea
P	63	Rubini	Kata
P	64	Ruggieri	Silvia

P	65	Shuangying	Wei
P	66	Telese	Dario
P	67	Tramarin	Anna
P	68	Turrin	Giulia
P	69	Vardè	Massimiliano
P	70	Vergine	Giulia
P	71	Volanti	Mirco
P	72	Voronov	Aleksandr
P	73	Vulcano	Fabio

EFFICIENT ACTIVE-TEMPLATE SYNTHESIS OF CALIX[6]ARENE-BASED ORIENTED ROTAXANES AND PSEUDOROTAXANES

Margherita Bazzoni,[a] Valeria Zanichelli,[a] Giulio Ragazzon,[b] Guido Orlandini,[a] Margherita Venturi,[b] Alberto Credi,[c,d] Serena Silvi,[b] Arturo Arduini,[a] and Andrea Secchi [a]

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Mechanically interlocked molecules (MIMs) such as rotaxanes, catenanes and related species, are attracting great interest in view of their potential application in materials science, information technology, nanoscience, catalysis and medicine[1]. The growing interest in these species is strictly related to the development of simple and efficient synthetic methodologies that rely on template-directed approaches.

Within this context our research group investigate how the engulfment of a positively charged pyridil-pyridinium-based guest inside the π-rich cavity of a tris-(N-phenylureido)calix[6]arene host affects its reactivity towards a SN¬¬2 reaction[2]. We found that the alkylation of the complexed substrates leads to the formation of oriented pseudorotaxanes and rotaxanes with faster kinetics and higher yields with respect to the standard SN2reaction. More importantly, the strategy described here expands the range of efficient synthetic routes for making mechanically interlocked species with a strict control of the mutual orientation of their nonsymmetric molecular components[3].

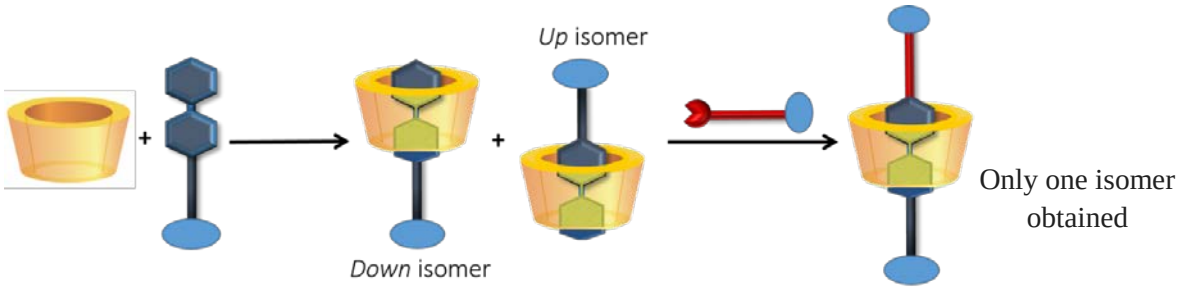

Figure 1: Supramolecularly assisted synthesis of a oriented-rotaxane.

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[3] V. Zanichelli, G. Ragazzon, G. Orlandini, M. Venturi, A. Credi, S. Silvi, A. Arduini, A. Secchi, *Org. Biomol. Chem.* **15** (2017) 6753–6763.

STUDY OF THE ADSORPTION OF THE AMINO ACID L-LYSINE ONTO MICROPOROUS MATERIALS

Tatiana Chenet[(a)], Mirco Cescon[(a)], Luisa Pasti[(a)], Annalisa Martucci[(b)], Alberto Cavazzini[(a)]

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ABSTRACT

Zeolites are aluminosilicate minerals composed of $[SiO_4]^{4-}$ and $[AlO_4]^{5-}$ tetrahedral units linked through the oxygen atoms creating a regular crystalline structure with microporous cavities that confer a high superficial area. The physico-chemical properties of zeolites depend strongly on the composition of their framework, in particular the hydrophilic/hydrophobic behaviour is affected by the SiO_2/Al_2O_3 ratio (SAR). Moreover, the different shapes and dimensions of the internal channels and cages influence the adsorption selectivity towards host molecules [1].
The ability of zeolites to adsorb biologically active biomolecules such as amino acids is of particular interest in industrial biotechnology [2] due to the fact that these adsorbent materials could be used as solid solvents to stabilize the different charged forms of the amino acids. In addition, these materials can also be employed in enrichment and separation processes of amino acids from complex mixtures.
In the present study the adsorption of the amino acid L-lysine onto zeolites L and ZSM-5 from aqueous solutions was evaluated. Zeolites presenting different framework structures were selected in order to evaluate the effect of the intra-crystalline characteristics of the material. Moreover, different SAR values were considered to determine the adsorption behaviour according to this factor.
Kinetic experiments were carried out at different lysine initial concentrations to study the adsorption processes. Adsorption isotherms for each material were determined in order to evaluate the saturation capacity of the zeolites.
X-ray diffraction analyses were carried out in order to localize the amino acid molecules in the microporous materials and the stability of the adduct resulting from the interaction between zeolites and L-lysine was studied by performing thermogravimetric measurements (TG-DTG-DTA).
The results showed higher adsorption capacity for zeolite L which is characterized by larger pore size and lower SAR compared to zeolite ZSM-5.

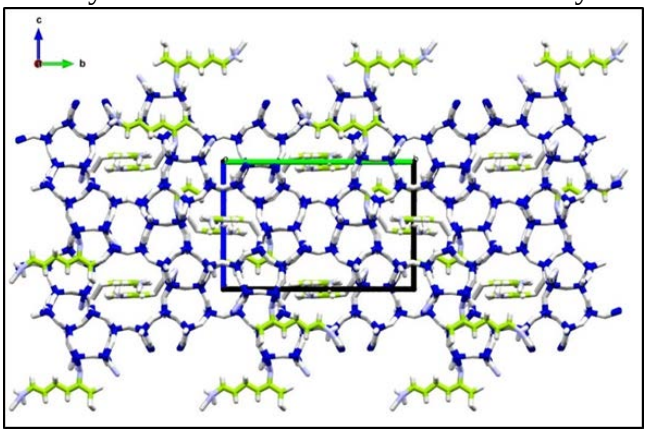

Figure 1. Lysine molecules adsorbed onto zeolite ZSM-5 (view along [100] direction)

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[2] K. Stückenschneider, J. Merz, and G. Schembecker, J. Phys. Chem. C **118** (2014) 5810-5819.

ELECTRON TRANSFER AND CATALYTIC PROPERTIES OF REDOX PROTEINS IMMOBILIZED ON FUNCTIONALIZED ELECTRODES

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ABSTRACT

Cytochrome c

Cytochrome c is a protein involved in the processes of cellular respiration with the main function of an electronic transporter[1]. The heme-iron can change reversibly his oxidation state between the Fe+3 and Fe+2. A subject of enormous interest in the chemical and biochemical field is the protein folding: how a polypeptide is organized in the tertiary conformation to obtain the specific and selective properties, that characterize the different proteins present in biological contexts. Moreover, site-specific mutagenesis provides a formidable tool for studying the role played by certain amino acids in specific polypeptide chain positions on the structure and behavior of the protein[2]. In this work two yeast cytochrome c mutants were used: M80A and M80AY67A, where methionine 80 is substituted with an alanine and also tyrosine 67. An in vitro approach to the problem of the protein folding consists in the study of thermodynamic and kinetic properties of the protein, which are subjected to progressive unfolding induced by an appropriate chemical agent (urea, guanidinium chloride) or physical agent (temperature, pH, ionic strength). Recent studies hypothesize a key role of cytochrome in the process of cell apoptosis. The interaction between cardiolipin and cytochrome c has a key role in inducing programmed cell death (apoptosis). The formation of the adduct cyt c/cardiolipin causes the release of cyt c into the cytoplasm, where it acts as a pro-apoptotic factor, causing the activation of some proteases (caspases), that lead to the death of the cell. In particular, the effect that increasing concentrations of CL have on the redox properties of the M80A and M80A / Y67A mutants of cytochrome c has been studied using voltammetric techniques. The voltammetric signal for the two immobilized mutants on hydrophilic SAM show small variations of E°' with increasing urea concentration. In solution, the presence of urea leads, instead, to a modification of the axial ligands of the heme-iron, in particular the substitution of an OH^- with a histidine. The interaction between cytochrome c and cardiolipin leads to a stabilization of the penta-coordinate form, which prevails in the reduced state. The penta-coordinate form is able to reduce (electrocatalytically) oxygen and hydrogen peroxide. These effects, therefore, could be involved in lipid peroxidation leading to the initiation of the cascade of reactions involved in apoptosis. Both cytochrome denatured by urea and the adduct with cardiolipin are able to activate the reduction of oxygen and oxygen peroxide[3], this aspect encourages the study of these systems for the construction of future biosensors.

Neuroglobin

Neuroglobin (Ngb) is a bis-histidinate heme-protein, belonging to the globin family, present in all vertebrate species[1]. It is expressed mainly in neurons of the central and peripheral nervous system and in rods of the retina. Despite the large amount of information on the Ngb structure that derive from XR and NMR studies and from the spectroscopic properties, the physiological Ngb function is not yet clear. In the years following its discovery, various physiological roles were hypothesized, from oxygen reserving storage to that of membranes protector from radical species produced during cell activity.The interaction of neuroglobin with ROS formed in cases of cerebral hypoxia (lower oxygen supply to the central nervous system) is of particular interest[4]. It is possible that Ngb is able to reducing the concentration of these partially oxidized species. In the present work we studied the electronic transfer process of human neuroglobin immobilized on SAM anionic on gold electrodes, both in the absence and in the presence of a possible redox partner as nitrite ion in order to evaluate its electrocatalytic activity. The data obtained show the ability of human neuroglobin to reduce NO_2^-. The adduct between hNgb and NO_2^- is unstable, this demonstrates a tendency for Ngb to reduce the bound species rather than store it. This last property, besides defining a possible physiological role for the protein, makes neuroglobin an interesting candidate for the development of electrochemical devices dedicated to sensors and biocatalysis.

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STRUCTURE, MORPHOLOGY AND MAGNETIC PROPERTIES OF Au/Fe_3O_4 NANOCOMPOSITES FABRICATED BY A SOFT AQUEOUS ROUTE

Chiara Parise[(a)], Barbara Ballarin[(a)], Maria Cristina Cassani[(a)], Daniele Nanni[(a)], Davide Barreca[(b)], Giorgio Carraro[(b)], Alberto Riminucci[(c)], Ilaria Bergenti[(c)], Vittorio Morandi[(d)], Andrea Migliori[(d)]

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ABSTRACT

Magnetic Fe_3O_4 (magnetite) nanoparticles were synthesized via a chemical precipitation route in different alkaline environments (NH_3 or NaOH) and subsequently functionalized with a (propynylcarbamate)triethoxysilane moiety, with the aim of promoting the nucleation and subsequent stabilization of gold nanoparticles (AuNPs). The propynylcarbamate group was able to first capture the gold precursor ($HAuCl_4$), spontaneously reduce it, and finally stabilize the resulting Au nanoaggregates (Figure 1).

The obtained results showed that though the dimensions of the starting magnetite substrate depend on the base used in the preparation, they remained unaltered upon the subsequent modification. Conversely, the average AuNPs dimensions could be conveniently tailored as a function of the base used in the Fe_3O_4 preparation and the presence/absence of the organic functionalization. The smallest dimensions (15 nm) were obtained for AuNPs supported on propynylcarbamate-functionalized Fe_3O_4 prepared in the presence of ammonia.

Magnetization measurements highlighted that all the Au/Fe_3O_4 nanocomposites display a superparamagnetic behavior and those obtained using ammonia showed consistently smaller Hc and Mr values (av. values of 7.4 Oe and 0.8 emu/g) than those prepared with sodium hydroxide (av. values of 28 Oe and 2.8 emu/g).[1]

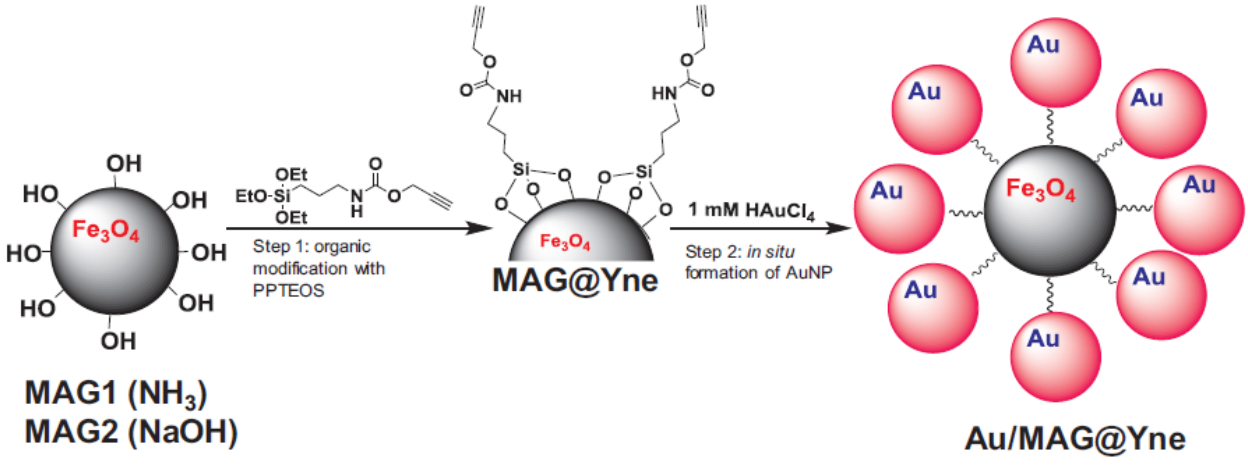

Figure 1. Preparation of Au/MAG@Yne.

REFERENCES

[1] *Structure, morphology and magnetic properties of Au/Fe_3O_4 nanocomposites fabricated by a soft aqueous route*, B. Ballarin, M. C. Cassani, D. Nanni, C. Parise, D. Barreca, G. Carraro, A. Riminucci, I. Bergenti, V. Morandi, A. Migliori,.E. Boanini, *Ceram. Int.*, **2019**, *45*, 449 – 456.

DESIGN AND SYNTHESIS OF BRCA2-RAD51 DISRUPTORS TO INDUCE SYNTHETIC LETHALITY IN CANCER TREATMENT

Greta Bagnolini[a,b]*, Andrea Balboni,[a,c] Fulvia Farabegoli,[c] Giuseppina Di Stefano,[c] Marinella Roberti,[b], Andrea Cavalli[a,b]

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Synthetic lethality is a lethal phenotype arising from the combination of two specific gene mutations, which are harmless when they occur individually (fig.1a). [1] Targeting a pair of synthetic lethal genes represents an attractive opportunity in pharmaceutical field for the development of novel therapeutics. One straightforward application of synthetic lethality in anticancer drug development is the use of Olaparib, the first approved PARP inhibitor, in BRCA2-defective oncology patients. BRCA2 and PARP are proteins involved in two independent mechanisms of DNA repair. PARP is important for repairing single-strand breaks, whereas BRCA2 is essential for repairing double-strand breaks by homologous recombination (HR) as it recruits protein RAD51 from the cytosol and stabilizes the complex RAD51-DNA. [2]

In this context to develop a new anticancer drug discovery concept, we explored the possibility to trigger a fully-small-molecule-induced synthetic lethality combining protein-protein (PP) BRCA2-RAD51 disruptors with Olaparib. Targeting PP interactions is an attractive strategy for designing innovative drugs. However it was proven to be challenging due to the typical PP large and flat interfaces. [3] BRCA2-RAD51 PPI is mediated by two critical “hotspots” on RAD51 surface, zone I and II, which can be suitable targets for the development of small molecule PPI inhibitors. [2] Following a structure-based approach, we initially performed a virtual screening campaign, focusing on zone I. The triazole compound ARN19793 was identified as the best candidate as it proved to increase the response to Olaparib in pancreatic cancer cells expressing a functional BRCA2. [2] To explore the chemical space around ARN19793, structure-activity relationship (SAR) studies were performed, optimizing a synthetic strategy to build a library of analogues with preserved triazole core (Fig.1b). To promote sustainable chemistry, I privileged protocols that exploit microwave-assisted synthesis.

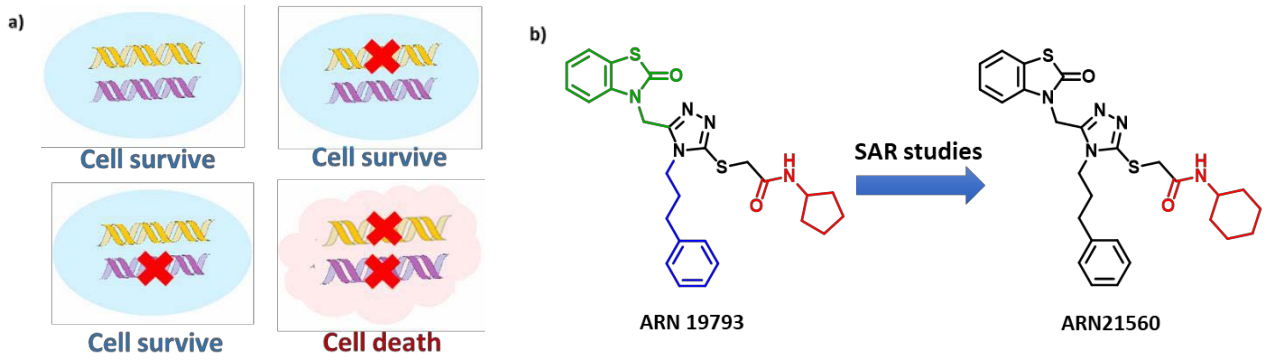

Figure 1. (a) Synthetic lethality mechanism. (b) Identification of ARN21560 through SAR studies on ARN19793.

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[3] Ivanov A.A. *et al*. Targeting protein-protein interactions as anticancer strategy. *Trend Pharmacol Sci*., 34, **2013**, 393.

MULTISTIMULI-RESPONSIVE MATERIALS FROM BENZOTHIADIAZOLE-BASED CHARGE-TRANSFER CHROMOPHORES: INTERDEPENDENCE OF OPTICAL PROPERTIES AND AGGREGATION

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ABSTRACT

Molecular materials based on charge-transfer (CT) chromophores are widely studied for application in optoelectronic and photonic devices. Optical properties of these materials are strongly affected by aggregation phenomena, and cooperative and collective effects may be beneficial -or sometimes detrimental- for the device performance. Competition between core-driven and side chain-driven interactions could also lead to multistimuli-responsiveness, of outmost interest for switching applications. Consequently, engineering of molecular materials relies not only on the appropriate choice of the molecular building blocks, but also on the convenient introduction of side-chains in order to govern supramolecular interactions. Although CT materials are widely investigated from an experimental point of view, less attention has been paid to the in-depth understanding of aggregation effects. Optical properties of aggregates are usually described according to the exciton picture, whose approximations do not apply for highly polarizable systems[1]. In this work we aimed at setting the correct scenario for the interpretation of the optical properties of polarizable quadrupolar dyes. Specifically, we focused on a representative family of 2,1,3-benzothiadiazole (BDT) derivatives, bearing a V-shaped R-D-A-D-R structure. The central acceptor (A), BDT, is conjugated to two electron donors D of different size (thiophene or 2,2'-bithiophene), corresponding to different lengths of the π-conjugated backbone. In order to address side-chain effects, alkyl-cyanoacetate terminal groups (R) with linear and branched chains were compared. Spectroscopic properties were investigated in the solid state (powders) and in spin-coated thin films, and were found to be strongly affected by soft external stimuli such grinding (of the powders) and annealing (of the films), as depicted in Figure 1. These changes were assigned to specific variations of molecular packing assisted by intermolecular interactions. The detailed analysis of experimental data, supported by theoretical modelling with an essential-state approach, allows to discuss aggregation phenomena in a more general perspective, overcoming the limitations of the classical exciton theory[2].

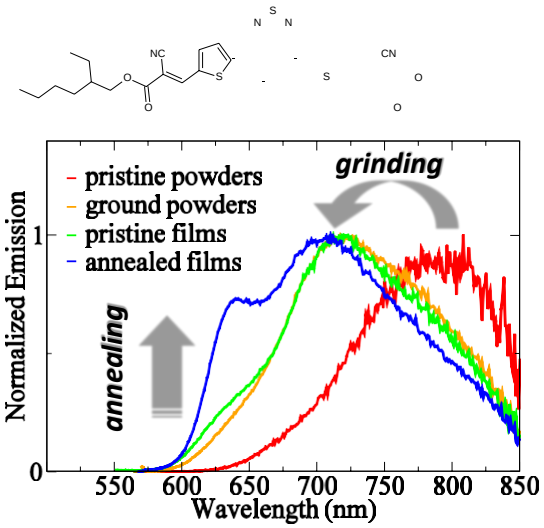

Figure 1. Effect of soft stimuli on the solid-state emission spectra of the BDT derivative sketched at the top.

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AEROBIC OXIDATION OF BIOMASS-DERIVED 5-(HYDROXYMETHYL)FURFURAL THROUGH HETEROGENEOUS NHC-CATALYSIS

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ABSTRACT

The biomass-derived 5-(hydroxymethyl)furfural (HMF) represents a promising platform chemical owing to its sustainability and functional groups availability for further transformations.[1]
In the present work,[2] we propose the derivatization of HMF through heterogeneous NHC-oxidative catalysis. Aerobic oxidation conditions were optimized using a biomimetic strategy based on the use of iron phthalocyanine as electron transport mediator (ETM).
HMF reactivity was investigated via two different synthetic routes: direct coupling and one-pot two-step process through a poly-HMF intermediate; both strategies allow efficient access to 5-hydroxymethyl-2-furancarboxylic acid (HMFCA) and ester, amide, thioester derivatives.
The disclosed one-pot two-step procedure involved sequential oxidative esterifications of HMF to afford a polyester oligomer having hydroxyl and carboxyl terminal groups, which in turn was hydrolyzed by a supported base (Ambersep 900 OH) to yield HMFCA in 87% overall yield. The same strategy was adopted for the effective synthesis of ester and amide derivatives of HMFCA by nucleophilic depolymerization of the oligomeric intermediate with methanol and butylamine, respectively. The utilization of the disclosed oxidative system for the direct conversion of furfural into their corresponding ester, amide and thioester derivatives is also reported.

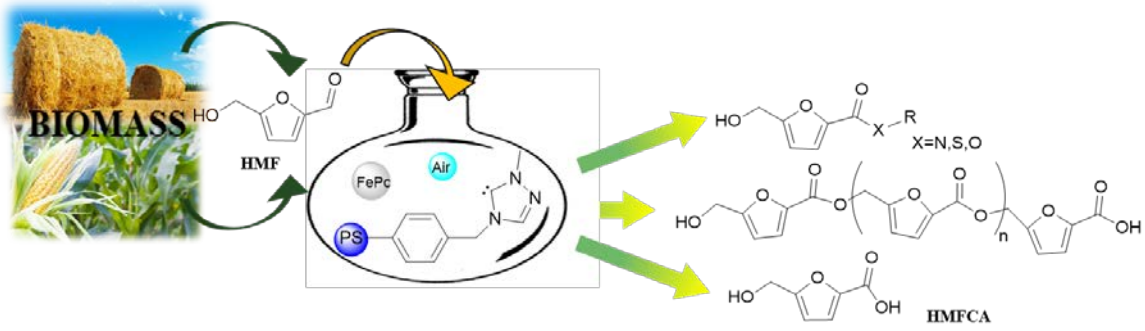

Figure 1. Heterogeneous NHC-oxidative catalysis for the selective conversion of 5-(hydroxymethyl)furfural into the added-value 5-hydroxymethyl-2-furancarboxylic acid (HMFCA) and derivatives.

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SYNTHESIS AND CHARACTERISATION OF THIOPHENE BASED ACCEPTOR-DONOR-ACCEPTOR SMALL MOLECULES

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ABSTRACT

Small conjugated molecules, such as oligothiophenes, have proved to be good photoactive acceptor materials for organic solar cells [1] and several optoelectronic devices like OLEDs [2] and OFETs [3-5]. Among small molecules, the push-pull ones are drawing increasing attention due to their widely delocalized π-electron system, resulting in a low energy absorption band. Different building blocks of electron donors (D) and acceptors (A), linked through a π-bridges, may be variously combined (i.e. A-π-A, D-π-D, A-π-D, A- π-D-π-A, D-π-A-π-D) and the choice of the donor and acceptor groups makes possible a fine tuning of their electronic band gap. Furthermore, the photoinduced intramolecular charge transfer in A-π-D-π-A and D-π-A-π-D quadrupolar molecular systems has been recently studied in relation to their nonlinear optical (NLO) properties, which make them usable in bio-imaging applications and photodynamic therapy [6]. Here, we present the synthesis and the characterization of two A-π-D-π-A small molecules, **OT1** and **OT2**, where the central unit is a dithienosilole, the terminal units are methyldicyanovinyl groups and the π-bridges are alkyl or alkylsulfanyl functionalized bithiophenes, respectively. The aim of this research is to study the structural, the electronic and the optical properties of these molecules to better understand the role of the sulfur atom of the alkylsulfanyl chains and to gain insight on the properties of these materials in view of their application in optoelectronic and photovoltaic devices.

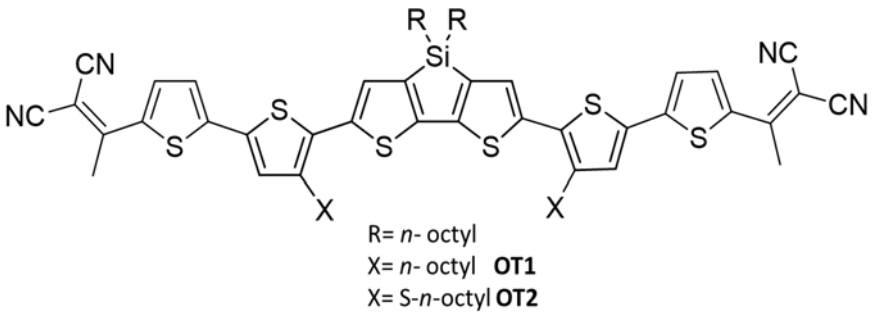

Figure 1. The target thiophene-based small molecules

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SMART UREA IONIC CO-CRYSTALS WITH ENHANCED UREASE INHIBITION ACTIVITY FOR IMPROVED NITROGEN CYCLE MANAGEMENT

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ABSTRACT

Nitrogen is an essential element for plants due to its role in the formation of proteins, nucleic acids and other cellular components. For this reason, in soils with nitrogen deficiency it is necessary to use fertilizers based on nitrogen compounds,[1] among which urea is the most common. However, urea is a highly soluble compound and is quickly hydrolyzed into ammonia and carbon dioxide due to the enzyme *urease*,[2] which is contained in the soil. Consequently, the crop supply is lower and, at the same time, the reaction's products are released to the atmosphere, which causes pollution and an imbalance of the nitrogen cycle.[3] In order to reduce these negative effects, urea has been co-crystallized with inorganic metal salts.[4] The inorganic coformer has been chosen in order to (1) modulate the physical properties of urea (i.e. decreasing the solubility and the dissolution rate of urea compared to pure urea), (2) act as an inorganic micronutrient for the soil and (3) inhibit the activity of *urease*. The most successful result has been a new co-crystal based on urea, KCl and $ZnCl_2$ (ZnKU) in a 1:1:1 stoichiometry. Depending on the method of the synthesis, the co-crystal has been obtained in two different crystalline forms and it has been evidenced, through a DSC analysis, that the system is monotropic. Then the physical properties of ZnKU have been investigated, obtaining that (1) the co-crystal is more stable with respect to the physical mixture of the reagents, (2) it has a lower solubility compared to the pure urea and (3) it presents an efficient inhibition activity towards the enzyme *urease*. In conclusion, a smart ionic co-crystal of urea with KCl and $ZnCl_2$ has been obtained in two polymorphic modifications by mechanochemical and solution methods and proven to be a very efficient urease inhibitor while, simultaneously, able to provide soil nutrients to complement N supply.

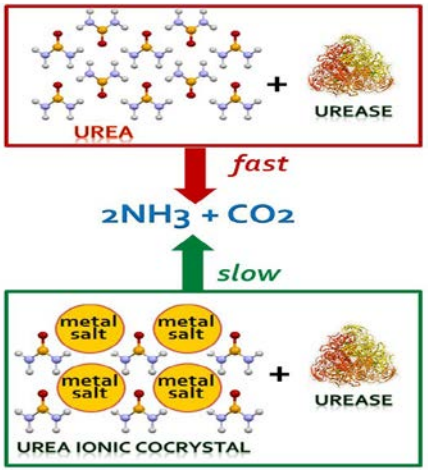

Figure 1. Scheme of the purpose of the research.

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RECYCLE OF THERMAL TREATED CEMENT-ASBESTOS AS SECONDARY RAW MATERIAL IN CERAMIC TILES

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ABSTRACT

Italy was one of the European countries where asbestos-containing materials (ACM) were extensively used in the past, and in fact ~2 billion m^2 of cement-asbestos slates still cover roofs of industrial and civil buildings [1,2]. The use of landfills to decrease free ACM cannot be regarded as the ultimate solution; zero risk of fibres dispersion in air and water cannot be guaranteed. Besides that, the disposal in controlled landfills and their maintenance for an indefinite time is rather expensive. Alternative solutions are recycling of both hazardous and non-hazardous wastes as secondary raw materials. Recently, an industrial process for the thermal destruction of asbestos containing wastes, mainly cement–asbestos, has been developed and patented [3]. Sealed packages of cement–asbestos slates are subjected to prolonged annealing at a temperature in the range 1200 – 1300°C, during which asbestos are transformed into newly-formed silicates, mainly composed of SiO_2 and CaO [3]. This secondary raw material is commercially called KRY·AS.

This work is part of a project in collaboration with the Ministry of the Environment defined as "Trattamento e riciclo di rifiuti contenenti amianto (RCA)" [4]. The purpose of the present research is to study an application for KRY·AS in ceramic products, in particular creation of ceramic frits used for ceramic tiles, specifically porcelain tiles.

Two different ceramic frits, defined as IR1 and IR2, were prepared with KRY·AS, recycled glass and other natural raw materials; the composition was defined with respect to a commercial frit (F0). Successively 10 different ceramic samples were synthesised. All samples were characterised through qualitative and quantitative analysis.

In conclusion it was highlighted that samples prepared with frits IR1 and IR2, produced with KRY·AS, present comparable behaviour compared to RIW and RIW_F0. These results support the possibility to use thermal treated asbestos as secondary raw material, improving the recycling and avoiding the use of landfill.

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NYLON 66/GRAPHENE ELECTROSPUN NANOFIBERS AS NANO^2 MATERIALS: MORPHOLOGICAL, THERMAL AND MECHANICAL CHARACTERIZATION

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ABSTRACT

Nanoscale reinforcements, such as nanofibers, nanoparticles and carbon based nano-reinforcements, i.e. graphene, represent a versatile tool for modifying polymer and polymer composite properties. Nanofibrous mats may be conveniently used for enhancing the interlaminar fracture toughness in laminated composites, preventing or, at least, hindering delamination, one of the most dangerous failure of laminates [1]. Graphene (G) has dimensions sufficiently small to be incorporated in polymeric nanofiber, allowing the creation of nanoreinforced nanobjects (Nano^2) with enhanced mechanical properties. [2] Such improved Nano^2 nanofibers can be effectively used in composite laminates for hindering delamination.

In this work, we present the production and the morphological, thermal and mechanical characterization of graphene reinforced Nylon 66 nanofibrous mats obtained via electrospinning technique. Moreover, their properties have been investigated both as produced and after 20 months, with the aim of establishing the effects of the graphene on the thermal and mechanical properties upon ageing. In particular, the Authors have been focussed on the mechanical properties of the mats, providing an uncommon way to normalize the force/displacement data of tensile test: the load has been normalized with respect to specimen weight (*Equation 1*) instead of section area (*S*) (*Equation 2*).

$$\sigma = \rho \frac{F}{m} L \qquad \textit{Equation 1} \qquad\qquad \sigma = \frac{F}{S} = \frac{F}{l \cdot t} \qquad \textit{Equation 2}$$

where "*m*" is the specimen mass (measured in mg), "ρ" is the polymer density (1.14 mg/mm^3 for Nylon 66), "*L*" is the specimen initial length (in mm), *F* is the force (measured in N), "*l*" is the specimen width (in mm), "*t*" is the specimen thickness and σ is the stress (in MPa).

This approach allows to overcome the tricky and not reliable measurement of mat thickness, due to the high mat porosity, which usually reaches 80-90% of the total volume. The mass measurement appears to be simpler and more reliable than the thickness one, since the latter needs a mechanical system to its estimation, thus the measurement action locally perturbs the material in a way which is difficult to be evaluated. Moreover, a mathematical model has been put forward to provide help in understanding the mechanical behaviour of the electrospun fibers.

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MOFs AS SPME COATINGS FOR THE ANALYSIS OF ENVIRONMENTAL POLLUTANTS

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ABSTRACT

Metal organic frameworks (MOFs) are porous coordination polymers made up of metal ions or metal clusters and ligands. Various properties of MOFs like high mechanical and thermal stability as well as high surface area make them unique candidates for applications in the field of adsorption, sensing, drug delivery and catalysis. By carefully selecting metal ions and ligands, different MOFs can be designed and synthesized. Solid-phase microextraction (SPME) is a simple and effective analytical technique used for the pre-concentration and extraction of a wide range of analytes of environmental, food and forensic concern[1-3]. In this field, the development of new coatings is highly desirable to increase both selectivity and sensitivity towards target analytes. In this study, PUM 210-a zinc based MOF- and its fluorinated analogue PUM 210F were synthesized and proposed as new coatings for the SPME-GC-MS analysis of environmental pollutants like benzene, toluene, xylenes, and ethylbenzene (BTEX) as well as polycyclic aromatic hydrocarbons (PAHs). The proposed MOF structure has Zn-nodes combined with a dicarboxylic acid and a bis-pyridyl-bis-amide linker, forming pillared 3D frameworks. The porous structure and the presence of aromatic rings make the MOF frameworks ideal candidate for the extraction of the aromatic analytes. The coatings were characterized by PXRD, SEM, TGA and N_2 adsorption analyses. The thermal stability was found to be nearly 380°C for both the MOFs.The uniform and homogeneous coating on the SPME fiber show an average thickness of 84.2 ± 4.4µm (n=3). Both extraction time and extraction temperature were optimized by using a 2^2 full factorial design, thus allowing to obtain detection limits in the 2-9 µg/l and 0.1-10 ng/l level for BTEX and PAHs, respectively. The performance of PUM 210F toward the detection of fluorinated anesthetics commonly used in operating rooms like sevoflurane and isoflurane is under investigation.

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SYNTHESIS AND EPR STUDY OF A [2]-ROTAXANE BASED ON A PERSISTENT PARAMAGNETIC MACROCYLE ACTING AS MOLECULAR MACHINE

Cecilia Poderi[(a)], Valentina Bleve[(a)], Paola Franchi[(a)], Evangelia Konstanteli[(a)(b)], Lorenzo Gualandi[(a)], Steve M. Goldup[(c)], Elisabetta Mezzina[*(a)], and Marco Lucarini[*(a)]
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ABSTRACT

The synthesis of a new crown ether macrocycle (*cis*-**2, Figure 1**) containing a dialkyl nitroxide radical and its incorporation in a rotaxane system have been investigated in this work. The nitroxidic unit of the macrocycle was used as spin-probe and as recognition site in a [2]-rotaxane containing 4,4'-bipyridinium (BPY^{2+}) and dialkylammonium (NH_2^+) stations (**1H·PF$_6$, Figure 1**).[1] This rotaxane may be employed as molecular machine, since by treating with an excess of base, we could force the movement of the macrocycle on the BPY^{2+} station, forming rotaxane **1·PF$_6$** by a reversible process. The EPR studies of the rotaxane evidenced an increase of the nitrogen hyperfine constant (a_n) after the switching to **1·PF$_6$**, due to a charge-dipole interaction between the nitroxide unit and the BPY^{2+} group**.** Thus, it was possible to probe the displacement of the macrocycle between the two recognition sites by measuring the nitrogen hyperfine constant in the EPR spectrum of the [2]-rotaxane, before and after treatment with a base. For this reason, this work represented the first example of a rotaxane system in which the paramagnetic unit on the wheel acts as recognition site during the threading process.[2] In addition, reduction kinetics studies were performed in order to investigate the persistence in water of nitroxide *cis*-**2** and its derivative *cis*-**3 (Figure 1)**. The reduction rate constants calculated for these compounds evidenced promising persistence properties, being 20 times higher than that reported for **TEMPO** radical. According to these results, it could be affirmed that these paramagnetic systems may be of great interest for many *in vivo* and biological applications.

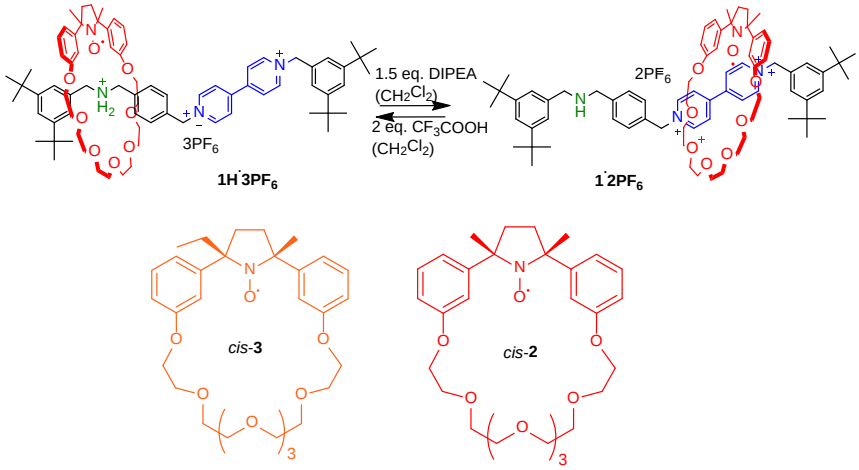

Figure 1. Structures of rotaxanes **1H·PF$_6$**,**1·PF$_6$** and macrocycles *cis*-**2** and *cis*-**3**.

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DIFFERENT SETUPS OF ASCORBIC ACID A-CELLULAR ASSAY FOR MEASURING OXIDATIVE STRESS POTENTIAL OF AIRBORNE PARTICULATE

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ABSTRACT

As there is increasing evidence that the mechanism of adverse effects caused by inhaled ambient particulate matter (PM) is mediated by the generation of reactive oxygen species (ROS), the oxidative potential (OP) has been proposed as a biologically relevant metric for assessing PM toxicity [1, 2].
Among the different cell-free assays developed for measuring OP, in this work we characterize the ascorbic acid assay, as an inexpensive and user-friendly method based on spectrophotometric measurements of depletion rate of ascorbate oxidized by redox-active species (OP_{AA}) [2].
Given the important role of lung lining fluid antioxidants in ROS formation, the purpose of our study is to investigate the effects of different compositions of antioxidants to be more representative surrogate lung fluid (SLF).
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.
To address this, we quantified OP_{AA} from standard solutions of two transition metals − Cu^{2+} and Fe^{2+} − and three quinones − 1,2-naphthoquinone (1,2-NPQ), 1,4-naphthoquinone (1,4-NPQ) and 9,10-phenantrenequinone (9,10-PNQ) − which are commonly found in atmospheric PM.
We find that the antioxidant composition of our SLF significantly affects the AA depletion rate from all the investigated species, but with different dependence on the mixture complexity.
Both citrate and glutathione decrease OP_{AA} from Cu, if singly added to AA, and from Fe, if present in combination.
This behaviour may be ascribed to formation of metal complexes, altering the reactivity of the metals. GSH suppress AA oxidation also for the investigated quinones, mainly if combined with Cit, independently of the additional presence of urate.
These effects are likely due to the increase on the reductant properties of the composite SFL, due to the concomitant presence of several antioxidants.
Although it is impossible to in vitro reproduce the complexity of particle−lung interactions, the composite surrogate lung lining fluid investigated in this work may represent an useful experimental set up for a screening assay for the oxidative potential of ambient PM.

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SYNTHESIS AND STUDY OF PEPTIDE-BASED CHELATORS FOR ZIRCONIUM-89

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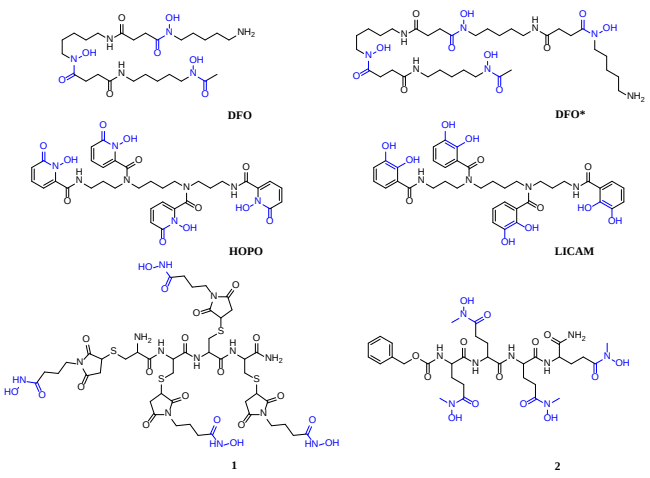
Positron emission tomography (PET) is an imaging technique used in nuclear medicine for diagnosis of some diseases and study of metabolic patterns. PET is highly sensitive and this is beneficial because it reduces any toxicity concerns and ensures that PET tracers do not saturate biological receptors. Recently, several positron-emitting metal isotopes, such as ^{68}Ga, ^{64}Cu, ^{89}Zr and ^{44}Sc, have been employed in research of new radioactive tracers for medical applications. These isotopes are characterized by longer half-lives in comparison to the common organic PET isotopes ^{11}C or ^{18}F; this feature allows them to be produced off-site and transported to the imaging location and also enables the study of slow biological processes. The metal nucleus must be stably chelated to an organic moiety because otherwise the imaging signal will not be well resolved. The selection of the suitable chelating agent for PET depends on the metal used, which in turn depends by the half-life required for the imaging investigation.[1]

^{89}Zirconium (^{89}Zr) is an ideal radionuclide for PET: it has a half-life of 78.4 hours, which complies with the time required for an appropriate body-distribution of the imaging agents. Currently, the most commonly used chelator for ^{89}Zr is Desferrioxamine B (DFO) although it is generally accepted that DFO is not the ideal chelator because the ^{89}Zr-DFO complex is partly unstable due to the inability of DFO to saturate the eight coordination positions of the radiometal. Thus, there is a need for novel chelators that form more stable complexes with ^{89}Zr. First of all, the ideal chelator for ^{89}Zr should be octadentate; in addition, zirconium is a “hard” metal ion and prefers oxygen donor atoms. In the past few years some new chelating agents have been studied for Zr(IV). Both Deri *et al.* [2] and Patra *et al.* [3] reported two linear octadentate chelators named HOPO and DFO*. A catechol-based version of the HOPO-ligand (LICAM) has been investigated, as well.[4]



Here we presented the synthesis of two linear ^{89}Zr-chelators based on a peptide backbone: compound **1** is characterized by the presence of four primary hydroxamic moieties; compound **2** is functionalized with four N-methyl-hydroxamate functions as chelating agents. The peptide chelators were obtained combining solid/solution phase peptide synthesis approaches. Preliminary chelating properties towards ^{89}Zr(IV) will be presented.

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SYNTHESIS OF BENZOTHIAZOLE-BASED MULTI-TARGET LIGANDS FOR AMYOTROPHIC LATERAL SCLEROSIS

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a progressive and lethal multifactorial neurodegenerative disease characterized by a loss of motor neurons in the brain and spinal cord, leading to progressive muscle loss and paralysis.[1] Nowadays, there are only two palliative drugs approved by FDA for ALS treatment: riluzole, a glutamate modulator,[2] and edaravone, a radical scavenger, approved only in U.S. and Japan.[3] There is no disease-modifying treatment of ALS, and many clinical trials have failed. The difficulty in finding a cure is probably associated to the use of the reductionist approach currently predominant in drug discovery, centered on single molecular targets. Drugs hitting a single target may be inadequate for ALS treatment, because it involves multiple pathogenic factors.[1] Considering the previous aspects, A promising clinical trial started in 2013 suggests a synergic effect between riluzole and rasagiline, a monoamine oxidase B (MAO-B) inhibitor approved by FDA for the treatment of Parkinson's disease.[4]

In this trial, the two drugs are co-administrated. The aim of this project is to design and synthesize multi-target ligands based on the combination of the riluzole and rasagiline pharmacophores.

The multi-target approach involves the administration of a single molecule, potentially able to modulate simultaneously multiple disease pathways involved in ALS. Multi-target approach has several advantages over polypharmacology such as a simpler pharmacokinetic profile, the absence of risk of drug-drug interactions, and the guaranteed simultaneous presence of the two pharmacophores of interest at comparable concentrations.[5] The unknown products (AB-1, AB-2, AB-3) were planned rationally, by the fusion of rasagiline and riluzole's pharmacophores (Figure 1). They conserve the 2-aminobenzothiazole nucleus present in riluzole, and they have a propargylaminomethyl group in 6 position, to trace rasagiline's structure. The three compounds obtained will be tested for their ability to inhibit MAO-B and their antiglutamatergic activity will also be evaluated in cellular assays. The compounds will also be studied as neuroprotectants in suitable cellular models. Then, the results obtained will be compared to parent compounds' activity, to evaluate a possible addictive or synergic effect.

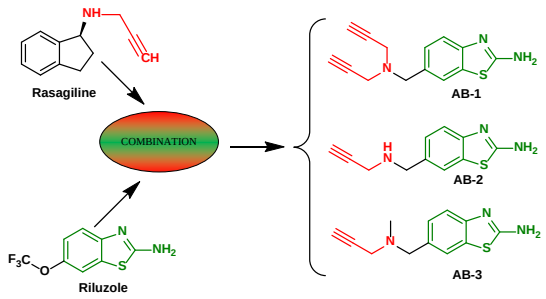

Figure 1. Schematic representation of project aim.

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Zwitterionic Metallates of Pd, Ni and Co: Synthesis and Characterization of Tris-Chelated Coordination Compounds

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ABSTRACT absgrab

The nucleophilic addition of aminophosphanes to alkyl- and aryl- isothiocyanate leads to the formation of zwitterionic thioamidyl-phosphonium ($P^+C(S)N-R$) functional group. Within this family of compounds, $EtNHC(S)Ph_2PNPPh_2C(S)NEt$ (HEtSNS) can be prepared by reacting Ph2PNHPPh2 (dppa) in EtNCS as the reaction medium[1]. HEtSNS is a versatile and conformationally flexible mono-, bi- and tri- dentate ligand for a wide range of metal cations[2,3,4]. In this work, we present a comparison between Pd(II), Ni(II), Co(II) and Co(III) complexes (Figure 1), as these two family of compounds show how the ligand may switch from bi- to tri- dentate, and how the atom donors may vary from S-N-S to N-N-N with a conformational adjustment, depending on the metal requirements.

Pd^{2+} (d8) is bound to HEtSNS through S-N-S coordination, forming [(HEtSNS)PdCl]Cl. A chloride completes the square planar geometry, the second chloride forming a hydrogen bond with the NH group of the ligand. In solution, this species is in equilibrium with the palladium dimer $[(EtSNS)Pd_2Cl_4][(HEtSNS)PdCl]$. HCl may be salified with NEt3, thus obtaining the neutral complex [(EtSNS)PdCl] (Figure 1-a). Co^{2+} (d7), in the presence of NEt3, reacts with HEtSNS forming two pentacoordinate complexes. The neutral complex "(EtSNS)CoCl", analogous to [(EtSNS)PdCl], form the dimer $[(EtSNS)CoCl]_2$ (Figure 1-c), where the two Co^{2+} are bridged by two chlorides and the square pyramidal geometry is completed by EtSNS, chelating in an N-N-N coordination fashion. If [EtSNSCoCl]2 is crystallized in the presence of HNEt3Cl, the ionic compound $[EtSNSCoCl_2]^-$ $HNEt_3^+$ is formed (Figure 1-d), displaying a trigonal bipyramidal geometry. In presence of DMF the resulting compound is the octacoordinated $[(EtSNS)CoClDMF_2]$. Ni^{2+} (d7) form a stable complex only if DMF is present $[(EtSNS)Ni(NO_3)DMF]$.

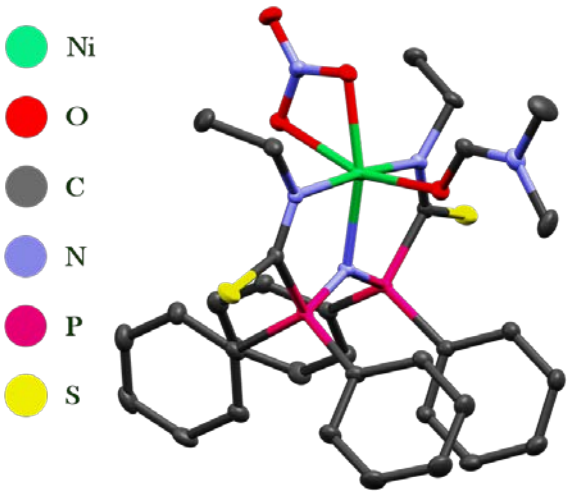

Figure 1. Nikel compound $[(EtSNS)Ni(NO_3)DMF]$

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OPTIMIZATION OF A PYRO-GASIFICATION PROCESS FOR CARBON FIBRES RECOVERY

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Carbon fibres (CFs) are unique reinforcing elements due to their unrivalled properties, which lead to lightweight and strong composite materials. The great versatility of CFs makes them suitable in a wide range of applications: automotive, aerospace, sports equipment, but also in the medical, energy (e.g. wind turbines) and construction fields.

The advantages deriving from the use of CFs in these areas of application have brought to an increase of the scientific researches aimed at the development of more efficient and competitive production technologies, more effective composite formulation and production processes and, not last, CFs reclaiming from scraps and end–of–life manufactured goods, the latter being indeed an urgent topic. In fact, a consequence of the increasing production and use of carbon fibres reinforced polymers (CFRPs) is the increase of production scraps and end–of–life wastes containing CFs [1].

In this regard, researchers have developed technologies capable to retrieve CFs from CFRPs, obtaining recovered carbon fibres (rCFs) that can be used for secondary productions, following the concepts of circular economy.

The recycling of carbon fibres with properties comparable to those of virgin fibres is a challenging task. To date, among the various proposed recycling processes (mechanical, thermal, chemical), the most promising seems to be pyrolysis, a thermal treatment at moderate temperatures in inert atmosphere. However, the quality of the rCFs after the pyrolysis treatment is not suitable for a direct reuse due to the presence of a thin layer of pyrolytic carbon (char) adhered to the fibres. In order to obtain clean and reusable rCFs, a post–treatment aimed at char removal is therefore necessary. A possible method is a controlled oxidation process, otherwise referred to as gasification, which proved to yield clean and undamaged rCFs [2].

The present work focuses on the study of an innovative pyro-gasification process for the recovery of CFs from CFRPs wastes, obtained in a single batch reactor. The goal was to scale–up the process from laboratory to pilot scale, identifying the optimal process parameters in order to obtain rCFs with properties as close to those of virgin fibres as possible and, thus, suitable for a reuse in new composite materials. At first, a tuning phase was carried out. The influence of the different process parameters (e.g. temperature, residence time, airflow rate during gasification) has been evaluated at the end of each test by means of thermal, morphological and surface rCFs characterization. These analyses were performed by thermogravimetric analysis (TGA) and muffle furnace thermal stability tests, scanning electron microscopy (SEM) and Raman spectroscopy.

Secondly, a validation phase of the pyro-gasification process was carried out repeating pyro–gasification cycles with the best parameters previously identified, in order also to demonstrate the repeatability of the process. The rCFs characterization was performed using the same analyses described for the tuning phase.

The obtained data demonstrates the validity of the process. The rCFs obtained via pyro–gasification exhibit properties similar to the ones of virgin fibres and can be thus considered suitable for their reuse in new composite materials.

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Changing the Dress to a MOF through Fluorination and Transmetalation

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Among porous materials, Metal-Organic Frameworks (MOFs) are well-known for the high versatility of their structural design and tailoring. [1] This comes from the possibility of selecting the most appropriate ligands and metal nodes to reach the desired architecture, which can be further tuned by post-synthetic modifications (PSM). Two novel pillared Zn(II)-based Metal-Organic Frameworks were *de-novo* synthesized exploiting *N,N'-(1,1'-biphenyl)-4,4'-diylbis-4-pyridinecarboxamide* (bpba) and its fluorinated analogous *N,N'-(perfluoro-1,1'-biphenyl-4,4'-diyl)diisonicotinamide* (f-bpba) as suitable pillar linkers and 2,6-naphtalen dicarboxylic acid as carboxylic ligand. The resulting heteroleptic MOFs, namely **PUM210**, $[Zn_4(bpba)_{1.5}\cdot(ndc)_4\cdot(H_2O)]_n$ and **PUM210F**, $[Zn_3(bpba)_1\cdot(ndc)_3\cdot(DMF)]_n$, feature an uncommon truncation of the Zn(II) paddle-wheel nodes along the pillaring direction. **PUM210** and **PUM210F** exhibit a polycatenated architecture, resulting in microporous channels decorated by amide moieties. The activated forms **PUM210a** and **PUM210Fa** show a permanent porosity and a selective adsorption of CO_2 over N_2. Moreover, the heterometallic **Cu-PUM210** and **Cu-PUM210F** were obtained by convenient transmetallation protocol and their adsorption propriety towards CO_2 were subsequently investigated. [2]

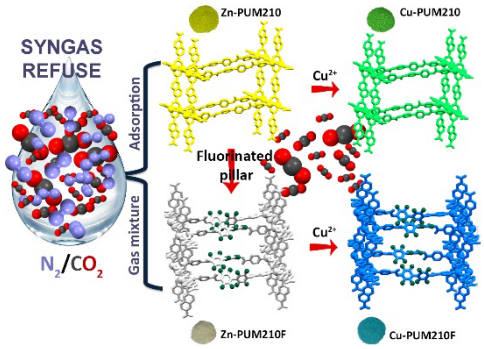

Figure 1. PUM210 MOF series

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2,3-DIHYDRO-6,7-DIHYDROXY-1H-ISOINDOL-1-ONES as metal-chelating influenza virus ENDONUCLEASE INHIBITORS

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ABSTRACT

Seasonal human influenza A or B virus infections are an important cause of morbidity and mortality. Moreover, there is a permanent risk of sudden influenza pandemics, such as the notorious 'Spanish flu' in 1918 and the swine-origin H1N1 pandemic in 2009[1]. Commercially available anti-influenza drugs present problems regarding central nervous system side effects and widespread resistance phenomena [2],[3],[4]. Therefore, there is an urgent need for new antiviral compounds, preferably based upon novel pharmacophores and different modes of action. Recently, endonuclease activity has become an attractive target to develop efficient inhibitors. Our research includes the synthesis of small molecules, as possible inhibitors for acid polymerase (PA) of influenza virus (**Figure 1**).
This enzyme, as others like HIV Integrase, is a metal-dependent enzyme with two metal ions (Mn^{2+} or Mg^{2+}) as co-factors. Therefore, chelation could be exploited as a successful strategy to efficiently chelate the metals within the active site, blocking the enzymatic activity and the viral lifecycle.
We have decided to use an isoindol-1-one scaffold, previously designed as HIV-1 Integrase inhibitors, to inhibit the activity of PA endonuclease: in fact, this kind of scaffold could be able to contemporary chelate the two metal ions in the active site, impairing the catalytic activity of the protein.
The compounds were fully characterized and tested to evaluate their activity on PA endonuclease: they inhibit influenza virus endonuclease *in vitro* at nanomolar concentration, revealing a very good potential for the development of novel anti-influenza virus inhibitors.

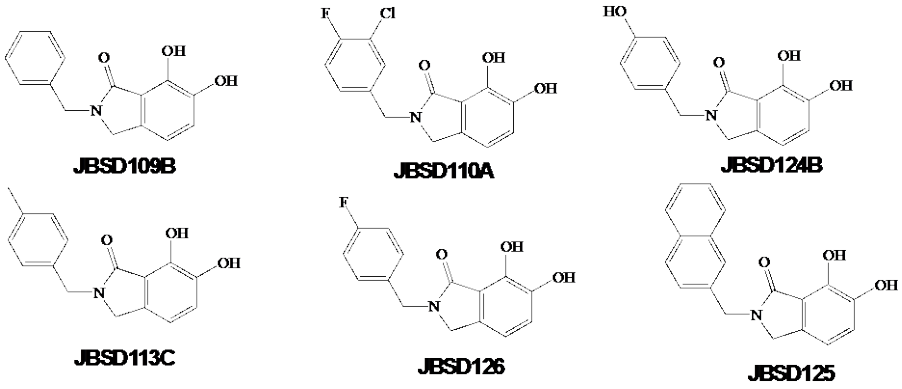

Figure 1. Molecular structures of synthesized inhibitors

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PRO-ELECTROPHILIC COMPOUNDS AS PHARMACOLOGIC TOOLS FOR INVESTIGATING THE AMYLOIDOGENIC PATHWAY IN ALZHEIMER'S DISEASE

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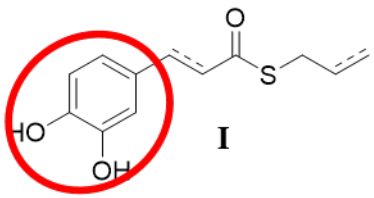
ABSTRACT

Alzheimer's disease (AD) is a progressive brain disorder characterized by a complex interplay of genetic and biochemical factors contributing to the cognitive decline. AD progression involves misfolding and aggregation of β-amyloid peptide (Aβ) into soluble oligomers and insoluble fibrils, which are thought to mediate a variety of neurobiological events. They include oxidative stress, neuroinflammation and excitotoxicity, which in turn amplify Aβ neurotoxicity.

To investigate the mechanistic connection between the process of protein aggregation and tissue degeneration we previously synthesized nature-inspired hybrids with anti-aggregating and antioxidant properties [1,2]. While diverse aromatic substituents led to direct and indirect antioxidant effects, only the catechol moiety was able to switch on anti-aggregating activity, as the removal or masking of one or both the hydroxyl substituents of compounds **I** (Figure 1) resulted in a complete drop of activity.



I

Figure 1. General structure of catechol-based hybrids **I**.

Thus, we herein wanted to investigate the anti-aggregating properties of this scaffold at molecular level. New hybrids bearing catechol bioisosteres were synthesized, and their efficacy in inhibiting fibrilization was studied *in vitro* by a ThT-based fluorometric assay. The experimental outcomes corroborate the importance of the catechol group in limiting amyloid aggregation. They also suggest that the pro-electrophilic properties of the catechol, which becomes *ortho*-quinone on oxidation [3], might have a role in mediating the anti-aggregating efficacy of the catechol-based derivatives. To test this hypothesis, the oxidation potential of selected pro-electrophilic compounds was studied performing cyclic voltammetry experiments, and the results were compared with functional biological activity. Interestingly, a correlation was found between chemical and biological effects, suggesting a redox-controlled conversion to the active quinone form to be plausibly responsible for the anti-aggregating effect.

In conclusion, the new hybrids emerge as valuable tools for investigating the molecular mechanisms potentially involved in redox-mediated Aβ damage.

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NANOELECTROCHEMISTRY AS NEW TREND FOR ROS AND RNS INVESTIGATION IN SINGLE CELL DOMAINS

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ABSTRACT

Electrochemical methods are becoming increasingly important to investigate highly dynamic and complex systems in the biological field. They permit real-time, highly sensitive and selective measurements with high spatial resolution. Moreover, cell viability is preserved and real-time detection can be performed also allowing studying fast kinetic processes.
Scanning electrochemical microscopy (SECM) is a powerful tool to investigate cells and their surroundings. Employing utramicroelectrodes (UME) SECM provides functional images of cells in which both topography and chemicals information are provided with micrometric resolution[1].

Biological relevant reactive species as reactive oxygen species (ROS) and reactive nitrogen species (RNS) became of great interest in the last years as their overproduction is correlated to several pathogenic conditions such as cancer. A novel electrochemical set up, consisting of screen printed electrodes and a nano-porous black platinum UME, allows for the detection of H_2O_2 production from human cell mitochondria upon activation of the respiratory chain [2]. The use of such a tool will lead to a better comprehension of the oxidative stress and the redox balance of living cells.

Reactive species detection is challenging because those molecules are localized inside specific domains of the cells and, in low abundance. Thanks to the development of sub-micrometer electrodes it will be possible to penetrate the cells without damaging them performing intracellular analysis. Nanoelectrodes and functionalized pipettes with radii about 100 times smaller than the cell dimension, open the door to a new field of nanoelectrochemistry. The development of the miniaturized tools could help in the elucidation of the role of each single cell in the whole system.
During my PhD period I will develop SECM nanoprobes able to sense chemicals in specific compartments of cells, in order to understand in depth single cell metabolism and chemical trafficking.

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METALLO PEPTIDES IN THE DESIGN OF NEW, HIGHLY SELECTIVE CLINICAL TREATMENTS

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ABSTRACT

The necessity of new antimicrobial agents is unarguable, since current therapeutic treatments are not always effective: pathogenic microorganisms capable to adapt and resist against drug action have significantly increased over the last decades and their associated mortality rate still remains a global concern. Several studies have shown that metal acquisition and regulation greatly contribute to virulence and physiology of pathogenic species. In particular, to prevent infections humans restrict the access to essential micronutrients by means of an innate immune response termed "nutritional immunity", on the contrary pathogens rely on sophisticated systems (e.g. siderophores) to overcome the scarce metal bioavailability. From this perspective, a deeper insight into the mechanism of metal trafficking in pathogens and host nutritional immune response can provide crucial information to design new effective antibiotic therapies, e.g. by developing species-selective transport or imaging drugs, based on metal complexes, which can be recognized only by specialized metal transport proteins ("Trojan Horse" approach). Furthermore, metal complexes cannot be only a promising tool in antimicrobial treatments, but they can also find application against pathologies which – in general – involve metal ions (e.g. neurodegenerative diseases or cancer) [1-3].

As a first step, it is essential to obtain information about thermodynamics and coordination chemistry of the metal chelators, in order to point out the most effective metal binding sites. Both natural and artificial peptides can be exploited for this purpose. Aiming at the design of new clinical treatments, we focused on Zn(II) and Cu(II) binding behavior towards both the putative metal transporter C4YJH2 (a protein sequence of 199 residues found in the genome of *Candida albicans* [4]) and the antimicrobial peptide Calcitermin [5], isolated in the human airways.

The characterization of the complexes required a variety of techniques. The stoichiometry of the formed species has been determined through high-resolution mass spectrometry as well as by potentiometry which also provided the stability constants of all the formed metal complexes; thermodynamic description of metal-ligand interactions has been also investigated by calorimetry. The identification of binding sites and the coordination geometry of the formed species have been achieved by several spectroscopic techniques (NMR, UV-Vis, fluorimetry, CD and EPR).

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HIGHER ORDER CYCLOADDITIONS: FROM A STEREOSELECRIVE REDISCOVERY TO A COMPUTATIONAL FASCINATION.

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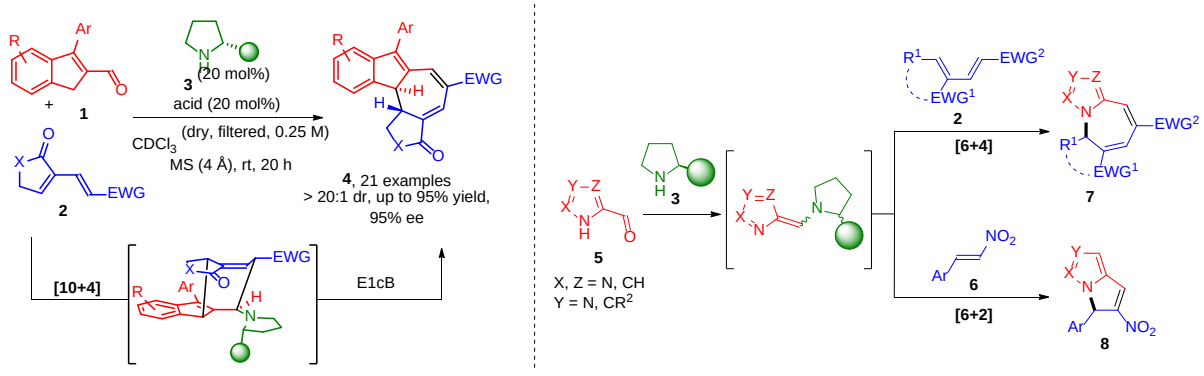
ABSTRACT

Higher order cycloadditions (HOCs), i.e. cycloaddition reactions involving more than six π-electrons, became a popular research topic in organic chemistry, following the computational and experimental reports of Woodward, Hoffmann and Houk.[1] Numerous examples of thermally allowed HOCs have been reported, but there is a remarkable lack of their enantioselective equivalents. Organocatalysis was shown to be a competent strategy to induce enantioselectivity in HOCs, as demonstrated by a recent report by Jørgensen.[2]

Following this principle, we developed a strategy to disclose the first catalytic stereoselective [10+4] cycloaddition. Amino isobenzofulvenes, generated *in situ* from aldehydes **1** and catalyst **3**, were reacted with dienes **2**, affording intriguing tetracyclic scaffolds **4**.[3] The methodology, displayed high yields, high peri-, diastereo-, and enantio-selectivity, and a broad substrate scope. Experimental and computational evidence suggest that the observed stereoselectivities arise from kinetically controlled amino isobenzofulvene formation.

Moreover, we have developed a novel concept for catalytic enantioselective activation of heteroaromatic compounds, such as pyrrole-, imidazole- and pyrazole-carbaldehydes **5** by organocatalysis, generating electron-rich hetero-6π-intermediates acting as nucleophiles.[4] These react in a highly chemo-, regio- and stereoselective manner with various types of electron-deficient dienes **2** and olefins **6**, in [6+4] and [6+2] cycloaddition reactions, respectively. The methodology provided bio-attractive pyrrolo-azepine scaffolds **7** and pyrrolizidines alkaloid scaffolds **8**. Based on computational studies, stereocontrol occurs at the second C–C bond forming step, rather than the N–C bond forming transition state. Based on these two examples, this presentation will demonstrate that HOCs, besides being a powerful tool to construct complex and biologically relevant scaffolds, are extremely fascinating on the computational point of view, revealing interesting and peculiar features in reactivity and stereoselectivity.



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

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$\alpha_V\beta_6$ INTEGRINS: TOWARDS NEW SMALL-MOLECULES PEPTIDOMIMETICS AS SELECTIVE LIGANDS

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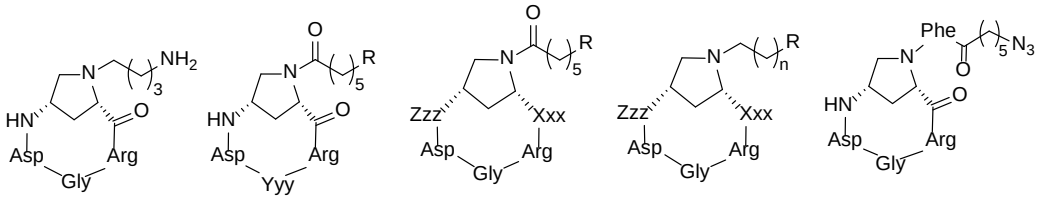
ABSTRACT

Integrins are heterodimeric cell surface receptors that cells use to modify, recognize and interact with the extracellular matrix; they play key roles in different physiological processes like embryogenesis, angiogenesis, immune control and regulation of the balance between proliferation and apoptosis. For this reason, their altered activity or expression is related to different pathologies including cancer development, metastasis spread, autoimmune diseases and fibrosis, rendering these membrane receptors attractive targets in biomedical research [1].

Among the RGD-recognizing integrins, the $\alpha_V\beta_6$ subtype is overexpressed in many aggressive epithelial tumors (pancreatic, gastric, lung, oral and ovarian carcinomas), as well as in liver and pulmonary fibrosis. This integrin has emerged as a biomarker of the epithelial-to-mesenchymal transition, which sustains the metastatization process, tumorigenesis and fibrosis, being its overexpression associated to the activation of the TGFβ pathway. This means that $\alpha_V\beta_6$ is an ideal target for both therapeutic and diagnostic application, provided that selective and potent $\alpha_V\beta_6$ ligands are available [2].



In this context, our purpose was to synthesize a small collection of cyclic peptidomimetics embodying a 4-aminoproline scaffold flanked by variable tri-, tetra- and pentapeptide sequences, and decorated with proper functional groups for covalent conjugation to bioactive or imaging-active units. Inspired by compounds of type **1** [3,4], known for their $\alpha_V\beta_3$ integrin targeting capability, we synthesized a collection of cyclic peptidomimetics of type **2-5** by solid phase synthesis, followed by in-solution cyclization reactions. After purification and structural characterization, these compounds were evaluated for their binding affinity toward the isolated $\alpha_V\beta_6$ receptor giving promising results, which will drive us in the development of more potent and selective $\alpha_V\beta_6$ ligands as new relevant pharmacological agents.

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Design and synthesis of dual aromatase inhibitors and SERMs as potential agents targeting breast cancer

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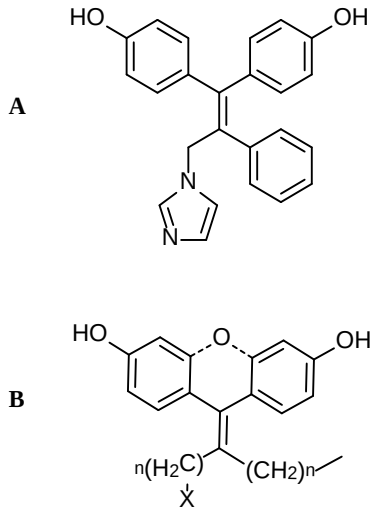
Breast cancer is the most common type of cancer among women and approximately 70% of human breast cancer are estrogen dependent (ER+). In pre-menopausal women, estrogens are primarily produced by the ovaries; after menopause, these hormones continue to be synthesized in peripheral tissues such as adrenal glands and adipose tissue. The enzyme responsible for a key step in the biosynthesis of estrogens is Aromatase (HA). It is a member of the cytochrome P450 superfamily and it is responsible for the aromatization of androgens to estrogens. The physiological actions of estrogens are mediated by estrogen receptors (ER), which exist in the α and β subtypes. They are dimeric nuclear proteins that bind to DNA and control gene expression. ERα, upon estrogen binding, exerts its pro-oncogenic effect promoting cell proliferation or decreasing apoptosis. In contrast, ERβ has anti-proliferative effects and therefore oppose the actions of ERα. The expression levels of the two receptors change in different tissues.

There are two main strategies for breast cancer treatment. SERMs (Selective estrogen receptor modulators) target ER receptors and act as either agonists or antagonists in different tissues. The representative compound of this class of drugs is Tamoxifen (TAM). Aromatase inhibitors (AIs) are steroidal or nonsteroidal compounds that bind the aromatase enzyme blocking estrogen production. Available AIs include Anastrozole, Letrozole and Exemestane.

It has recently been observed that TAM metabolites, in particular Norendoxifen (NOR) and Endoxifen (END), exert an inhibition on HA while still binding with good affinity to both ERs. Therefore, these two compounds are of great interest because they act on two different targets involved in the same pathology.



X= Imidazole; Pyridine

Figure 1. A. Strucure of Cushman's compound **B.** General structure of synthesized compounds

Starting from TAM structure, Cushman and co-workers[1] synthesized a molecule (A, fig. 1) that is a good inhibitor of HA and has good affinity for ERs.

We report now the design of new molecules inspired by this structure (B, Fig. 1). The bis-phenolic moiety was turned into a cyclic structure introducing an oxygen bridge, or the phenyl group was deleted and the imidazole was replaced with pyridine, still able to coordinate the iron of the heme group in the aromatase structure. Moreover, the distance between the nitrogen heterocycles and the central double bond was also modified.

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A SCXRD INVESTIGATION OF GUEST LOADING INTO HIGHLY FLEXIBLE MOF PORES

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MOFs (Metal Organic Frameworks) are a large class of ultraporous crystalline polymers deriving from the self-assembly of metallic ions or clusters with polytopic organic ligands. The high modularity of their synthesis allows a fine tuning of their porosity, making possible the confinement of molecular species of different shape and size.

Starting from the pioneeristic concept of crystalline-sponge method [1], we here propose a systematic way to embed small molecular aggregates inside tailored porous crystalline materials, with the aim of exploring the structural aspects of nanoconfinement and stabilizing the guest molecules inside the cavities of the structure. The challenge of this idea stands in the possibility to neatly “freeze”, within a crystal, ordered supramolecular clusters of molecules that would form a liquid in their natural state at ambient conditions, and visualize their supramolecular aggregation, at different loading time.

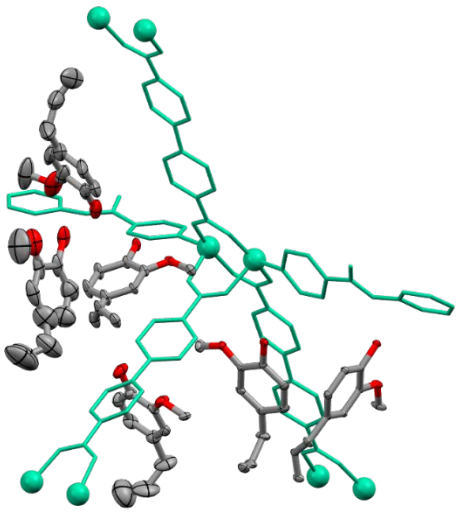

Figure 1. Structural motif of MOF with guest inclusion after 7 days of soaking

In particular, we propose a characterization of the evolution of the guest loading into metal-organic framework driven by host-guest interactions, focusing on the description of supramolecular aggregate of the guests inside the pores guided by guest-guest interactions. The MOF crystals were soaked for different time into the pure liquid guest and sequentially characterized via SCXRD (Figure 1).

The guest we focused on is eugenol, which is a volatile phenolic constituent of clove essential oil obtained from Eugenia caryophyllata buds and leaves. It is a functional

ingredient of numerous products which have been used in the pharmaceutical, agro-food and cosmetic industry. The wide range of eugenol activities derived from it antimicrobial, anti-inflammatory, analgesic and antioxidant properties.

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CYCLIZATION OF PROPARGYLIC UREAS: EASY ACCESS TO PHARMACEUTICAL RELEVANT HETEROCYCLES

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ABSTRACT

Imidazol-2-ones and imidazolidin-2-ones play an important role in pharmaceutical and medicinal chemistry due to the presence of this moiety in a wide variety of biologically active compounds [1]. The high value of heterocyclic compounds for synthetic and pharmaceutical chemistry has driven the continuous efforts in the development of sustainable and more efficient protocols [2].

The intramolecular hydroamidation of unsaturated ureas offers an environmentally friendly, atom- and step-economical alternative route to easily access richly decorated 5-membered cyclic ureas.

Herein, we report the first base-catalyzed intramolecular hydroamidation of propargylic ureas to highly substituted imidazolidin-2-ones and imidazol-2-ones [3] (Figure 1). Notable features of our methodology include (i) excellent chemo- and regio-selectivity to 5-membered cyclic ureas, (ii) wide substrate scope and high functional group tolerance, (iii) very mild reaction conditions and (iv) remarkably short reaction times.

Intrigued by the complete chemo- and site selectivity features as well as by the unexpected fast formation of imidazol-2-ones under very mild conditions, we carried out computational studies to gain insights into the reaction mechanism.

DFT calculations provided support for the non-assisted cyclization of deprotonated urea in the imidazolidin-2-one formation, and revealed the involvement of an allene intermediate in the imidazol-2-one pathway.

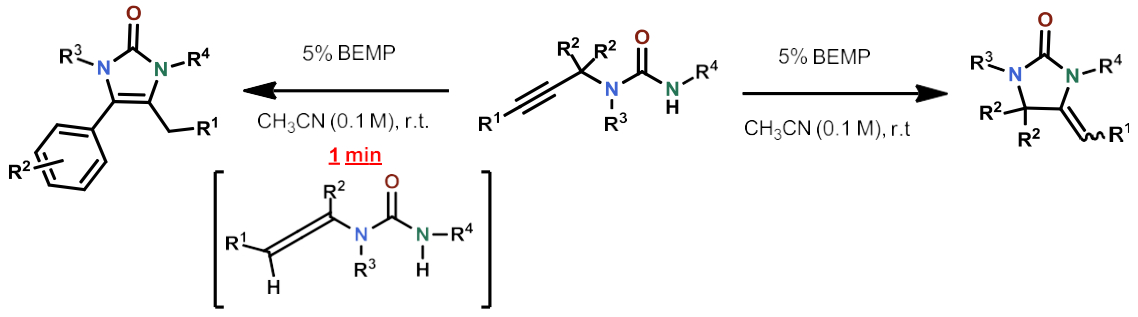

Figure 1 Base catalyzed hydroamidation of propargylic ureas

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[3] Paper submitted

BARLEY'S CHILDREN: ANALYSIS OF BEER AND WHISKY DATA BY INTERVAL-BASED METHODS

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ABSTRACT

The production processes of beer and whisky are so similar that these two beverages can be imagined not only as siblings, but also as homozygous twins: almost indistinguishable when they are young but destined to grow up very different. Everything starts with a mother which in our case is a source of sugars, barley. Barley is tricked into sprouting, but then it gets roasted and dried, in a process called malting. Malting allows sugars and enzymes to become available for fermentation. Malt is then soaked with water to produce a malty-tea called “wort”. Here we have the first time in the twin’s life when they start to differentiate: beer likes hops and spices, but whisky is pickier, and avoids them. Then yeasts come in as puberty suddenly does and change everything. Fermentation yields ethanol and a myriad of other aroma and flavour compounds, and the character of the two siblings starts to get defined. However, the most drastic change happens next: whisky undergoes double (or even triple! [1]) distillation, while beer ripens for a while and quite soon it gets bottled, ready to start exploring the world. Whisky needs more time, as it prefers to stay home at least three years before even considering leaving the family nest [2].
During this very standard life-development, a lot of deviations may occur, resulting in very different beer and whisky products: even if both products have proud and long traditions, experiments for brewing new flavours has been on the rise for over a decade. New beer styles, spices and malts are mixed nowadays, and even cross-overs between whisky and beer meet the market[1].
In this context, our work was aimed at the characterization, using different spectroscopic and chromatographic techniques, of one-hundred samples of and fifty-four whisky samples. Spectroscopies such as Visible, NIR and NMR were employed for studying the beer [3,4], while in the whisky case dynamic headspace GC-MS [5] was chosen. Chemometrics tools were used for exploring the data and for extracting relevant chemical features. Specifically, interval-based [6] methods were employed for the integration of the NMR peaks and for the mathematical deconvolution of the GC-MS chromatographic peaks.
The contribution is aimed at presenting two real-case applications of interval-based methods for enhancing information extraction and interpretation.

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REACTIVITY OF TRIPLATINUM CLUSTERS IN ENYNES CYCLIZATIONS

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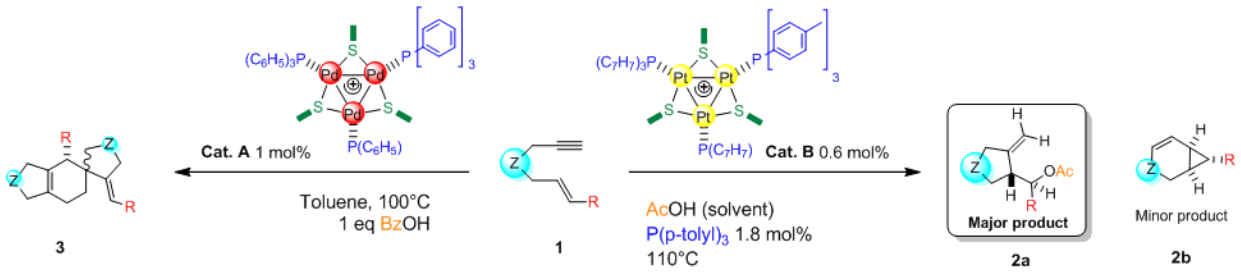
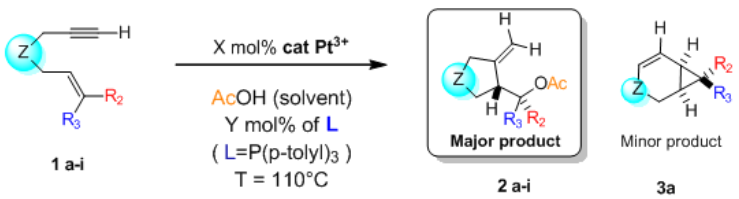
ABSTRACT

All-metal aromatic compounds are a fascinating class of cyclic molecules which present a delocalized bonding network similarly to their organic counterparts. However, their limited stability has hampered experimental applications so far. In this regard, our group developed a synthetic route which easily allowed the isolation of a family of bench-stable Pd_3^+ complexes,[1] demonstrating their utility as competent catalysts for the selective reduction of internal alkynes and for the polycyclization of terminal 1,6-enynes (Scheme.1(a)) and internal dienynes[2]. We then wanted to test isolobal Pt_3^+ complexes in the presence of unsaturated reagents. In particular, the reaction of 1,6-enynes with Pt_3^+ (0,6% mol), acetic acid as solvent, and an excess of P(p-tolyl)$_3$ (1.8% mol) led to the formation, as major product, of the carbocylic derivatives **2a** (Scheme.1(b))**.** The reaction scope included 1,6-enynes bearing different tethering groups, and a trisubstituted or disubstituted alkene moiety with both alkenyl and aryl groups (Scheme.2)**.**



Scheme 1. Reactivity of $[Pd_3]^+$ **(a)** and $[Pt_3]^+$ **(b)** in the presence of 1,6 enynes.



1a : Z = NTs, R_2 = Ph, R_3 = H
1b : Z = NTs, R_2 = Me, R_3 = Me
1c : Z = NTs, R_2 = Me, R_3 = H
1d : Z = NTs, R_2 = R_3 = Geranyl fragment
1e : Z = NTs, R_2 = (*p*-$CF_3C_6H_4$), R_3 = H
1f : Z = NTs, R_2 = (*p*-$OMeC_6H_4$), R_3 = H
1g : Z = $(CO_2Me)_2$, R_2 = Ph, R_3 = H
1h : Z = $(CO_2Me)_2$, R_2 = Me, R_3 = Me

Entry	Sub	X mol %	Y mol %	t (h)	Yield 2 (%)	Yield 3 (%)
[a]1	1a	0.3	-	16	42	9.7
[b]2	1a	0.3	0.9	16	53	9
3	1a	0.3	1.8	24	57	8
4	1a	0.3	2.7	44	72	9
5	1a	0.6	1.8	24	70	7
6	1b	0.6	1.8	24	70	-
7	1c	0.6	1.8	24	59	-
8	1d	0.6	1.8	24	43	-
9	1e	0.6	1.8	24	36	-
10	1f	0.6	1.8	24	44	-
11	1g	0.6	1.8	24	70	-
12	1h	0.6	1.8	24	56	-

[a] The counteranion of cat. A is PF_6^-
[b] Yield calculated by ^{1}H NMR

Scheme 2. Reaction Scope for $[Pt_3]^+$

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UDP-GlcNAc ANALOGS AS INHIBITORS OF *O*-GlcNAc TRANSFERASE (OGT): SPECTROSCOPIC, COMPUTATIONAL AND BIOLOGICAL STUDIES

Mattia Ghirardello[(a)], Daniela Perrone[(b)], Nicola Chinaglia[(b)], David Sádaba[(a)], Ignacio Delso[(a)], Tomas Tejero[(a)], Elena Marchesi[(b)], Marco Fogagnolo[(b)], Karim Rafie[(c)], Daan M. F. van Aalten[(c)], and Pedro Merino[(d)]

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ABSTRACT

A series of glycomimetics of uridine diphosphate *N*-acetylglucosamine (UDP-GlcNAc), in which the β-phosphate has been replaced by either an alkyl chain or a triazolyl ring and the sugar moiety has been replaced by a pyrrolidine ring (Figure 1), have been synthesized in the search of less-polar compounds to increase bioavailability of potential *O*-GlcNAc transferase (OGT) inhibitors. OGT is used as a model system of glycosyltransferases (GTs), enzymes that carry out the protein-glycosylation [1]. Inhibiting these enzymes provides a therapeutic target against several diseases [2], including cancer and neurodegenerative diseases. Affinity of synthesized glycomimetics for human *O*-GlcNAc transferase (hOGT) has been evaluated [3] and both spectroscopically and computationally studied. The binding epitopes of the best ligands have been determined in solution using saturation transfer difference (STD) NMR spectroscopy [4]. Experimental, spectroscopic and computational results are in agreement, highlighting how the absence of β-phosphate should be adequately counterbalanced in glycomimetics to have inhibition at micromolar concentrations.

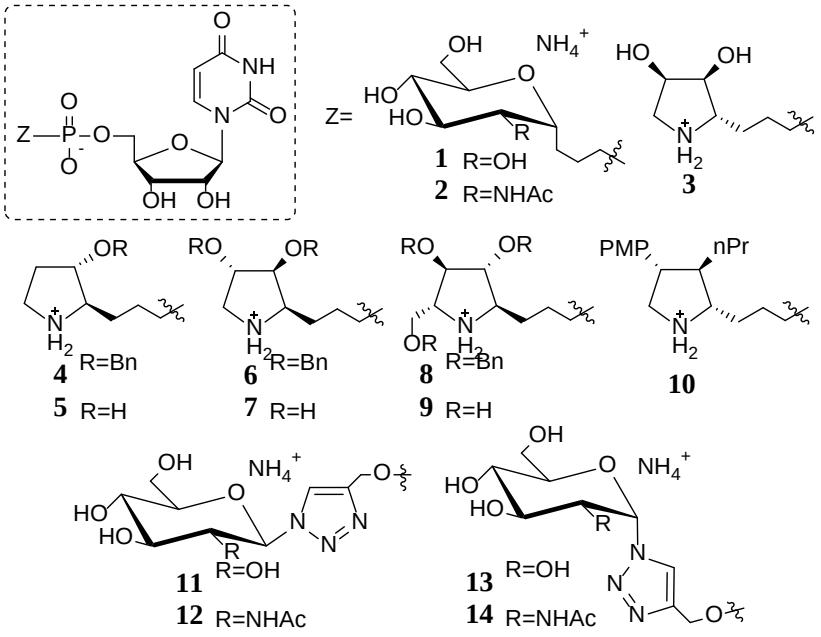

Figure 1. Synthesized glycomimetics of UDP-GlcNAc.

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SYNTHESIS AND INVESTIGATION OF CROCONATES AS SMART ORGANIC COATING FOR NOBLE METALS NANOPARTICLES

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ABSTRACT

Croconic acid is a cyclic organic molecule, belonging to a particular family of compounds called oxo-carbon acids. This molecule properly functionalized exhibit an absorption in NIR region and this property can be exploited in the design of NIR-harvesting materials obtained with a hybridization of a nano-material, characterized by a NIR absorption, with this organic molecule.
The purpose of this research is to combine a particular type of gold nanoparticles, called nanorods (AuNRs), with a specific aspect ratio (AR) in order to have an absorption in NIR region (900-1100 nm), with a croconic acid. This latter must be properly functionalized with an alkyl spacer (for example thiol-ending) in order to allow the anchoring to the AuNRs.

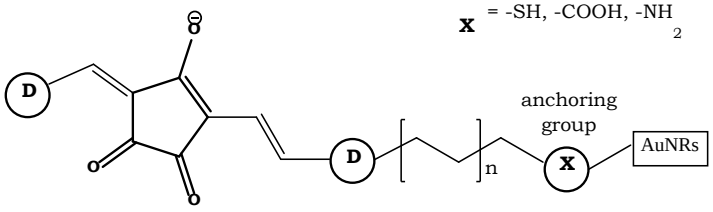

Figure 1: NIR-harvesting material.

Croconic acid absorption in the IR region can be tuned by varying donor moieties. Some experiments reported in the literature have revealed that increasing the conjugation in the donor part of the croconic unit leads to a red shift in NIR region (~1000 nm).
Croconic acid is synthetized following the method reported by Fatiadi et al. [1]. For the synthesis of gold nanorods the Seed-Mediated Growth method is followed [2].

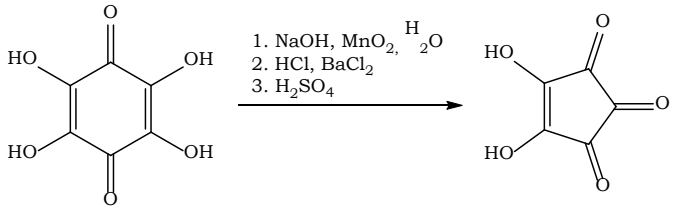

Figure 2: Croconic acid synthesis.

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

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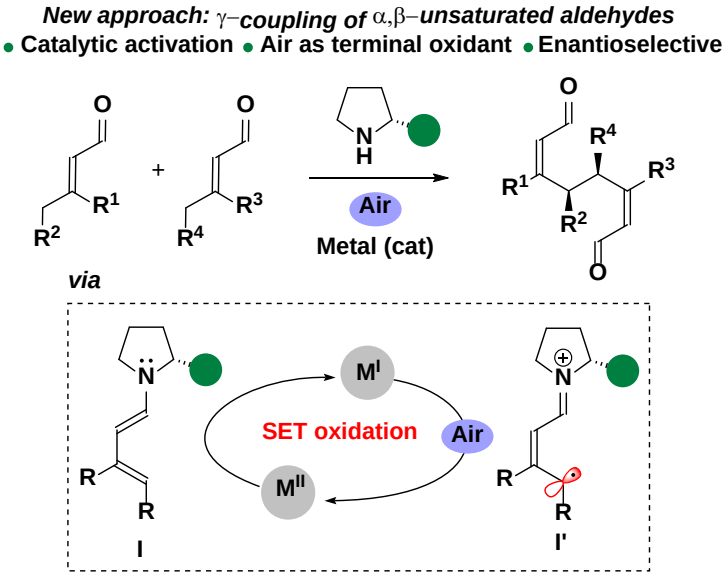
Asymmetric catalytic transformations present prominent routes to generate chiral molecules in an enantioenriched form [1]. Readily available chiral amines have been extensively used as catalysts for the activation of carbonyl compounds in the field of polar reactivity, which by reaction of electrophile and nucleophiles, provide products in a highly stereoselective manner [2]. In contrast, the involvement of short-lived open-shell species in asymmetric catalysis has remained relatively unexplored until recently, due to the inherent challenge of efficiently controlling the stereoselectivity of the product formation from high-energy intermediates [3]. The use of radicals in open-shell strategies can give access to different reactivity, for instance the coupling of two nucleophiles such as enol ethers, which would not be feasible with polar reactivity [4]. This communication presents the catalytic enantioselective coupling of two nucleophiles generated from α,β-unsaturated aldehydes *via* dienamine catalysis and a sub-stoichiometric amount of a single electron transfer-oxidant (SET-oxidant), that is reoxidized by air (Scheme 1). Merging organocatalysis with a transition metal featuring the appropriate redox properties provides the synergy necessary for the oxidation and subsequent radical coupling of the activated dienamine **I**. Air is used as the terminal oxidant of the process (Scheme 1) [5].



Scheme 1

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INJECTABLE BONE CEMENT FOR THE PREVENTION OF BACTERIAL INFECTIONS

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ABSTRACT

The need to fill bone cavities, caused by trauma, resection of tumors or diseases such as osteoporosis, still represents a sore point for orthopedic surgery, which nowadays must also tackle the problem of risky bacterial infections occurring in postoperative periods [1]. This leads to the continuous demand for new biomaterials to be used as fillers, being biocompatible, osteogenic and able to reach the target site in a non-invasive way, avoiding the onset of infections. Since bone is a dynamic tissue with a precise architecture, it is necessary to develop a material able to support the bone metabolism and then to be reabsorbed in situ, allowing the growth of the new tissue.

Our attempt was to create a biomimetic, affordable and minimally invasive therapeutic platform that would assist in the regeneration of bone tissue, following eradication of the infection source and able to fill bone cavities through injection [2]. We have therefore focused our attention on the development of a calcium phosphate cement (CPC) able to release the antibiotic Gentamicin sulfate (GS) with a double tunable rate. In order to obtain a dual release, the antibiotic was loaded both in powder form in the cement paste and into the solid/lipid microparticles (MPsGS) of Cutina HR, produced by means of spray congealing technique. The cements were also radiopaque thanks to the addition of barium sulphate. The cements were produced by mixing a phase-powder, consisting of DCPD, α-TCP and gelatin with a proper amount of water, thus obtaining moldable pastes. Different amounts of GS were added to the cement composition in order to choose the best one: the characterizations performed on the cements have shown that the properties of the material worsened as the amount of GS increased. In contrast, the addition of $BaSO_4$ strengthened the material, leading only to a negligible delay in the conversion reaction. The MPs were added to the powder phase of the cements without interfering with their mechanical properties neither with the phase conversion kinetics. The simultaneous addition of MPsGS and GS in powder has allowed to obtain a material showing a double and tunable kinetic release of the same antibiotics: this system represents the formulation of interest of this work. The injectability of our cements has been successfully achieved (Fig. 1) evaluating the proper liquid/powder ratio for each composition. Morphological analysis by SEM allowed to confirm the absence of phase separation, as well as the good distribution of the MPs along all over the sample. The excellent cohesion of the obtained materials was also demonstrated. Cytotoxicity and bacterial tests revealed that the obtained cements are able to promote cell viability and to express a great inhibitory activity against all the bacterial strains tested.

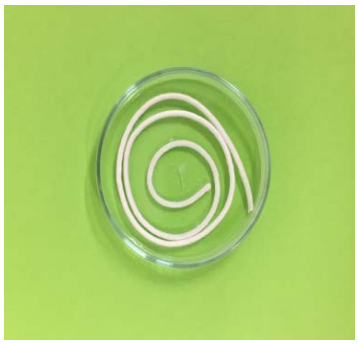

Figure 1. Injected CPC

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SYNTHESIS OF NEW TRYPTAMINE DERIVATIVES FOR BIOLOGICAL INVESTIGATION AS ANTITUMOR AGENTS

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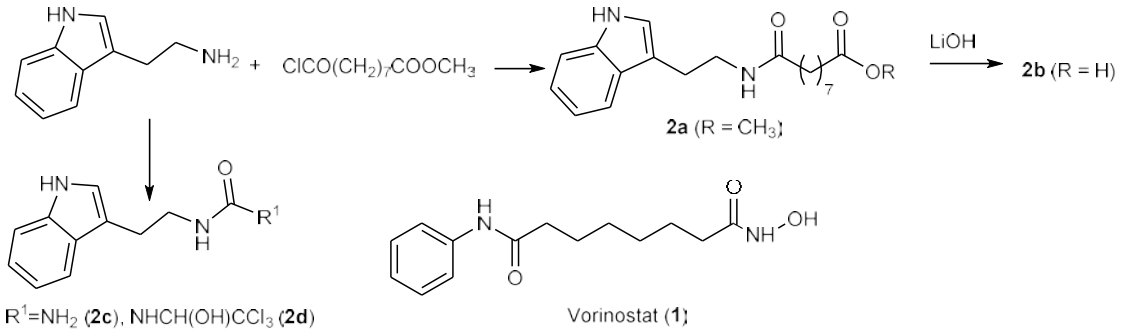
Tryptamine and its derivatives are heterocycles present in many natural compounds.[1,2] For example, endogenous molecules as serotonin and melatonin are simple tryptamine derivatives with a well-known biological role. Thus, compounds bearing tryptamine scaffold are object of growing interest from both synthetic chemists and biologists due to their potential for therapeutic purposes. In continuation of our research aimed to the synthesis of new compounds bearing structure similar to Vorinostat (1), a FDA approved drug for the therapy against cancer, we recently designed and synthesized new compounds bearing benzothiazole moiety instead of the phenyl moiety in Vorinostat and with little modifications in aliphatic carbon chain. The compounds showed good antiproliferative activity in HT29 human cancer cell line and act as histone deacetylase inhibitors (HDACi).[3]

Now we report the synthesis of two tryptamine derivatives **2a** and **2b** which, based on molecular docking predictions, might be active as HDACi. Compound **2a** was obtained through Schotten-Baumann-type reaction from tryptamine and methyl 9-chloro-9-oxononanoate; selective hydrolysis of the ester group gave **2b** (Scheme 1). Moreover, by reacting tryptamine with potassium cyanate we obtained almost quantitatively **2c**. In turn, **2c** was treated with chloral hydrate under MW irradiation giving **2d.** These latter constitute useful intermediates for further functionalization to obtain new compounds to be tested as antiproliferative in the fight against cancer.



Scheme 1. Synthesis of tryptamine derivatives **2a-d** and structure of Vorinostat.

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THE ROLE OF VEHICLE METAMORPHOSIS ON DRUG DELIVERY TO THE SKIN FROM MICROEMULSIONS

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ABSTRACT
It is well known that the vehicle used in topical formulations is probably more important than any other kind of formulation, since the excipients present in a topical vehicle can affect all the phases of drug release and absorption [1].
When a topical formulation is applied to the skin surface, it is submitted to the so called "vehicle metamorphosis" [2], i.e. changes in composition produced by evaporation of volatile components (e.g. water), penetration of components into the skin (e.g. propylene glycol) and extraction of skin components (e.g. skin lipids). These changes may have a deep impact on formulation characteristics and drug absorption by the tissues. In this regard, triamcinolone acetonide (TA) has been chosen as a model drug. TA is a long acting corticosteroid used systemically and topically, alone or in combination. Commercial formulations for topical use include ointments and creams.
Microemulsions (MEs) are microscopic emulsion-like structures composed of water, oil and surfactants/co-surfactants, visually transparent, single optically isotropic and thermodynamic stable liquid solutions [3]. These systems are easy to prepare and characterized by high thermodynamic stability; they can solubilize both hydrophilic and lipophilic drugs and it has been demonstrated their capability of enhancing tissue absorption.
The aim of this work was to study microemulsions metamorphosis and its influence on skin delivery. For comparison purposes, a commercial o/w cream and an o/w galenical cream were tested. The formulations were characterized for water evaporation kinetics, in order to simulate what happens when the formulation is applied on the skin in real use conditions: the results obtained show that all formulations reached within approx. 1 h the theoretical weight values, apart from the W/O formulation. Probably Transcutol (the other volatile component), available in the external phase of microemulsion, can evaporate, while when water is the external phase (O/W formulations) Transcutol is somewhat "segregated" in the inner phase.
TA permeation across pig isolated epidermis, in infinite dose condition, was very low and the concentrations recovered in the receptor compartment were below the limit of quantification of the analytical method. This result suggests that topical application of TA is at low toxicological risk.
Regarding skin retention experiments, TA accumulates preferentially in the epidermis, reaching local concentrations comparable to the values values reported by Schaefer at al. [4] as effective in psoriatic patients (2 to 13 µg/g of epidermis). ME containing oleic acid in combination with TPGS or Tween showed better performances; in particular, epidermis concentration obtained with ME-TPGS and ME-Tween were twice the value of commercial cream, suggesting that the concentration could be reduced, thus reducing possible side effects. Lastly TA recovered from experiments in finite and infinite dose conditions showed no important differences.
In conclusion, vehicle metamorphosis does not seem to modify skin retention, probably for the lipophilic nature of TA, which remains associated with the lipophilic components.

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TOWARDS REVERSIBLE ENERGY TRANSFER TO LANTHANOID IONS MEDIATED BY CALIXARENES

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The near infrared emission of lanthanoid ions is highly sought after for a number of applications including biological imaging and sensing, night vision displays as well as telecommunication signalling [1]. Previous work in this area investigated the binding and sensitisation of visible emitters such as trivalent Eu, Tb, and Sm to calix[4]arene scaffolds functionalised on the lower rim by three amide groups [2]. The sensitisation originated from electronic transitions occurring on the aromatic rings of the calix[4]arene structure. However, the process was found to be inefficient due to an energy mismatch between the triplet excited state of the ligand and the 4f* accepting state of the lanthanoid ions [3]. Furthermore, very limited energy transfer was observed for complexes formed with near-infrared emitting lanthanoid ions, such as Er, Nd, and Yb.
We report here our work towards improving the near infrared emission of calix[4]arene/lanthanoid ion complexes by covalently grafting a suitable antenna to the lower or upper rim of the calix[4]arene systems (**Figure 1**). Possible antennae include naphthalimide and flavin-based components.

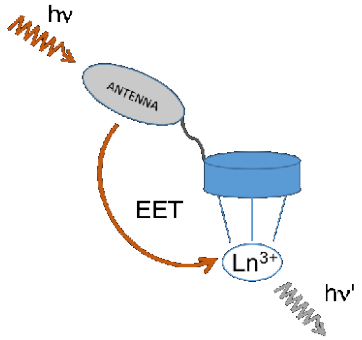

Figure 1. Schematic representation of a generic calix[4]arene/antenna system for the sensitization of lanthanoid ions.

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CAVITANDS RECOGNITION IN WATER: A NEW FRONTIER FOR AMINO ACIDS SENSING

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ABSTRACT

Amino acids (AA) represent an ideal playground for testing complexation ability and selectivity of synthetic receptors, due to their biological relevance and chemical diversity.[1] Synthetic receptors are highly studied in the biological sensing field.[2] In particular, tetraphosphonate cavitands, calixarenes, cyclodestrins and cucurbiturils have been already employed in biochemical sensor devices for amino acids, proteins and in analytical separation.[3] Sensors for aromatic and essential AA such as phenylalanine and tryptophan are very little investigated even if an overabundance of these can cause Phenylketonuria or Hartnup disease. For this reasons, quinoxaline cavitands (QxCav) can be used as sensors because of their remarkable molecular recognition properties already proven towards aromatic hydrocarbons both at the solid/air [4] and solid/liquid [5] interfaces. The origin of QxCav selectivity towards these species can be attributed to the presence of three different, well-separated rims of electron-rich surfaces, preorganized for weak intermolecular attractive interactions with the aromatic guests: (i) at the lower rim, the four aromatic surfaces of the resorcinarene skeleton can interact with two "bottom" C−H groups of aromatic guests via C−H···π interactions; (ii) at the medium rim, the nitrogen atoms of the quinoxaline rings can act as hydrogen bond acceptors toward the two "equatorial" C−H groups of the guests; (iii) the aromatic surfaces at the upper rim become available for attractive intermolecular C−H···π interactions with one or two methyl groups in the case of toluene and xylenes, respectively. Along this line, we synthetized new water soluble quinoxaline based cavitands in order to verify their ability in complexing aromatic guests also in biological medium.

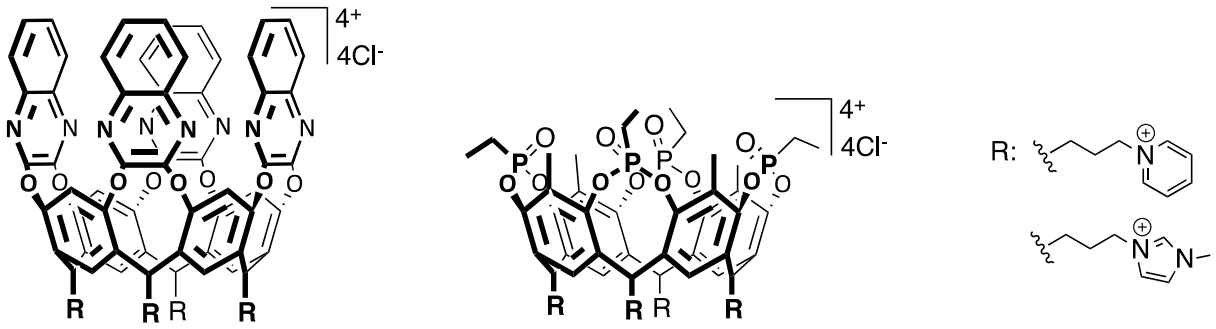

Figure 1. Water soluble supramolecular receptors.

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THERMODYNAMIC ASPECTS AND COMPARISON OF TWO TEICOPLANIN-BASED CHIRAL STATIONARY PHASES FOR ULTRAFAST LIQUID CHROMATOGRAPHY

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ABSTRACT

Nowadays, more than 50% of drugs and molecules of pharmaceutical interest present in the market are chiral. Among those, roughly 90% are racemates, i.e. a mixture of the two enantiomers [1]. Since biological interactions are strictly stereospecific and stereoselective, drug enantiomers, despite having the same chemical structure, may differ in their biological activity (pharmacokinetics, pharmacodynamics, toxicology, metabolism, etc.), resulting inactive or even toxic to the organism or the environment. For this reason, for the production of pharmaceuticals or biomedical products, it is of fundamental importance to develop high performance analytical methodologies able to perform chiral separations and analysis of racemates in order to detect, identify and remove possible impurities or the unwanted isomer from the preparation. To this end, the study and understanding of adsorption and enantiorecognition mechanisms between chiral analytes and stationary phases is essential [2].
In this work, thermodynamic performances of two zwitterionic teicoplanin-based chiral stationary phases (CSPs) prepared respectively on 2.0 μm superficially porous particles (SPPs) and on 1.9 μm fully porous particles (FPPs) of narrow particle size distribution (nPSD) have been analysed and compared [3]. More in details, the adsorption isotherms of Z-D,L-Methionine enantiomers have been studied under Hydrophilic Interaction Liquid Chromatography (HILIC) mode by using the so-called Equilibrium Dispersive (ED) model [4]. The Inverse Method (IM) has been used for isotherm determination.
Results have shown the competitive Bi-lanmguir isotherm model to be suitable for the description of the separation of Z-D,L-Methionine enantiomers on the two columns, indicating the presence of two different types of adsorption sites: one selective, responsible for the chiral recognition mechanism, and one nonselective, in which the two enantiomers behave the same. On the one hand, FPPs show higher selectivity values in comparison to SPPs, highlighting the greater enantioselective potential of these particles. On the other hand, SPPs are characterized by slightly larger selective and nonselective binding than FPPs. These data correlate with the specific loading of chiral selector, which was found to be larger on SPPs than on FPPs. This could negatively impact when moving to ultrafast separations.

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COMPOSITES OF MECHANOCHROMIC ELECTROSPUN NANOFIBERS FOR DIRECTIONAL STRESS-SENSING APPLICATION

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ABSTRACT

Mechanochromic polymers are stimuli-responsive materials capable of changing their optical properties when subjected to a mechanical force. Mechanochromism is conferred by the presence of mechano-active species in the macromolecular chain called *mechanophores*. If the polymer-mechanophore system is properly designed, it is possible to induce an evident color change in the material under mechanical loading. Providing this feature is a clever way to obtain stress-sensing materials with the autonomous function to self-report eventual damages that occur during their life cycle. These materials are of great interest for those advanced applications in which it may be difficult to locate damages, as for example aerospace application or medical implants. An effective stress-sensor should be very sensitive to small deformations (possibly far from its failure) with the appearance of a clear, immediately appreciable color, it should also display quick discoloration upon force unloading and it must be ensured that no other stimuli will compete on the mechanophore activation except for mechanical loading.
The aim of this work is to design new mechanochromic composites consisting of an elastomeric polydimethylsiloxane matrix reinforced with nanofibers of a mechanochromic polymer produced by electrospinning [1]. The chosen mechanochromic polymer is functionalized with a large number of Spiropyran (SP) [2] units which can undergo a ring-opening isomerization to a colored form, known as Merocyanine (MC) [3], under the application of a mechanical load. The composites are subjected to different mechanical tests and the change of color is measured in real-time. It isdemonstrated that in these composites the mechanochromism threshold activation is very low thanks to the high degree of molecular orientation alongside the nanofiber axis provided by electrospinning process. Furthermore, it is demonstrated that it is possible to control the mechanochromism directionality by controlling the spatial arrangement of the nanofibers in the elastomeric matrix. Finally, via cyclic stress-strain measurements it is highlighted that the mechanochromic response is quickly reversible upon force unloading thanks to the particular substitution pattern of the chosen spiropyran in the polymer.
In conclusions, these results demonstrate the high potential of using mechanochromic nanofibers as fillers in composite materials for the development of smart, stimuli responsive materials for real-time stress-sensing application.

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DYNAMICAL PROCESSES IN CRYSTALLINE SOLID SOLUTIONS OF IONIC SUPRAMOLECULAR COMPLEXES

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ABSTRACT

Dynamic processes like rotation and libration of molecules within crystals have long attracted the attention of researchers. Partly because this phenomenon undermines what the crystal is considered to be, that is a static entity, in part because the understanding, control, and exploitation of such movements can provide new functional materials. For example, rotation of molecules in crystals has been investigated for applications such as thermal modulation of birefringence, nonlinear optics, switchable ferroelectrics, gas and vapor sensors, and dielectric constant modulation.
Solid solutions can be defined as non-stoichiometric multi-component crystals in which two, or more, components combine homogeneously in a single crystalline phase.[1] To attain the formation of a solid solution, miscibility of the components is a key condition, which in turn depends on the similarity of the components in terms of size and shape.
We are presently studying the reorientational motions in the crystals of supramolecular complexes comprising crown ethers and organic salts, such as the complexes of general formula $[(12\text{-crown-}4)\cdot(DABCOH_2)]X_2$ (where DABCO=1,4-diazabicyclo[2.2.2]octane and X=Cl^- or Br^-). Their key feature is that a temperature-dependent order-disorder phase transition is associated to the onset of a complex precessional motion of the $(DABCOH_2)^{2+}$ unit.[2] The phase transition is fast and completely reversible; it alters the optical properties of the crystal, such as its birefringence, showing promises for the realisation of a stimuli-responsive material. The low- and high-temperature phases were characterised by single-crystal XRD while the dynamical behaviour of the crystals was studied with solid-state NMR techniques and hot-stage polarised-light microscopy.
This work focuses on the realisation of binary solid solutions of the above-mentioned ionic complexes. Solid solutions over the entire compositional range were prepared by means of mechanochemical methods. Powder XRD analyses and Pawley refinement were employed to probe the accordance of the so obtained solid solutions with Vegard's law,[3] while thermal analysis was used to characterise the order-disorder transition. Finally, it was observed that the solid solution approach has a profound influence on the temperature at which the phase transition occurs.

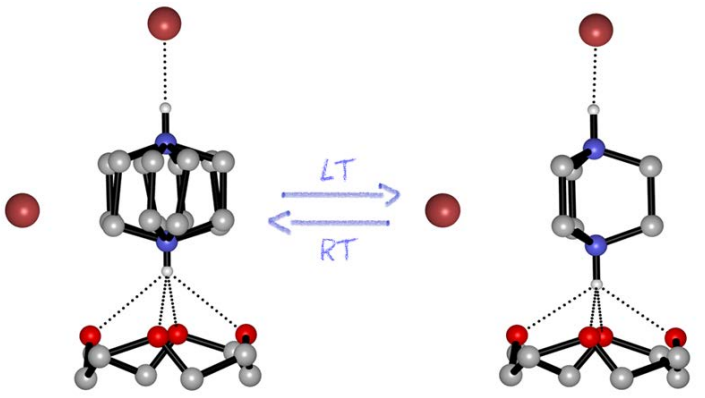

Figure 1. Schematic representation of the structural features at different temperatures of the complexes of general formula $[(12\text{-crown-}4)\cdot(DABCOH_2)]X_2$

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OSTEOINDUCTIVE MULTISCALE COMPOSITE BIOMATERIALS FOR ORTHOPEDIC APPLICATIONS

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ABSTRACT

Polymeric scaffolds provide a temporary matrix into which cells can migrate, proliferate and differentiate to regenerate functional tissues. Consequently, scaffolds have excellent potential in a number of tissue engineering applications, including bone regeneration. Scaffolds should be biomimetic of the tissue to be regenerated, which means that they should mimic as much as possible the extracellular matrix (ECM) of the native tissue in terms of physico-chemical, mechanical and biological properties. The aim of this work was to produce and characterize a biocompatible and biomimetic composite scaffold to be used for the regeneration of bone tissue in case of an arthrodesis surgery. The developed scaffold consisted of a fibrous polymer matrix produced by the electrospinning technology, closely mimicking the fibrous component of the ECM, inserted between two layers of gelatin, crosslinked with genipin, and loaded with osteoconductive and inductive molecules (i.e. hydroxyapatite and tantalum nanoparticles), to achieve a sandwich structure. Blends of poly(lactide-co-glycolide) copolymer (PLGA, with 75 mol% of lactide units and 25 mol% of glycolide units) and polyethylenglycole (PEG) were investigated to obtain a polymeric fibrous mat through electrospinning. Different electrospun mats were prepared by varying the composition of the fibers, and they have been characterized by differential scanning calorimetry, thermogravimetry, water contact angle measurements, and morphological analysis. It has been verified that the presence of PEG blended with PLGA in the electrospun fibers was crucial to produce composites with good dimensional stability and appropriate mechanical properties. Moreover, the presence of PEG increased fiber hydrophilicity, allowing the fibers to be properly wetted by the gelatin solution in the subsequent step of composite production, thus improving the adhesion between the fibers and the gelatin layers. Gelatin layer thickness and degree of crosslinking were optimized in order to achieve the desired swelling degree and gelatin release kinetics. The composites were also functionalized by adding osteoconductive hydroxyapatite and osteoinductive tantalum nanoparticles to the gelatin layers. The final composite systems have been characterized by means of atomic force microscopy, electron transmission microscopy, and X-ray diffraction. Since cell viability and the release of the lactic dehydrogenase enzyme are key parameters widely used as predictors of potential toxic effects of biomaterials, the biological response of the composite was finally evaluated through cytotoxicity tests performed by direct contact of the materials with osteoblasts. The obtained results demonstrated that the composite system is biocompatible. The overall characteristics of the scaffold developed in the present work make it an excellent candidate for biomedical applications. In particular, given its 3D structure and its functionalization, it can provide a useful support for the regeneration of the bone tissue. The presence of multiscale elements (nanoparticles, sub-micrometric fibers, macroscopic scaffold) makes the developed scaffold suitable to mimic the ECM of the native tissue, which results in improved cell adhesion and growth. Moreover, the presence of osteoconductive and inductive components is expected to stimulate tissue healing and regeneration.

ULTRASENSITIVE NON-ELECTROCHEMICAL SENSOR FOR DOPAMINE

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ABSTRACT

We demonstrate an ultra-sensitive and selective sensor for dopamine (DA) by means of a neuro-inspired device platform without the need of a specific recognition moiety. DA is a neurotransmitter of catecholamines family that controls functions of cardiovascular, renal, hormonal and central nervous systems. DA deficit is a hallmark of Parkinson's disease (PD), due to the degeneration of dopaminergic neurons in *substantia nigra pars compacta.* The sensor is a whole organic device featuring two electrodes made of poly(3,4-ethylenedioxythiophene):polystyrene sulfonate – PEDOT:PSS – directly patterned through laser ablation on a polydymethylsiloxane – PDMS – flexible substrate. One electrode is pulsed with a train of voltage square waves, to mimic the pre-synaptic neuron behavior, while the other is used to record the displacement current, mimicking the post-synaptic neuron. The current response exhibits the features of synaptic Short-Term Plasticity (STP) with facilitating or depressing response according to the stimulus frequency. We found that the resulting current decreases with a characteristic time, υ_{STP} , depending on DA concentration in solution. The sensor detects [DA] down to 1 pM range. We assess the sensor also in the presence of ascorbic acid, uric acid, homovanillic acid and 3-methoxytyramine, which are all physiologically present in cerebrospinal fluid. Our detection strategy successfully discriminates DA from the other analytes in model solutions (i.e. Phosphate Saline Buffer). The selectivity of the sensor was also teste d in operational conditions nearer to the *in vivo* ones creating mixed solutions with the physiological concentration of one of the four analytes and increasing concentration of DA. The sensor appears still more sensitive to DA than to the others, even in presence of moieties with similar chemical structures. The synapse appears ultrasensitive to DA (from physiological to pathological concentrations) and selective thanks to the interaction mechanism with PEDOT:PSS. The whole organic synapse, being biocompatible, soft and flexible, is attractive for implantable devices aimed to real-time monitoring of DA concentration in bodily fluids, to be used as a diagnostic tool, for instance, in chronic neurodegenerative diseases such as Parkinson's disease. [1]

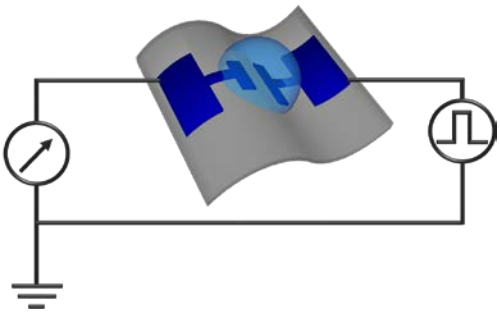

Figure 1. Schematic layout of the sensor

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SUPRAMOLECULAR HYDROGELS CONTAINING TiO_2 NANOPARTICLES FOR WATER DECONTAMINATION

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Low-molecular-weight gelators (LMWGs) are receiving great interest because of their capability to form functional gels in a very simple and sustainable way.
These are molecules with a molecular weight lower than 1000 Da, with a specific stereochemistry and able to form weak interactions such as hydrogen bonds and π-π stacking.
The formation of a gel requires a partial dissolution of the selected LMWG into a chosen solvent: by means of a trigger (such as temperature variation, ultrasound sonication, salts addition, pH change) gelator molecules start assembling in long structures, most commonly fibers, which entangle leading to the formation of networks able to immobilize the solvent.
This kind of gels differ from permanently covalently cross-linked polymers gels because the cross-linking can be reversed by an energy input, for example by heating [1].
LMWGs, despite their small size, closely mimic biomacromolecules and are often biocompatible. Moreover, it is possible to tailor these molecules to obtain different materials, suitable for several applications, from regenerative medicine (3D cells culture or drug delivery), to biomineralization (influence on crystal nucleation and growth), to environmental remediation. About last application, a composite scaffold containing a tyrosine-oxazolidinone LMWG [2] and TiO_2 nanoparticles (NPs) was prepared to studying the photodegradation of a model pollutant compound (Rhodamine B) upon UV irradiation [3].
Hydrogels mechanical properties were investigated by means of rheological tests, while information about morphological structures was obtained by SEM analysis of aerogels, prepared by freeze-drying the samples. These characterizations showed that incorporation of TiO_2-NPs does not alter the mechanical and morphological properties of the hydrogel. In addition, TiO_2-NPs photoactivity is not affected by the incorporation inside the gel network, this resulting in a promising tool for pollutant degradation.

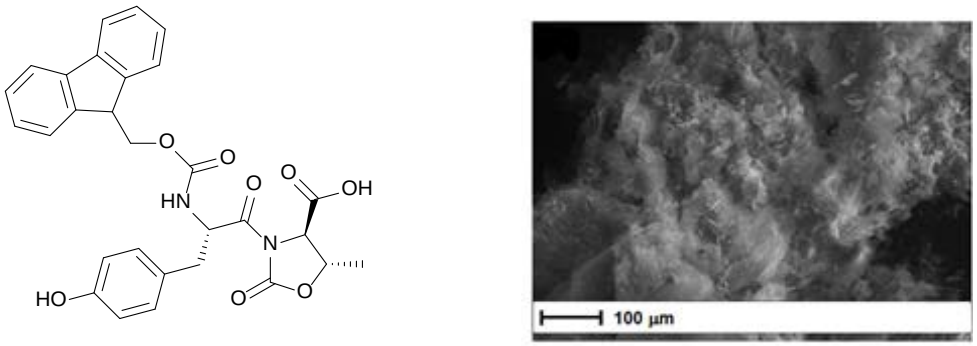

Figure 1. Chemical structure of the selected LMWG (on the left); SEM image of the control freeze-dryed sample (on the right).

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BIOLOGICAL EVALUATION OF A LIBRARY OF BIVALENT DERIVATIVES AS POTENTIAL THERANOSTIC TOOLS FOR ALZHEIMER'S DISEASE

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ABSTRACT

The Alzheimer's disease (AD) begins years earlier of cognitive symptoms appear, with aggregates of misfolding proteins, like β-amyloid and tau. The only way to have a definitive diagnosis is identifying these pathological hallmarks post mortem by autopsy. The lack of an early diagnosis leads to a failure on treatment, as the currently drugs are not effective in slowing or stop its progression. Thus, it is of great interest searching for theranostic small molecules, which integrate therapeutic and imaging functionalities, with great potential to simultaneously diagnose and effectively treat AD [1]. In light of this, we previously synthesized a small library of 24 bivalent 2,4-thiazolidinedione (TZD) derivatives (Fig.1), rationally designed with the aim to develop anti-aggregating compounds, able to fluorescently label misfolding proteins. Thus, the aim of the present study was to verify their fluorescence properties, their ability to inhibit the Aβ42 aggregation process in the *Escherichia coli* AD model, and to evaluate their neurotoxicity on primary cultures of cerebellar granule neurons (CGNs). To study the native fluorescence, the compounds were dissolved in ethanol to mimic the polarity of protein environment, and the spectra were recorded using spectrophotometer and spectrofluorometer. The method used to track Aβ aggregation using *E. coli* as in vivo amyloid reservoir is a simple and powerful method that permits screening anti-amyloid drugs. *E. coli* cells BL21 (DE3) carrying the DNA sequence of Aβ42 were treated with compounds and Thioflavin-S (Th-S), staining of amyloid-like structures that allowed the quantification of aggregation by fluorescence, as previous described [2]. Then, to assess neurotoxicity, the primary cultures of CGNs were treated with the compounds, and after 24 h the Hoechst 33342 staining was used to quantify apoptotic nuclei of cells [3]. Among the 24 synthesized compounds, fifteen were able to emit fluorescence, and 7 of them showed an emission wavelength higher than 500 nm. Moreover, the preliminary biological tests showed that 6 compounds were effective in inhibiting the Aβ42 aggregation process of more than 40% in the *E. coli* model, at 10 µM concentration. Finally, 22 compounds showed not to be toxic to primary neurons at the same concentration. Thus, these promising results will allow us to select the best performing compounds to be progressed for further studies. We will assess the neuroprotective effect of the selected compounds on Aβ42 toxicity in CGNs, verify their fluorescence properties when interacting with Aβ aggregates, and evaluate their theranostic profile in in vivo *Drosophila melanogaster* AD model.

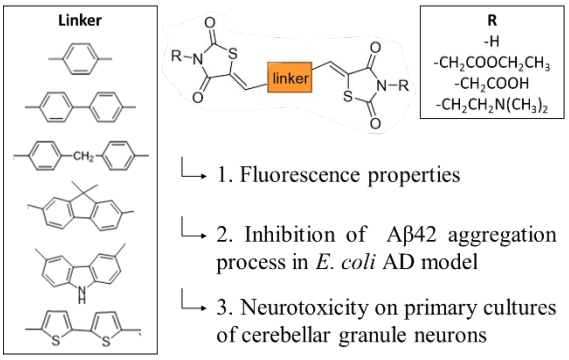

Figure 1. Library of 2,4-thiazolidinedione (TZD) derivatives and biological activities studied

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NANOCOMPOSITES BASED ON TITANIUM DIOXIDE AND GRMS FOR PHOTOCATALYTIC WATER DECONTAMINATION

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ABSTRACT

Air and water pollution is one of the most alarming problems of our generation. For this reason a large set of materials have been studied and developed in order to degrade organic and inorganic pollutants through sunlight-driven photocatalysed reactions. TiO_2 is one of the most promising materials because it's cheap, photostable and very photoreactive [1]. In contrast it has some drawbacks: i) low photocatalytic quantum efficiency, ii) high recombination rate of the photogenerated electron-hole pair and iii) his low absorption in visible light (most of sunlight wavelengths range)[1,3]. In order to solve the difficulties connected to these drawbacks, we modified different surfactant-assisted colloidal TiO_2 nanosystems with Graphene Related Materials (GRMs). The colloidal dispersions allow us to obtain TiO_2 nanoparticles of 5-6 nm with increasing surface area, and GRM modification inhibits the electron-hole recombination and also reduces the bandgap. These aspects enhance photocatalytic activity with respect to commercial TiO_2 [1]. Successively we tested the different colloidal nanosystems photocatalytic properties studying the Rhodamine B (RhB) kinetic of phodegradation. The kinetic study was carried out with a real time monitoring of RhB fluorescence via emission spectroscopy. The sample (a water solution containing the catalyst and dye), was irradiated with UV (λ_{exc} =340nm) light. We chose this method because it's automated, and because a good time resolved photodegradation trend can be obtained. Finally we focused our attention on photocatalytic dependency on excitation light intensity and wavelength.

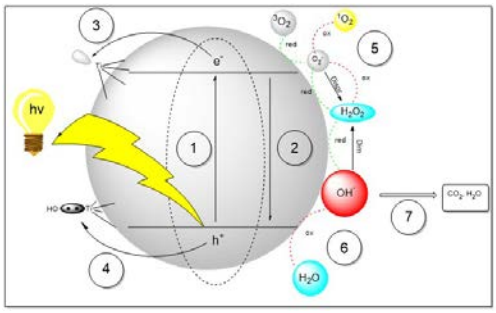

Figure 1. Photochemical reaction in TiO2 nanoparticles surface.

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PYRIDINE-2,6-BIS(1H-1,2,3-TRIAZOL-4-YL): A SELECTIVE CHELATING UNIT FOR MINOR ACTINIDE EXTRACTION FROM RADIOACTIVE WASTES

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ABSTRACT

One of the most important scientific, technological, and social challenges that humanity faces today is to manage the huge amounts of nuclear wastes accumulated in the last 70 year and, possibly, to make exploitation of nuclear energy as sustainable as possible.[1] Currently, the PUREX (Plutonium and URanium EXtraction) process is used worldwide to recover Pu and U from the spent fuel while the remainder of the waste contains the minor actinides (MAs) that account for most of the long-term radiotoxicity of radioactive wastes.[2] Interestingly the recovery of these MAs and their separation from Lanthanides would allow to re-use them in novel nuclear fuels thus closing the Nuclear Fuel Cycle. Soft-donor ligands are known to interact more strongly with trivalent actinide ions, An (III), rather than with trivalent lanthanide ions, Ln (III). Recently different heteroaromatic nitrogen donor ligands such as pyridine-bis-triazine (BTP, BTBP and BTPhen) ligands were developed showing a remarkable An/Ln selectivity, but most of them suffer of kinetic or stability problems in the harsh extraction condition.[3] In the last few years we have been exploring different chelating units based on heteroaromatic nitrogen ligands and found that the “clicked” pyridine-bis-triazole unit is rather effective and selective in An/Ln extraction from simulated nuclear wastes. We herein report the synthesis of both hydrophilic and lipophilic ligands based on pyridine-bis-triazole unit (Fig. 1), showing their ability to effectively and selectively separate An from Ln even at very high nitric acid concentration and in the presence of other fission products. We will focus on the synthesis of these ligands, the study of their complexation and extracting properties, and their resistance to the strong conditions imposed by the industrial processes.

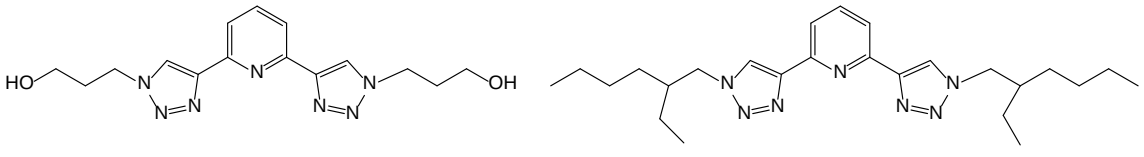

Figure 1. The hydrophilic (left) and lipophilic (right) versions of the pyridine-bis-triazole ligands studied.

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IRON OXIDE AND CURCUMIN LOADED SOLID LIPID NANOPARTICLES

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ABSTRACT

The site specific transfer of magnetic nanoparticles (MNP) under the influence of external stimuli has become a very useful diagnostic tool. However, naked MNP generally have some obstacles such as shorten time of circulation due to rapid clearance by mononuclear phagocyte system (MPS), unwanted interactions with plasma proteins, hepatic and renal toxicity [1].Therefore, surface modification of MNP is required to make them more biocompatible by minimizing the toxicity associated with them. The incorporation of MNP into lipid shell could be auspicious approach for theranostic applications.
The aim of this study was to develop maghemite MNP followed by their further incorporation into solid lipid nanoparticles (M-SLN) as a magnetic resonance imaging (MRI) contrast agent and also as good candidate for drug delivery in cancer therapy.
The MNP have been synthesized in aqueous solution by using $FeCl_3$ and $FeCl_2$ with co-precipitation method. The prepared MNP have been lyophilised and further entrapped into lipid matrix by microemulsion dilution technique [2].
Embedding of MNP into SLN was very challenging due to its heavy weight resulted in earlier settlement of MNP. To resolve this issue, three different ratios by weight of lipid to MNP (3:1, 7:1 and 10:1) have been used and characterised to achieve effective loading of MNP into lipid shell. The resulted preparations were stable for 30 days with mean diameter ranging from 650-850 nm, 400-550 nm and 450-650 nm in ratios 3:1 w/w, 7:1 w/w and 10:1 w/w respectively.
The obtained product has been subjected to lyophilization by using a 10% trehalose aqueous solution as a cryoprotectant. Bidistilled water was used as the dispersion medium for resuspension of M-SLN. The reconstitution time has been recorded and formulations were found to be stable for 30 days in terms of dimensions.
Curcumin is derived from curcuma longa, a plant belonging to ginger family and is considered as a safe drug due to its antioxidant, anti-inflammatory, wound healing and anti-bacterial properties. It also has been categorised as anticancer agent due to its ability to modulate the expression of numerous proteins involved in tumor cell proliferation [3].
The curcumin loaded SLN have been developed by the same aforementioned technique. The ratio of curcumin to lipid has been optimised. The formulation was evaluated for its physical stability by means of average particle size and found to be stable for 90 days.

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SYNTHESIS OF P-SUBSTITUTED DIMETHYL TYROSINE DERIVATIVES THROUGH PD CATALYSED C-H ALKYLATION

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ABSTRACT

Tyrosine is a fundamental amino acid usually sited in the N-terminal message domain of opioid peptides, it has been demonstrated to be extremely important for the binding and activation of opioid receptors.

In the way to evaluate new peptides with increased potency and biological activity than natural opioid peptides, it has been investigated a Tyr derivative, the 2',6' dimethyl tyrosine (Dmt) that showed an interesting potential when inserted in the message domain of opioid peptides instead of tyrosine[1]. There are different synthetical strategies to obtain a tyrosine derivative with two methyl functions in symmetrical position of the aromatic ring[2,3], but recently X. Wang et al. reached in good yield Dmt derivative through a new branch of reactions: C-H alkylation catalysed by a transition metal, Pd (II)[4]. The main characteristic aspects of these reaction are the possibility of adding some substituents directly to the aromatic ring, through the cleavage of the C-H bond, and the maintenance of the optical activity of the starting material.

This work was born from the synthetical pathway just described, leading to the synthesis of different Dmt-like aromatic amino acid derivatives, replacing the tyrosine -OH phenol with other functions, to evaluate how the biological activity could be influenced by the presence of different electron withdrawing or donating groups and steric hindrance of the species substituted in position 4'.

In fact, it is possible to synthesize p-halogenated Dmt derivatives starting from the p-nitro-phenylalanine: the nitro group is firstly reduced to an amine function, compatible with the reaction of C-H alkylation, and subsequently it is used to produce an aromatic diazonium salt that is replaced by fluorine through Balz-Schiemann reaction or by other halogens via Sandmeyer reaction, by the way it is possible to insert other different species like methoxy group instead of the tyrosine phenol, or even stopping at the aromatic amine instead of proceeding through the diazonium salt.

Once protected the amino acid amine function with Boc group it is possible to insert these aromatic amino acid derivatives in unnatural peptides through solid phase peptide synthesis (SPPS).

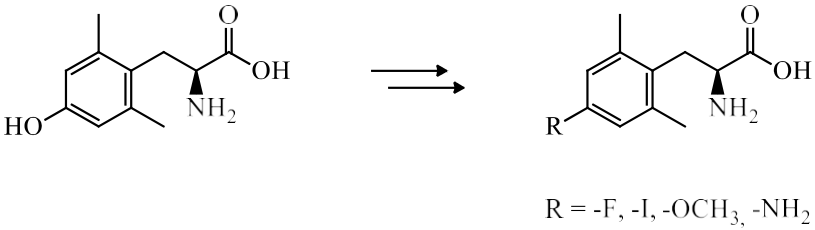

Fig.1 Tyrosine and para-halogenated Dmt-like derivatives

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FACE TO FACE WITH ANTIBIOTIC RESISTANCE: NEW BORONIC ACID TRANSITION STATE INHIBITORS (BATSIs)

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ABSTRACT

The World Health Organization (WHO) has recently identified antimicrobial resistance as one of the three most important problems facing human health. *Acinetobacter baumannii* is a gram-negative bacterium associated with hospital-acquired infections, designated as a "red alert" human pathogen.

Bacterial production of β-lactamase enzymes represents the most clinically concerning mechanism of resistance to β–lactam antibiotics.[1] BATSIs are a new classes of non β–lactam β–lactamase inhibitors, which have recently reached the market. The boronic moiety mimics the highly reactive β-lactam ring of antibiotics and the carbon α to the boron is substituted with different groups able to confer high activity and selectivity towards β–lactamases.[2] In the last 18 years our laboratory has developed several highly potent classes of BATSIs: in particular, α–acylamidoboronic acids (Figure 1, **1**) are characterized by the presence of an amide side chain bearing substituents typical of commercially available β–lactams. The replacement of the amide group with a bioisoster, such as a sulphonamide (**2**) or a triazole (**3**), gave compounds active against ADC-7, a highly resistant β–lactamase in *A. baumannii*.

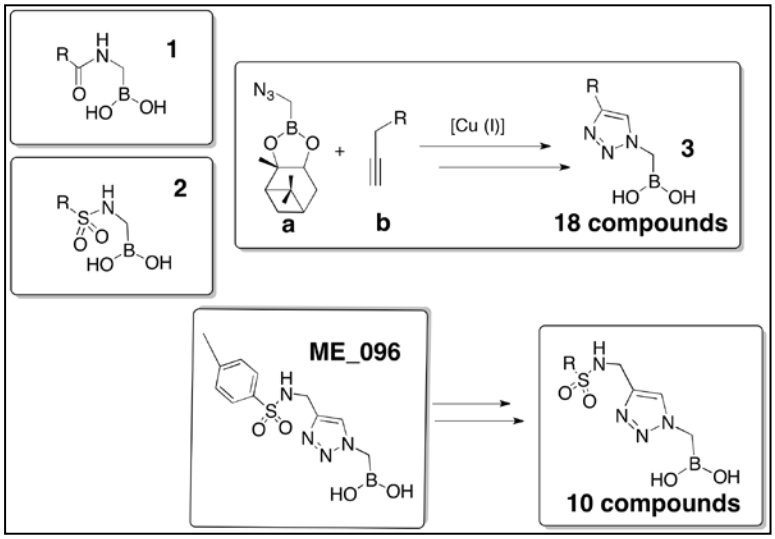

Figure 1. A new class of β-lactamases inhibitors

Here we describe our attempt to improve the α–triazole series in order to identify a lead compound with enhanced pharmacological profile. The 1,4-disubstituted 1,2,3-triazoles are easily accessible through copper-catalyzed azide-alkyne cycloaddition (CuAAC) as the key reaction, starting from the protected azide (**a**) and alkynes (**b**).[2] Initially, 18 compounds were synthesized and tested for Ki determination, Disc Assays (DA) and Minimal Inhibitory Concentration (MIC) evaluation. Compound **ME_096** (Figure 1) resulted to be the most active (Ki= 0,09 μM; MIC= 2 μg/ml) and 10 new molecules were synthesized, based on its structure, but no significant improvement in activity was observed.

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GRAPHENE BASED ELECTROCATALYST FOR OXYGEN REDUCTION REACTION

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ABSTRACT

The Oxygen Reduction Reaction (ORR) is a fundamental process for sustaining life and is an important process utilized in biosensing analysis. Additionally, this process is applicable to artificial energy devices such as fuel cells and metal-air based batteries. The reaction proceeds at a very slow kinetic rate requiring a catalyst to reduce the activation barrier. Platinum is an ideal catalyst but it is neither cheap nor environmentally friendly[1]. The prospect of a cheap and green alternative is intriguing and has yielded considerable research in the past decade. Amongst the most promising materials as catalysts carbon-based systems, such as carbon nanotubes (CNT) and graphene derivatives are particularly intriguing.

New synthetic strategies[2] allow to produce tunable graphene-based materials, starting from graphene oxide (GO). These are based on the reduction of the oxidized groups of GO in the presence of compounds capable of adding functional groups or heteroatoms to the carbon lattice.

We were particularly interested in the material obtained by doping GO with nitrogen and boron through its reduction in presence of idrazine and borazine. Such reduced graphene oxides (rGO) show almost the same electronic properties as graphene, with some X-C (X= N or B) regions within the graphene lattice that have a useful dipole moment which helps the interaction between the oxygen molecule and the catalytic substrate; thus, such sites represent those active for the ORR catalysis.

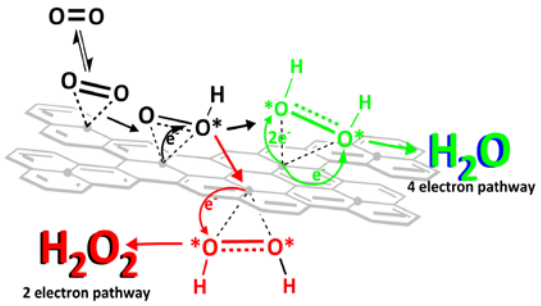

Figure 1. ORR 2 electron and the most efficient 4 electron processes

We have investigated the electrochemical behavior of a selection of such material and their electrocatalytic activity for the ORR.

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Design and synthesis of new polypharmacological compounds with antioxidant properties in Alzheimer's disease.

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ABSTRACT

In a world where life expectancy is increasing, Alzheimer disease (AD) is the main cause of dementia, and touch approximatively 17% of people who are more than 75 years in France. This is a progressive neurodegenerative disorder characterized by memory loss and cognitive decline. Despite the fact that the physiopathology of AD is not entirely known at the time, some molecular causes were found such as the ß-amyloid peptides aggregation, tau-dependent neurofibrillary tangles, as well as oxidative stress and neuroinflammation. Currently, treatments available for patients are mainly Acetylcholine esterase (AChE) inhibitor, which only have symptomatic benefits and do not cure AD. Then there is still a strong medical need in the AD population.

In this context, the concept of Multi-Target Directed Ligands (MTDLs) was applied to design a drug with several therapeutic targets. The MTDL should be able in first hand, to limit the development of ß-amyloid plaques obtained by the aggregation of ß-amyloid peptides (Aß). Our compounds are designed to promote the cleavage of amyloid protein precursor (APP) by α -secretase activation in order to produce a neuroprotective and soluble peptide sAPPα. This is the role of the $5HT_4R$ agonists (blue part – fig 1.) which are already studied in the CERMN in other MTDL projects and led to the discovery of Donecopride[1].

In another hand, it appears that the oxidative stress has a central role in AD[2]. Adding antioxidant moiety such as polyphenol, lipoic and ferulic acid (red part- fig 1.) could trap free radicals or reactive oxygen species (ROS) and also have neuroprotective effect. This aspect has been widely studied in Prof. Maria-Laura Bolognesi's laboratory over the years[3]. To that end, different compounds will be designed and synthetized, with both the expertise of CERMN and Prof Maria-Laura Bolognesi, in order to evaluate their *in vitro/in vivo* properties regarding their agonist activity on 5-HT_4R and antioxidant property. The first promising results of the benzisoxazole's moiety line will be described in this poster.

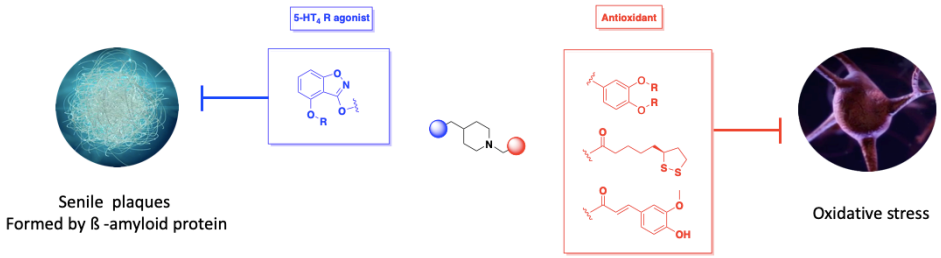

Figure 1. Targeted structure, with 5-HT4 R agonist moieties in blue and antioxidant moieties in red.

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STUDY OF ACCELERATORS AND HARDENERS TO IMPROVE PROPERTIES OF EPOXY-MATRIX COMPOSITES

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Recently the development of composite materials led to the investigation of new ways to optimize and increase productivity of industrial processes. One of the most employed production methods is autoclave curing, since it allows, at the same time, to process products of different dimensions and shapes. However, the autoclave thermal inertia and the lack of flexibility in the production are two of the main problems associated to this technique, leading to a loss of product quality. In order to increase the productivity, one of the possibilities is to reduce the curing time of the process. For this reason, in the last years "fast curing resins" for pre-pregs production have been studied and, as reported in literature, the use of different kinds of accelerators and hardeners, may lead to the reduction of curing time. The epoxy resins may be cured using such curing agents as polyamide, polyamine, urea, phenolic and substituted phenolic curing agents, Lewis acid curing agents and carboxylated curing agents [1]. In order to obtain the desired resin properties, the nature and the structure of the curing agents, which are the active promotors of epoxy precursors cross-linking to generate hard, infusible, thermoset networks, is also highly crucial [2]. The effects of different type and concentration of hardeners or accelerators on the crosslinking reaction of a resin may be studied by differential scanning calorimetry (DSC) in both dynamic and isothermal mode. Hence, the aim of this work is to find a new "fast curing" formulation for epoxy resins with a high glass transition temperature (T_g) using different systems of accelerators and hardeners. Specifically, three different types of formulations (A1, A1U, A2) were prepared and tested trough DSC analysis. The most promising formulations were studied in DSC, simulating an industrial autoclave curing processes at 100 and 130°C. The reaction time and T_g post curing were evaluated and compared with a reference formulation (R) used for pre-pregs production. Only A2 formulations led to an increase of the T_g and a decrease of the reaction time at both 100 and 130°C. The other formulations led to an improvement on the T_g value only at 130°C but, at the same time, a longer reaction time. The encouraging results obtained with A2 formulations both in terms of curing efficacy and glass transition temperature of the epoxy resin pave the way for further investigations.

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RECENT ADVANCES IN THE SYNTHESIS OF p-DODECYLCALIX[n]ARENES

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ABSTRACT

Calixarene macrocycles are known and studied for more than 30 years. Ease of synthesis, isolation and functionalisation provide products of relevant interest for many branches of chemistry. In particular, calixarene derivatives were conceived and realised for applications in sensoristics, hydrometallurgy, innovative materials, medicine and biotechnology.[1,2] They are attractive for fundamental research and for industrial processes as testified by hundreds of patents. Even though calixarenes have exceptional properties, their synthesis has been limited to a few para-alkylphenol precursors (tert-butyl, tert-octyl, benzyl and benzyloxy). Indeed, there is an increasing demand for calixarenes with long branched alkyl groups for special industrial applications. Following this need, we speculated that p-dodecylphenol could be a good candidate for the synthesis of new lipophilic calixarenes, especially with the scope of improving their solubility in apolar solvents. In this work we report the synthesis (see Figure 1) and characterisation of this family of macrocycles based on para-dodecylphenol. Quite interestingly, the APPI-MS studies of the reaction product show the presence of calixarenes with different sizes and prevalence of calix[8], -[6]-, and –[5]arenes plus some linear oligomers. Also due to the large and non-homogeneous alkyl chains present at the upper rim of the macrocycle, the final products are liquid at room temperature and this prevents easy separation of the macrocyclic components from the linear oligomers by simple precipitation. It is possible to achieve the separation of the different macrocycles by flash chromatography. However, the yield of p-dodecylcalixarenes from the rather cheap starting materials, is rather high (> 80%) favoring (and argues for) the use of such macrocycles also for large-scale technological applications.

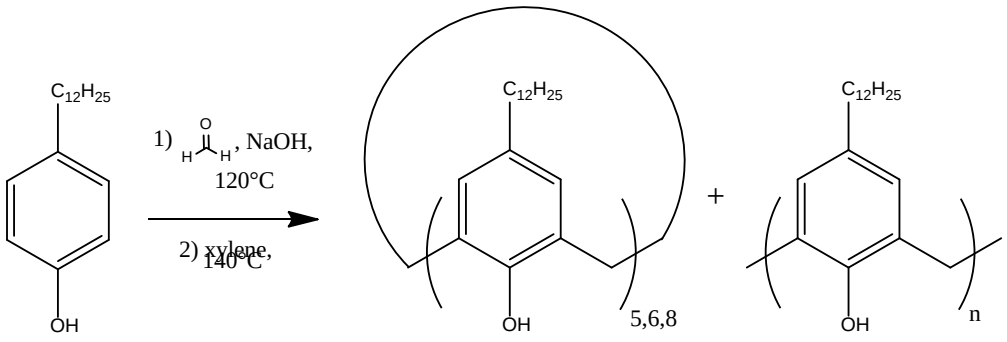

Figure 1. Synthesis of the para-dodecylcalix[n]arenes.

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HIGH CAPACITY SEMI-LIQUID LITHIUM SULFUR CELLS WITH ENHANCED REVERSIBILITY FOR APPLICATION IN NEW-GENERATION ENERGY STORAGE SYSTEMS[1]

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ABSTRACT

Semi-liquid configuration of sulfur cell is proposed as simple strategy to develop high-energy lithium battery. Two solutions of Li_2S_8 in diethylene glycol dimethyl ether (DEGDME), containing either lithium bis(trifluoromethanesulfonyl)imide (LiTFSI) or lithium trifluoromethansulfonate ($LiCF_3SO_3$) and lithium nitrate ($LiNO_3$), are studied as catholytes for Li/S cells exploiting the polysulfides electrochemical reaction at about 2.2 V *vs.* Li^+/Li. X-ray photoelectron spectroscopy (XPS) and thermal analyses, respectively, reveal composition and high-temperature stability of the catholyte solution. *Ad hoc* study conducted by impedance spectroscopy, voltammetry, and galvanostatic techniques suggests well suitable characteristics in terms of Li^+-transport ability, electrochemical stability window, and electrode/electrolyte interphase features. Cells with sulfur loading ranging from about 3 to 6 mg cm^{-2} into the solution are successfully studied with remarkable performances in terms of current rates, efficiency and cycle life. Hence, the lithium cells based on the catholyte deliver maximum capacity of the order of 1100 mAh g_S^{-1} at C/10 rate and stable capacity of about 800 mAh g_S^{-1} at C/3 rate with Coulombic efficiency exceeding 99 %. Therefore, the catholyte solutions studied herein are considered well suitable candidates for high-energy storage in next generation systems, such as the intriguing hybrid and electric vehicles.

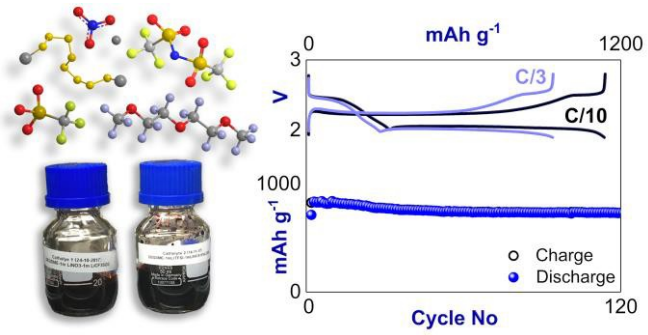

Figure 1. Photographs and composition of catholytes (left) and electrochemical behavior in lithium cell (right)

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AN EFFECTIVE DBS-LC-MS/MS STRATEGY FOR THE MONITORING OF ALCOHOL BIOMARKERS

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ABSTRACT

Workplace monitoring of alcohol consumption habits is highly advisable especially in the healthcare framework, due to the serious consequences alcohol use and abuse could bring. Within this project, two highly selective alcohol consumption biomarkers were selected, namely ethyl glucuronide (EtG) and ethyl sulfate (EtS), to perform a reliable quali-quantitative analysis as a tool to investigate alcohol consumption behaviours. The two analytes, as medium-term biomarkers, are suitable for workplace monitoring. To this aim, a minimally invasive biosampling strategy has been proposed and developed within this research, also allowing simplified sample storage and shipping of numerous samples: a dried blood spots (DBS) microsampling approach. It is based on haematic collection through a finger prick, avoiding an invasive procedure (i.e. phlebotomy). An accurate blood volume (10 µL) was collected from a fingertip and spotted on special cellulose DBS cards; after spot drying, the cards were stored at room temperature without the need for cryopreservation [1]. The use of a miniaturised, dried biological matrix also ensures enhanced EtG and EtS stability in blood, when compared to the same analytes in classic fluid blood samples [2]. On the other hand, the reduced volumes and the low expected analyte levels required the development and validation of a highly sensitive and selective instrumental analytical method: the microsampling approach was coupled to an original LC-MS/MS method. In the first phase of the project, an in-depth optimisation of mass spectrometry parameters was carried out and led to the definition of electrospray ionization (ESI) polarity, acquisition mode, fragmentation parameters, selection of mass ion transitions leading to the highest selectivity and sensitivity. Chromatographic conditions were also optimised for the simultaneous determination of both analytes in a short time (3.5 minutes) and validated according to the main International Guidelines. In the second phase of the research, the developed method was applied to evaluate the analyte levels in DBS from volunteers, after alcohol controlled dosing and aiming at discriminating between abstinence, accidental alcohol intake, acute and chronic consumption. At the same time, an attempt was made to define EtG and EtS baseline levels, as well as effective cut-off reference values. The original high-throughput analytical methodology proposed herein (Fig. 1) combines the advantages of microsampling for sample collection, transportation and storage with the high sensitivity and selectivity of LC-MS/MS. It has granted the successful analysis of samples from healthcare professionals, recruited in the last phase of the study, for the monitoring of workplace alcohol consumption. This study was funded by the Italian Ministry of Health within the Finalized Research Project 2011-2012 (RF-2011-02352096) and performed at the Pharmaco-Toxicological Analysis Laboratory (PTA Lab) of the Department of Pharmacy and Biotechnology (FaBiT), Alma Mater Studiorum - University of Bologna.

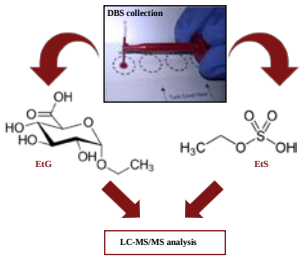

Figure 1. DBS-LC-MS/MS bioanalytical workflow

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LIFE MARKER DETECTION IN PLANETARY EXPLORATION: A NOVEL BIOSENSOR FOR ATP DETECTION BASED ON CHEMILUMINESCENT DNA SWITCH INTEGRATED WITH AMORPHOUS SILICON PHOTODIODES

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ABSTRACT

Several studies reported the presence of organic compounds in extraterrestrial environments in order to identify life markers, i.e., molecules [1]. The continuous evolving development of extremely compact systems relying on microfluidics, commonly known as lab-on-chip devices, has gained much attention thanks to their favorable characteristics in terms of reduced size and weight, very low sample and reagent consumption, and, often, superior achievable performances in terms of limits-of-detection. Herein we report about the design and optimization of new analytical platform for the detection of bio-organic molecules outside of the Earth. We optimized a DNA switch based on chemiluminescent (CL) detection for the identification of the life bio marker Adenosine triphosphate (ATP). Indeed, CL-based detection allows to ensure high analytical performance without external radiation sources and complex optical systems [2]. The DNA switch will be implemented into a portable device which will be composed by a microfluidic network, a set of functionalized detection sites where DNA nanomachine will be carried out and an array of thin-film hydrogenated amorphous silicon (a-Si:H) photosensors for the detection of the analytical CL signal.

Acknowledgements
The project PLEIADES (Planetary Life Explorer with Integrated Analytical Detection and Embedded Sensors) was supported by the Italian Space Agency (ASI) (Accordo n. 2015-037-R.0)

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DETERMINATION OF 1-DEOXYNOJIRIMYCIN (DNJ) IN MULBERRY LEAVES (*MORUS SPP.* L.), SILK WORMS (*BOMBYX MORI* L.) AND SILK BY HPLC-TQ-MS

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ABSTRACT

DNJ is a constituent of mulberry leaves and when consumed as part of the diet it showed beneficial properties on health: suppression of high blood glucose levels, antibacterial and antiviral activities [1]. In this work DNJ content in different matrices was investigated, the importance lies in the potential uses of these products as food and feed, nutraceutical and medical devices [2].
In this work twenty-nine samples of mulberry leaves from an experimental field (CREA-Padova), silk worms larvae and silk cocoons were analyzed by HILIC technique. EtOH:H_2O 50% solution and water 60° were employed for leaves extraction. Grinded cocoons and freeze-dried larvae were extracted with EtOH:H_2O 50% (at 60°C for cocoons). The detection was performed by using ESI in positive ion MRM mode. The optimized mass conditions allowed the identification of three usable transitions (one for the quantification of DNJ 164.1→146.1, others as qualifier ions 164.1→128.1, 164.1→110.1). DNJ was detected in all the considered matrices and determined by using its calibration curve (r^2=0.9865). In the case of leaves, water infusion resulted less efficient with respect to EtOH:H_2O extraction. The mean concentration value in leaves obtained with infusion is 0.073±0.004 mg/g while 2.56±0.3 mg/g for extracts. The mean concentration recovered in larvae is 0.034±0.001 mg/g whereas substantially lower amounts were obtained for silk ($3.12*10^{-5}$ mg/g).
The study showed that *Morus nigra* L. presents the highest content among the tested species and that DNJ is detectable also in larvae and silk. These results could be useful in the further development of herbal supplements and for the potential use of larvae as medicated feed or functional food.

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ANTENNA EFFECT IN THE SENSITIZATION OF SEMICONDUCTORS

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ABSTRACT

This work was aimed to develop a multinuclear system composed of a sensitizer and an antenna[1] unit that can absorb the high energy portion of the solar spectrum and transfer its photonic excitation to the sensitizer component, in order to improve the light harvesting efficiency of Dye Sensitizer Solar Cells.

The role of the sensitizer was covered by Z907, a Ru (II) complex widely known in literature as efficient sensitizer. The role of the antenna system was covered by a new complex synthesized for the first time by our group: $[Ru(TMAM)_2CN_2](TFSI)_4$ (Ru-TMAM) (where TMAM indicates 4,4'-bis(trimethylaminomethyl)-2,2'-bipyridine). The supramolecular self-assembly was obtained via Ag^+ bridges[2].

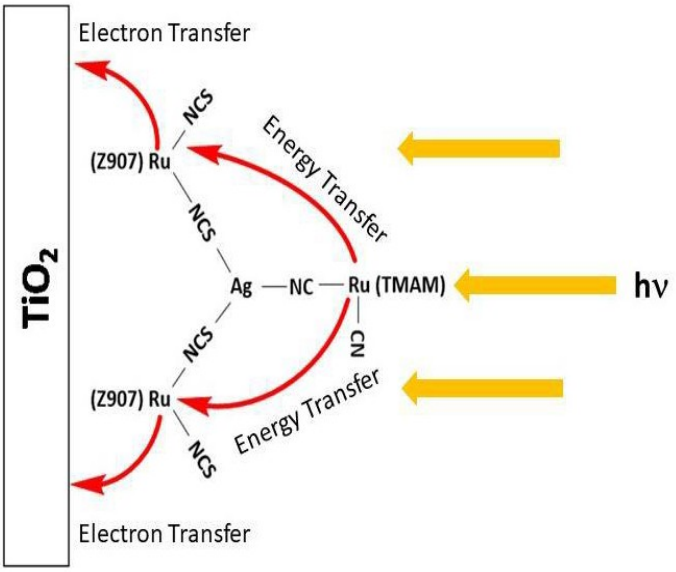

Figure 1. Schematization of the Sensitizer-Antenna assembly

Through the application of different analytical techniques, it was possible to confirm the formation of the multinuclear complex having a stoichiometry 2Z907-Ag^+-(Ru-TMAM). The emission spectra recorded on ZrO_2 showed an efficient energy transfer from Ru-TMAM to the Z907 units. Instrumental response limited (<300 ps) energy transfer was also confirmed by laser spectroscopy and time correlated single photon timing. The sensitized cell performance, recorded with $[Co(bpy)_3]^{3+/2+}$ redox mediator and PEDOT as counter electrode, showed an improvement when passing from Z907 to 2Z907-Ag^+-(Ru-TMAM). Besides energy transfer, the positive charges, localized on Ag^+ and on the quaternary ammonia units of TMAM contribute to electrostatically repel the oxidized form of redox mediator reducing recombination and enhancing thus energy conversion.

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DEVELOPMENT OF MICRO- AND NANO-SIZED SENSORS FOR LIVING CELLS ANALYSIS

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ABSTRACT

Recent advances in cell biology and tissue engineering have greatly boosted the development of new strategies for cell handling. Since the early 1900s, the established approach to study tissues *in vitro* has relied on 2D monolayer tissue cultures, however they have the major disadvantage of not reproducing the communication network that maintains the specificity and homeostasis of tissue in organs. These 2D objects have been unseated in the last years thanks to emerging scaffold free technologies, such as the hanging drop technique. Indeed, today it is possible to create 3D cell cultures that can reliably mimic in vivo tissue dynamics, with enhanced cell–cell and cell-extracellular matrix interactions. Besides cell networks, also single-cell handling is having significant impact in the biomedical arena. Indeed, individual cells can be imaged, isolated and sorted by plenty targeted techniques, thus paving the way to disclose cellular and subcellular organisation and activity. Nonetheless, the design of micro- and nano-sized monitoring platforms able to provide quantitative and physiologically relevant information about such systems is still a challenging task.
In this contribution, the development of two bioelectronic sensors will be discussed based on the Organic Electrochemical Transistor (OECT).
On one hand, an OECT impedance sensor was integrated within a microfluidic chip in order to monitor 3D spheroids' electrical properties, such as TEER (trans-epithelial/endothelial electric resistance) during drug screening. [1] The microfluidic device consists of a single microchannel in which a 'bottleneck' structure is used to trap the spheroid at the desired location (fig. 1). The sensor was used for real-time monitoring of co-cultured spheroids exposed to a porogenic agent. A gradual decrease of the spheroids' resistance, due to disruption of the spheroid cells membrane integrity, was measured.

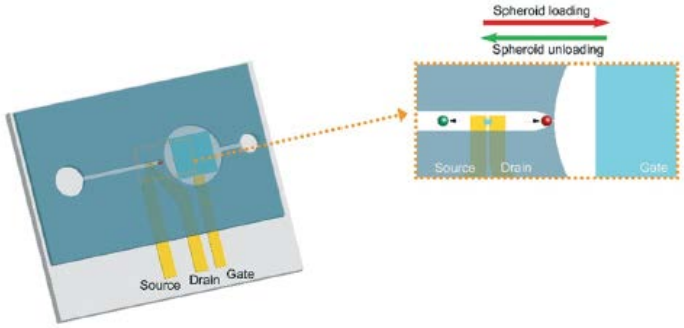

Figure 1. Sketch of the microtrap impedance sensing platform (left) and zoom indicating the loading and unloading flow direction to place the spheroid within the microtrap (right).

Focusing on single-cell analysis, a nanometre-sized OECT sensor was fabricated starting from spearhead Carbon Nano Electrodes [2], aiming at the local detection of metabolites inside or the close proximity of a single cell. The nano tips were functionalised with a semiconducting polymer in order to obtain a transistor-like architecture comprising a gate and a channel. Picomolar concentration of dopamine was revealed in buffer solution, but consistent sensing performance in unbuffered medium has yet to be assessed. Thanks to the sensor size, accurate positioning of the probe in a biological sample could be performed by Scanning Ion-Conductance Microscopy.

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REGIOREGULAR AND REGIORANDOM DOUBLE-CABLE COPOLYMERS FOR ORGANIC SOLAR CELLS

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In recent years, numerous π-conjugated materials (ICPs) containing thiophenic units for application in organic thin film devices have been developed. In particular, polymer solar cells (PSCs) have attracted much attention because of advantageous low cost, easy fabrication, light weight and the opportunity to realize flexible large-area devices.[1]

Oligo and polythiophenes, having excellent properties of charge transport and light absorption characteristics, are favourite candidates for use in organic photovoltaics. However, although high power conversion efficiency can be reached using these semiconductors as electron-donating materials in polymeric solar cells of the Bulk-Heterojunction (BHJ) type, the high energy level of the highest occupied molecular orbital (HOMO) of poly-(3-alkyl)thiophenes and their relatively large band gap, limit the solar spectrum fraction that can be exploited. Moreover, since the main parameters of this type of architecture are determined by the mechanism of carrier generation and transport processes, the synthesis of donor-acceptor double-cable polymers appears particularly intriguing in order to achieve an optimal phase segregation between the electron-donor/acceptor in the blend as well as maintain a continuous path in each phase for the efficient transport of electrons and holes.[2]

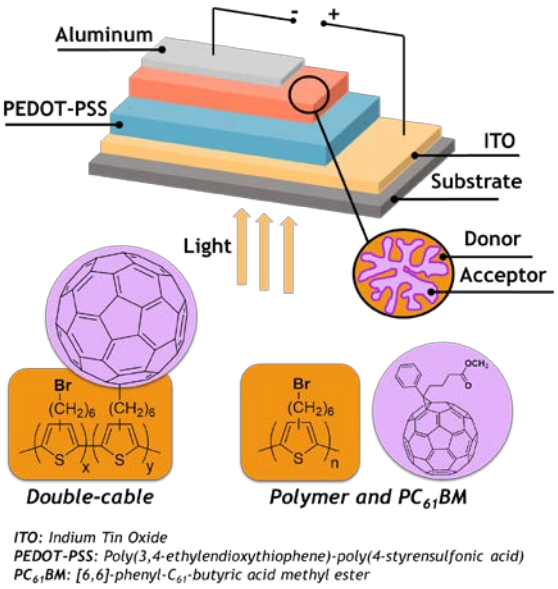

Figure 1 Structure of organic solar cell.

Starting from soluble, regioregular (PT6BrR) and regiorandom (PT6Br) homopolymeric precursors, new alkylthiophenic copolymers bearing the bromine atom and C_{60}-fullerene group at the end of a hexylic side chain at the 3-position of thiophene have been prepared with a simple and straightforward post-polymerization functionalization procedure based on Grignard coupling. The above derivatives were characterized by gel permeation chromatography (GPC), ^{1}H-NMR, thermal analysis (DSC, TGA), UV-Vis and FT-IR spectroscopy. Finally, homo- and copolymers were also tested as photoactive layers in organic solar devices, respectively blended with $PC_{61}BM$ (1:1 w/w) as the acceptor material and as double-cable materials.

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STUDY OF HETEROBIMETALLIC LN^{III}/GA^{III} 12-MC-4 COMPLEXES IN THE SOLID STATE AND IN SOLUTION

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ABSTRACT

The use of coordination complexes of lanthanide ions is of wide interest in areas such as biomedical analysis, catalysis, magnetic resonance imaging, luminescence, and single-molecule magnetism. In the study of these complexes, it is often useful to correlate the structural features of such compound in the solid state (e.g. from crystallographic data) with their properties in solution.[1] One common technique to that purpose is monodimensional ^{1}H NMR. Indeed, the lanthanide unpaired electrons influence the NMR features which are strongly related with the structure of the complex in solution. Although broader than those of diamagnetic species, the peaks in the NMR spectra of Ln^{III} complexes are in general observable. The presence of unpaired electrons produces, in the spectra of Ln-compounds, a paramagnetic shift (δ^{para}) of the protons signals, which contains the information related to the structure in solution. Thus, the analysis of the chemical shifts can confirm or refute if the solid-state structure is retained after dissolution or if a series of molecules made with the same ligand set but different lanthanide ions are isostructural in solution within the series.

Here the ^{1}H NMR behavior of the isostructural series of the Ln^{III} $Na^I(OBz)_4[12\text{-}MC_{GaIII(O)shi}\text{-}4](H_2O)_4\cdot xDMF$ paramagnetic metallacrowns is reported (where Ln represents respectively: the La, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu lanthanide ions and Y is included as diamagnetic reference). The paramagnetic shifts were studied by applying the "*all lanthanide*s" method, reported by L. Di Bari et al.[2]

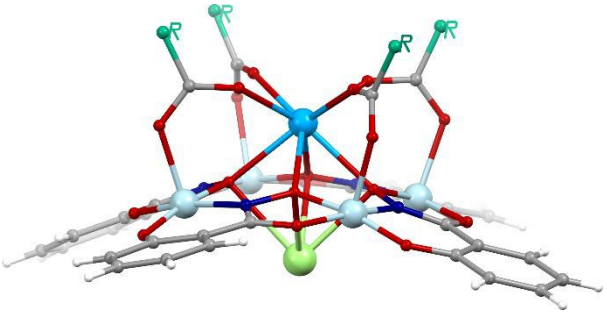

Figure 1. the $Ln^{III}[12\text{-}MC_{M,\,(O)shi}\text{-}4]$ structure, where the Ln^{III} ion encapsulation above the MC-ring is highlighted, thanks to the presence of four R-COO^- carboxylic bridges. Colours code: Ln-cyan, M-light blue, O-red, C-grey, R-emerald.

The investigated complexes, whose general structure is reported in Figure 1, are metallacrowns, that are metallamacrocycles, which result from the self-assembly in solution of metal ions and bischelating ligands. These class of supramolecules are characterized by a central cavity formed by the repetition of the M-N-O structural motif. A wide variety of building blocks (i.e. metals and ligands) may lead to metallacrowns differentiated by structures and features.[3] Within the variety of architectures achievable are the 12-MC-4, whose scaffolds result from the combination of four metal ions and four ligands. The 12-MC-4 complexes are capable to coordinate one additional metal ion within the central cavity. However, when the cation is as large as the lanthanides, it is coordinated above the cavity of the scaffold, thanks to four organic bridges (Figure 1).

Here we present the investigation of the NMR features in solutions of the Ln^{III} $Na^I(OBz)_4[12\text{-}MC_{GaIII(O)shi}\text{-}4]$ spices and the correlation between their properties in solution and those in the solid state. The "*all lanthanide*s" calculations allowed also to unequivocally assign the overall resonances of the ^{1}H NMR spectra, despite the paramagnetic chemical shifts and broadening.

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NEW TRANSPARENT COLLOIDAL TIO_2 NANO-SYSTEMS AS EFFICIENT PHOTOCATALYSTS FOR ENVIRONMENTAL REMEDIATION

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ABSTRACT

During the last years, the study of photocatalytic nano-materials (PNMs) to degrade organic/inorganic pollutants attracted a lot of interest. Powder of anatase TiO_2 is the most common PNM in industry. Nevertheless, the PC performances of commercial powders of TiO_2 are limited because they are made of aggregates of nanoparticles that can be badly dispersed in water with high torbidity and low suspension stability[1]. For these reasons, the production of the photo-generated electron-hole pairs[2] and the light activation of TiO_2 as PC are inhibited. Here, we successfully report the synthesis and characterization of colloidal TiO_2 nanoparticles (NPs) by using common ionic (Sodium Cholate, CTAB) and non-ionic (Triton X-100, Pluronic F-127) surfactants[3]. TEM and optical characterizations revealed stable and transparent dispersions of 5-7 nm size anatase TiO_2 NPs. The PC activity was tested by monitoring the degradation of an organic pollutant (Rhodamine B dye-RhB) in aqueous solution after a 15-minutes UV light irradiation. The best PC performance was achieved in the case of NPs with CTAB and Triton X-100 giving respectively an enhancement of +203%, +158% compared to commercial TiO_2 (Fig.1). The high transparency, stability and PC activity of these synthesized TiO_2 NPs can be exploited as alternative to the TiO_2 commercial powders, in order to develop highly PC transparent materials in the future.

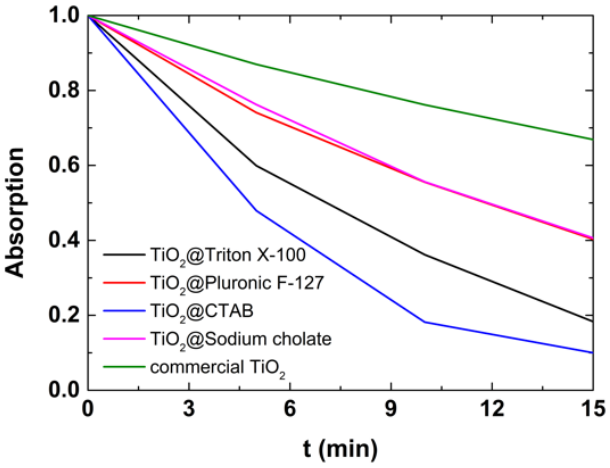

Figure 1. Decrease of the normalized absorbance of RhB in aqueous solution and in presence of the colloidal TiO_2 samples, compared to TiO_2 AHP 200, during 15-minute UV irradiation (313 nm).

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FUNCTIONALIZATION OF SILICON NANOCRYSTALS WITH AMINES

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ABSTRACT

Silicon nanocrystals (SiNCs) have unique properties that render them particularly suitable for biomedical applications. As a matter of fact, silicon is a non-toxic material: it is biodegradable and biocompatible [1]. Moreover, this element is well-known and very abundant on the Earth's crust, which make it more convenient than conventional quantum dots. Furthermore, silicon nanocrystals are expected to be optimal candidates for luminescence bioimaging thanks to these peculiar optical features: an emission energy tuneable to the red and near infrared spectral region (which is compatible with the biological window), a high photoluminescence quantum yield, that is not sensitive to molecular oxygen, and a long lifetime of emission due to silicon's indirect band gap, which enables a time-gated detection [2]. However, the main issues that hinder the use of SiNCs for this kind of application are related to the intrinsic low colloidal stability in aqueous environment and their low molar absorption coefficient. In each case, a functionalization of silicon nanocrystals' surface with amines could be a solution. In fact, amines could offer the possibility to link the SiNC with a high number of molecules (receptors, chromophores…), which can enhance the dispersibility or the absorption, by robust amide bonds. However, the direct interaction between the crystal lattice and the nitrogen atom seems to create a trap state that compromises the long-lived near infrared emission of the SiNC and makes a short-lived blue luminescence arise.[3]
The aim of our research is to accomplish this functionalization with amines but maintaining SiNCs' optical properties. To do this, we firstly passivate the quantum dot's surface with a chlorosilane. This group then reacted with a protected propargyl amine deprotonated on the terminal alkyne. The synthetical route was successful, but the presence of deprotected amines interacted with the lattice of the crystal leading to the blue emission.

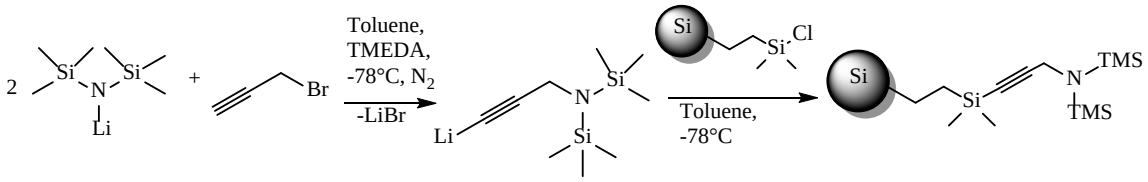

Fig.1 Adopted strategy for SiNCs functionalization with amines

Fig.2 Vial containing a batch of SiNCs functionalized with amines in MeOH under UV light

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ATRP POLIMERIZATION OF N-VYNILCAPROLACTAM EMPLOYING HIGH FLASH POINT SOLVENTS

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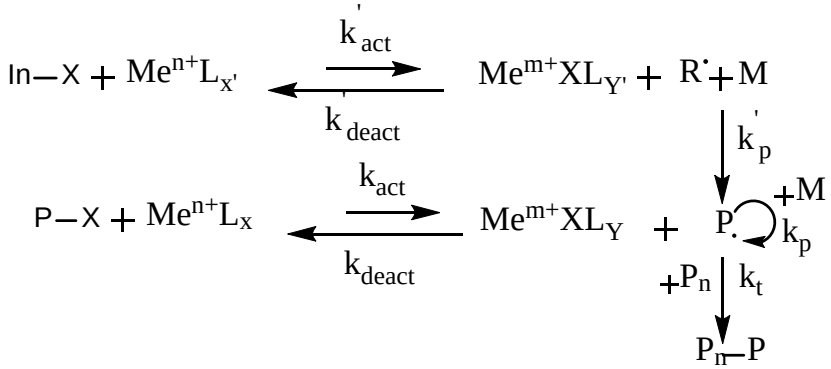
ABSTRACT

Il poli(N-vinil caprolattame) [poli(NVCL)] è un polimero che può trovare numerose applicazioni in ambito industriale, merito di alcune sue caratteristiche quali solubilità in acqua e nei solventi organici, non tossicità [1], biocompatibilità, termo sensibilità [1] e temperatura critica di solubilità inferiore (LCST) nel range della temperatura fisiologica [2]. Questo materiale viene molto utilizzato, ad esempio, in applicazioni biomediche *in vivo* e vengono molto studiati anche i suoi copolimeri a blocchi [1] in quanto, grazie al loro carattere anfifilico, trovano applicazione nel drug delivery a rilascio controllato di principi attivi[3]. In questo contesto, il gruppo presso il quale è stato svolto questo lavoro di tesi ha recentemente intrapreso lo studio della sintesi di copolimeri a blocchi del poli(NVCL) mediante tecniche di polimerizzazione controllata.[4] In particolare mediante Atom Transfer Radical Polymerization (ATRP, Schema 1) recentemente è stato possibile sintetizzare l'omopolimero poli(NVCL) con peso molecolare controllato e carattere vivente. [5] Quest'ultimo è stato quindi utilizzato come macroiniziatore per la polimerizzazione di vari monomeri vinilici con diversa polarità, ottenendo così copolimeri a blocchi con lunghezza dei blocchi controllata.[1]



Schema 1 – Meccanismo di un'ATRP

Il processo messo a punto, però, prevede l'utilizzo di alte temperature (90°C) e di solventi organici come l'1,4 diossano, che oltre ad essere un sospetto cancerogeno, ha un valore di flash point di 12°C. Allo scopo di poter portare la produzione di questi materiali a livello industriale, quindi, è stato deciso di studiare la loro sintesi mediante ATRP utilizzando solventi non tossici e con alto flash point e lavorando a temperature comprese tra 50 ed 80°C in modo da poter utilizzare acqua di torre come liquido di raffreddamento per abbassare anche i costi di processo. È stato quindi ritenuto necessario effettuare nuovi studi allo scopo di ottimizzare il processo di sintesi del macroiniziatore e dei copolimeri a blocchi in condizioni adatte ad un loro scale up industriale. Per fare ciò, è stata studiata approfonditamente la cinetica di omopolimerizzazione ATRP dell'N-vinil caprolattame (NVCL) a 60°C impiegando due diversi solventi ad alto flash point [poli(propilenglicole) con $\overline{M_n}$ = 425 e 1000g/mol (PPG-425 e PPG-1000)]. Una volta ottimizzata la sintesi dell'omopolimero poli(NVCL), questo è stato utilizzato come macroiniziatore per la successiva polimerizzazione del vinil acetato allo scopo di ottenere copolimeri a blocchi con pesi molecolari controllati.

1.1 Studi cinetici: sintesi del Poli(N-vinil caprolattame) [Poli(NVCL)]

La polimerizzazione di NVCL mediante ATRP in PPG-1000 era già stata studiata in precedenza, in presenza di Cu(I)/Cu(II) in rapporto 1:0.3 e alla temperatura di 80°C [6]. Il processo, però, risultava poco controllato per bassi tempi di reazione a causa, probabilmente, della presenza di reazioni di terminazione nello stadio iniziale di polimerizzazione. Al fine di ottimizzare il processo abbiamo ritenuto necessario effettuare degli studi cinetici variando la temperatura, il solvente e la quantità di co-catalizzatore presente [Cu(II)] nella miscela di reazione. Quest'ultimo, infatti, come

NEW ELECTROCHEMICAL STRATEGY FOR THE PREPARATION OF LAYERED DOUBLE HYDROXIDES (LDHS)

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ABSTRACT

Layered double hydroxides (LDHs) containing redox active transition metals are attractive compounds for electrochemical applications such as energy storage, sensors, fuel cells and catalysts for oxygen evolution reaction (OER). [1][2]

We here propose a novel and enhanced electrochemical route to deposit the LDHs through a potentiodynamic method. [3] In all cases studied, it results highly reproducible and the LDHs display a greater crystallinity in respect to those electrodeposited with the more commonly used potentiostatic method. [4] The films obtained have been characterized by a large number of techniques (such as CVs, PXRD, Raman spectroscopy, SEM and XAS) in order to confirm the obtained phase.

The as synthesized electrodes have been demonstrated as catalysts for oxygen evolution reaction and in the electro-oxidation of 2,5-hydromethylfurfural displaying interesting performances.

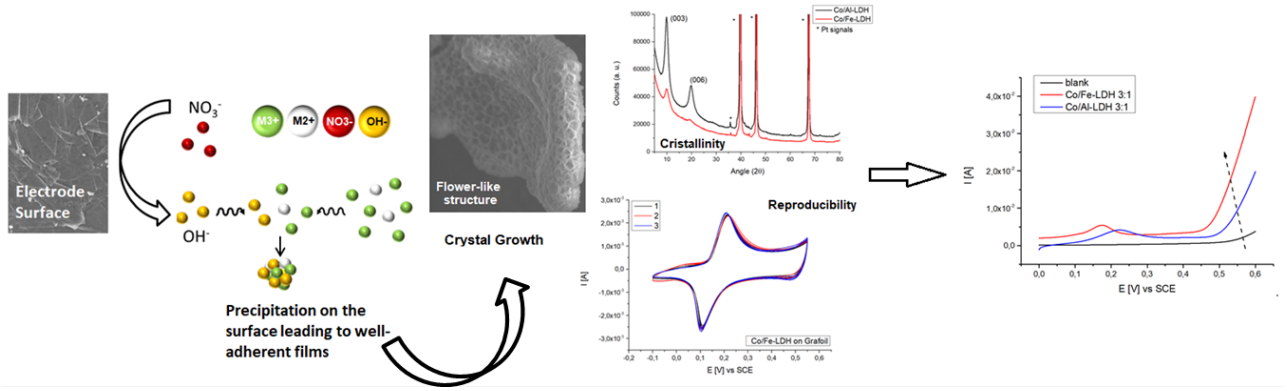

Figure 1. A schematic representation of the proposed work

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LOADING OF MICRORNA-TARGETING PEPTIDE NUCLEIC ACIDS (PNAS) INTO POROUS SILICON NANOPARTICLES

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Cystic fibrosis (CF) is ranked as one of the most widespread life-shortening genetic diseases. This pathology is caused by malfunctioning of cystic fibrosis transmembrane conductance regulator (CFTR) protein, due to genetic defects in its coding DNA sequence. MicroRNAs are short non-coding RNAs expressed in different tissue and cell types that suppress the expression of target genes. Several miRs have been described as regulators of CFTR translation.
It has been firmly demonstrated that peptide nucleic acids (PNAs), synthetic oligonucleotides resistant to nuclease and protease degradation, can be used as microRNA inhibitors.[1] One of the major limit in the use of PNA for regulation of gene expression is the low uptake by eukaryotic cells. [2] In order to provide an appropriate strategy for both systemic as well as intracellular delivery of PNAs, we tested their loading into inorganic nanocarriers. Porous silicon is a biodegradable and biocompatible material that has been widely studied for drug delivery application.[3] In the present work we loaded three specific PNA sequences targeting micro-RNAs, involved in the regulation of the CFTR, into porous silicon nanoparticles (pSiNPs). First, several batches of nanoparticles were prepared by electrochemical etching of single crystal silicon wafer in presence of HF. PNA was loaded into the pores of the pSiNPs at 10-20% mass loading and ~ 90% loading efficiency by precipitating an insoluble shell of calcium silicate simultaneous with drug loading. This core-shell structure slows the degradation of the porous silicon skeleton and the release of PNA. Furthermore, loading achieved by Ca^{2+} treatment was found to be much higher than that used for PNA delivery using PLGA nanoparticles previously reported.[4]

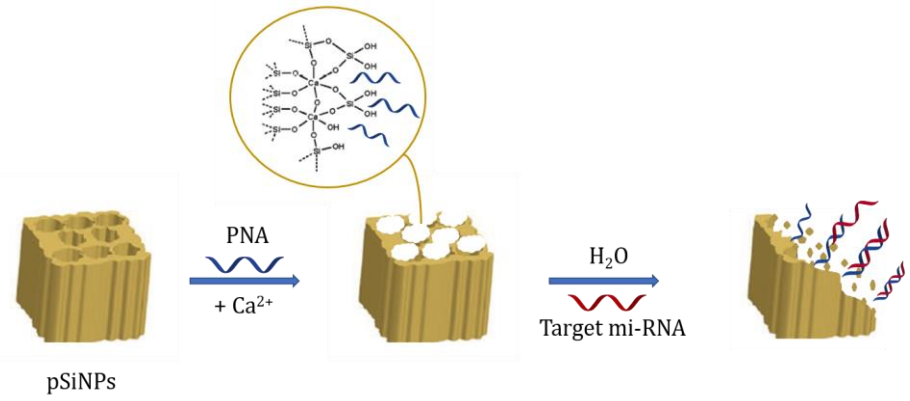

Figure 1. Process of loading of pSiNP with PNA and release by spontaneous degradation, leading to miRNA targeting.

Cumulative release of PNA payload from calcium silicate capped pSiNPs was measured in phosphonate buffered saline with a view to following in vitro assays on epithelial cell lines.

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FILLING THE GAP IN EXTENDED METAL ATOM CHAINS: FERROMAGNETIC INTERACTIONS IN A TETRAIRON(II) STRING SUPPORTED BY OLIGO-*α*-PYRIDYLAMIDO LIGANDS

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ABSTRACT

Extended Metal Atom Chains (EMACs) consist in arrays of metal ions, wrapped together by oligo-*α*-pyridylamido, or related ligands.[1-3] The arrangement of the donor atoms often promotes the formation of metal-metal bonds.[1] EMACs have attracted renewed interest since the pentachromium(II) complex $[Cr_5(tpda)_4Cl_2]$ (H_2tpda = N^2,N^6-di(pyridin-2-yl)pyridine-2,6-diamine) shows a directionally-bistable magnetic moment at low temperature (S = 2 ground state).[4] Here, in **strictly anaerobic and anhydrous conditions**, refluxing $[Fe_2(Mes)_4]$ (HMes = mesitylene), $Fe_4Cl_8 \cdot 6THF$ and H_2tpda in toluene, we isolated crystals of the first homometallic iron(II)-based EMAC supported by oligo-*α*-pyridylamido ligands: the tetrairon(II) complex $[Fe_4(tpda)_3Cl_2]$ **(1)** (Fig.).[5] The spectroscopic and electronic properties of **1** were investigated in dichloromethane by UV-Vis-NIR absorption spectroscopy, ^{1}H-NMR spectroscopy and cyclic voltammetry. The electrochemical measurements showed four fully resolved, quasi-reversible one-electron redox processes, implying that **1** can adopt five oxidation states in a potential window of only 0.8 V (Fig.).[5] Direct current magnetic measurements indicate dominant ferromagnetic coupling at room temperature, although the ground state is only weakly magnetic (Fig.).[5] Based on Density Functional Theory and Angular Overlap Model calculations, this magnetic behavior was explained as being due to two pairs of ferromagnetically-coupled iron(II) ions (J = –21 cm^{-1} using $J\hat{\mathbf{S}}i \cdot \hat{\mathbf{S}}j$ convention) weakly antiferromagnetically coupled with each other.[5] Alternating-current susceptibility data in the presence of a 2 kOe dc field and at frequencies up to 1.5 kHz revealed the onset of slow magnetic relaxation below 2.8 K, with an estimated energy barrier U_{eff}/k_B = 10.1(1.3) K.[5] The one-electron oxidized compound $[Fe_3(tpda)_3]PF_6$ (**2**) was isolated by reacting **1** with FcPF6 (1 equiv) in CH_2Cl_2 solution (Fc = ferrocene). UV-Vis-NIR spectrum of **2** is characterized by a significative broad band around 700-750 nm, typical of **mixed-valent compounds**, in which become operative the electronic interaction mechanism known as double-exchange, that could provides an effective source of ferromagnetic couplings between ions in different oxidation states.

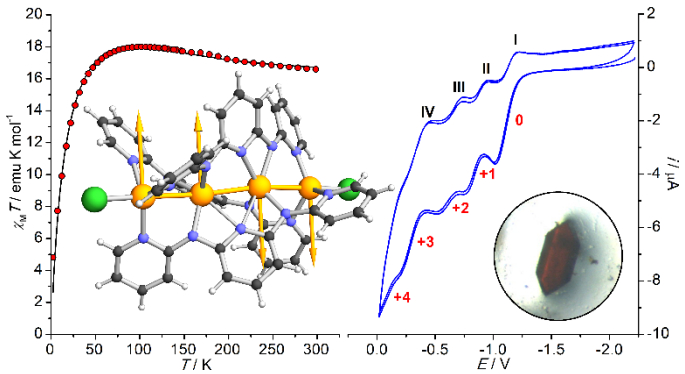

Figure 1. Structure of **1** and picture of one of the crystals. On the left the $\chi_M T$ vs T trend is represented (χ_M = molar magnetic susceptibility), while on the right the cyclic voltammetry measurements are shown.

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Investigating the gating mechanism of a two-pore domain channel under physiological conditions: a Molecular Dynamics study

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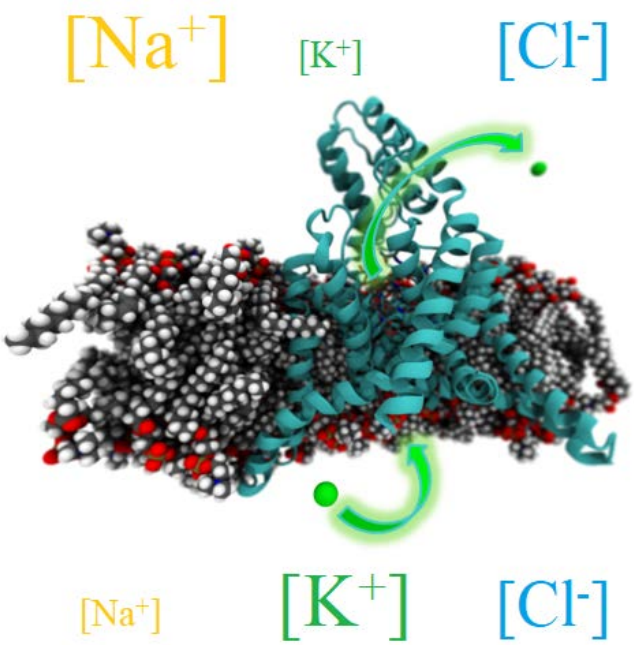

Two-pore domain channels (K2P) are a specific family of channels whose functionality is finely tuned by a rich ensemble of chemical and physical stimuli. The ionic currents produced by these proteins are usually referred to as ‘’leak’’ or ‘’background’’ potassium currents, because they stabilize the resting potential of membranes to highly negative values close to the K^+ equilibrium potential. In particular, the TRAAK channel (Twik Related Arachidonic Acid K^+ channel) is influenced by chemical (anesthetics or drugs), and physical agents (pH, temperature, membrane stretching or bending)[1].

Although the first crystal structure of TRAAK channel was released in 2012, a full comprehension of the gating mechanism and ion transport is still missing. Among the most influential theories on gating, we mention the two-states hypothesis advanced by MacKinnon and co-workers.[2]

Here, we investigate some mechanistic aspects of the TRAAK functionality through molecular dynamics (MD) simulations. In particular, we investigate the mechanosensitive channel properties through unbiased simulations in membrane-stretching regime. These calculations are complemented with ion permeation studies performed through a computational setup, which closely mimics physiological conditions of ions depletion across the membrane. Actually, the potassium conduction through the TRAAK channel is simulated by maintaining the K^+, Na^+, Cl^- concentrations gradients between intracellular and extracellular sides, and setting up the electrostatic potential across the simulation box.

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ARE HISTONES OR DNA THE TARGET FOR THE PROAPOTOTIC ACTION OF CITRONELLAL THIOSEMICARBAZONE METAL COMPLEXES?

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ABSTRACT

Among the characteristics of new antitumor drugs, great emphasis is given to selectivity. Presently, the main drawbacks in the use of cisplatin and its derivatives are a low selectivity, an induced pharmaco-resistance and a low antimetastatic activity [1]. We have used citronellal thiosemicarbazone (Htcitr) to obtain three metal complexes with nickel ([Ni(tcitr)$_2$]) [2], platinum ([Pt(tcitr)$_2$]) and copper ([Cu(tcitr)$_2$]). These are able to interact with DNA which may account for the cell-cycle block observed and the induction of apoptosis in proliferative cells.
The goal of this study is understanding the mechanism of interaction of these metal complexes with DNA. Indeed, DNA can be a direct target, when the metallodrug interacts directly with the strands. In other cases, DNA is an indirect target, and this happens when the metallodrug interacts with one of the components of chromatin. Chromatin is a complex of DNA and proteins (called "histones") whose primary function is packaging DNA in a more compact structure.
Firstly, we have performed DNA binding studies with thermal denaturation profiles, circular dichroism and atomic force microscopy. With the atomic force microscopy, we have observed the formation of knot- and hairpin-like structures induced by the metal complexes.
Subsequently, we have studied the interaction between these metal complexes with a model hexapeptide that represents the histone tail H2A. In this case we have used different spectroscopic techniques like NMR (for the diamagnetic metal complexes), UV visible and circular dichroism. These techniques confirm the ability of the metal complexes to interact with this peptide. [Pt(tcitr)$_2$] and [Ni(tcitr)$_2$] are able to interact with the H2A tail, but in different ways: the nickel complex coordinats the peptide with the release of the ligand, while the platinum complex acts as an entire and not dissociated entity. The copper complex shows the least relevant action.

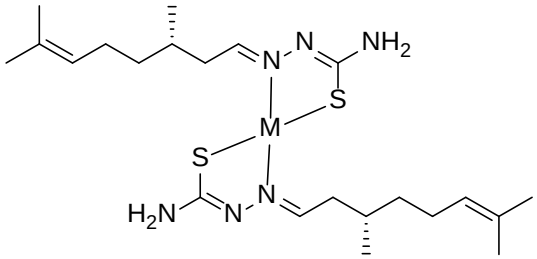

Figure 1. Bis(S-citronellalthiosemicarbazonato)metal(II)

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ANTIBACTERIAL SILVER NANO-COATING ON ELECTROSPUN POLYMERIC NANOFIBERS FOR WOUND HEALING

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ABSTRACT

Drug-resistance displayed by many bacteria is one of the main issues of the lack of successful chronic wounds healing. Therefore, there is a need to develop alternative strategies to the traditional antibiotic treatments based on the use of materials with antibacterial properties. A great attention has been placed by researchers onto the use of silver nano-coatings on electrospun polymeric nanofibers, thanks to the well-known antibacterial properties of this metal against a broad spectrum of bacteria [1] (more than 650 bacteria), and due to the highly biomimetic properties of electrospun scaffolds. However, the most commonly used techniques to obtain silver nano-coatings, usually involve chemical or physical pre-treatments of polymeric materials and lead to a slightly adherent coating with poor thickness control. This involves the detachment and cracking of the coating and a poor control of the release of silver ions.
The aim of this work is to implement a new strategy for the production of antibacterial silver nano-coating on polymeric nanofibers of different chemical nature (polyurethane, polyamide and polyester) by combining a nanofibers production method, i.e. electrospinning, and an innovative Pulsed Electron Deposition technique, i.e. Ionized Jet Deposition. The latter, performed at the NaBi laboratories of the Istituti Ortopedici Rizzoli, is a promising technology to realize compact and adherent nano-coating directly on the surface of a device, however it has never been used before to coat delicate substrates, such as electrospun polymeric nanofibers, In order to evaluate morphological, structural and chemical properties of electrospun materials before and after silver deposition, morphological (SEM and TEM), thermal (TGA and DSC) and spectroscopic characterizations (FT-IR) were performed. Wettability was estimated through water contact angle measurements for both uncoated and silver coated samples. The results of the material characterization demonstrate the presence of compact and adherent silver nano-coating on the three different types of polymeric nanofibers and suggest also the occurrence of possible cross-linking and/or degradation reactions, depending on the polymer considered, that however do not impair their use and performances.
Antibacterial efficacy of silver coated samples were evaluated against S. aureus and E. coli through agar diffusion tests. These tests confirmed the antibacterial properties of the coated samples, which were higher for gram-negative bacteria.

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STUDY ON PROPERTIES OF BIOBASED AMINE-CURED EPOXY RESINS

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ABSTRACT

Epoxy resins are thermosetting polymers which, thanks to their specific properties such as strong adhesion, chemical and thermal resistance, and good mechanical properties, nowadays are widely used in many applications, such as paints, adhesives, and matrices for composites materials. Worldwide 75% of the epoxy resins produced are based on the diglycidylether of bisphenol A (DGEBA)[1]. Bisphenol A is a presumed toxic compound and thus, its substitution in epoxy thermosets attracted a lot of attention recently. In addition, a more general drive for the substitution of petro-based compounds with bio-based ones is also a very actively investigated area of research and so in this context, a number of agricultural and food industry wastestreams, such as lignin and furanic derivatives, has been taken into account as new chemical resources. Epoxy products are commonly produced from the reaction of an epoxy monomer or pre-polymer (resin) with a curing agent. In order to obtain the desired final product properties, the nature and the structure of the curing agents (also known as hardeners, accelerants, late curing agents and catalysts), which are crucial in the generation of hard, infusible, thermoset networks in the crosslinking reaction of epoxy precursors, are highly fundamental. The most commonly used hardeners are amines, polyamines, anhydrides and mercaptans. Many of these compounds suffer from some environmental issues, in particular high toxicity before the crosslinking process[2]. Thus, finding alternative sustainable and low-toxic curing agents from renewable materials and biomass appears more and more important. In particular, considering the outstanding results reached in the area of epoxy precursors, the possibility of producing a fully renewable thermosetting epoxy resins represents an extraordinary opportunity to increase the environmental sustainability of the final products such as composite materials. For the reasons explained before, the aim of this project is to investigate the possibility of using amine-based hardeners from a renewable source for the formulation and production of new epoxy resin systems. After preliminary tests on various new bio-based hardener such as theobromine, theophylline, melamine and guanine, the best results have been obtained with adenine. Initially adenine was studied with the diglycidylether of bisphenol A (DGEBA). This formulation was used to validate the use of adenine as a hardener. Subsequently the DGEBA was replaced with a commercial infusion resin (Elan-tron® EC 157) to work in conditions more similar to the industrial ones. These two systems have been characterized by thermogravimetric analysis (TGA), differential scanning calorimetry (DSC) in dynamic and isothermal mode and through dynamic-mechanical analysis (DMA). The results obtained, have provided important informations on this new class of highly promising renewable amine hardeners.

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NHC-CATALYZED EXTERNAL OXIDATIVE DESYMMETRIZATION OF PHARMACEUTICALLY RELEVANT DIHYDROPYRIDINES

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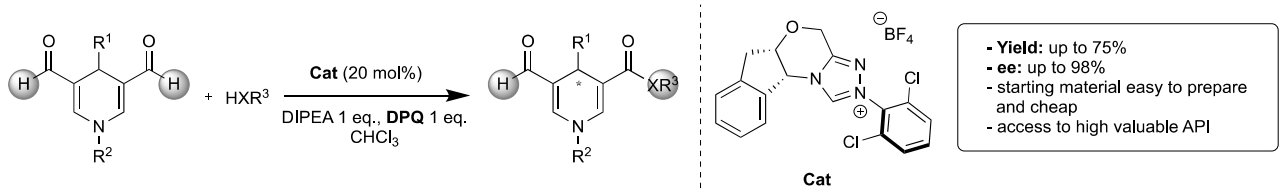

ABSTRACT

The synthesis of 1,4-dihydropyridines (DHPs) was first published by A. Hantzsch in 1882 via a multicomponent approach [1]. About 60 years later compounds of this class were found to exhibit pharmacological activities as analgesic, morphine agonist and antispasmodic and in 1975 they became the most important drugs used in the treatment of cardiovascular diseases when nifedipine (Adalat®) appeared on the market for the first time [2]. More recently, NHC (N-Heterocyclic Carbene) catalysis has emerged as powerful tool in desymmetrization and resolution of alcohols via external and internal oxidation of Breslow intermediate [3]. Thus, we envisioned the possibility to extend this approach directly to symmetric dialdehydes. Herein, we present a strategy for the synthesis of biologically relevant DHPs with high optical purity via NHC-catalyzed desymmetrization of 1,4-dihydropyridine-3,5-dicarbaldehyde. The Kharasch oxidant (DPQ) was found to be the best external oxidant in the process and a small library (18 entries) of DHPs was prepared. The reaction is robust and proceeds with good yield (up to 75%) and excellent enantioselectivity (up to 98%). Some synthetic elaboration of the compounds are presented as well.

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BODIPY-CARBON NANODOTS AS EFFICIENT LUMINOPHORES FOR ELECTROCHEMILUMINESCENCE

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ABSTRACT

Electrochemiluminescence is a luminescence induced by an electrochemical stimulus.[1] Since the excited species are produced with an electrochemical stimulus rather than with a light excitation source, ECL displays improved signal-to-noise ratio compared to photoluminescence. In the last decades, ECL results a very promising analytical technique for clinical applications. In order to electrochemically generated the excited state two different precursors are required: luminophore and co-reactant. The most employed ECL luminophore is ruthenium(II)tris(2,2'-bipyridyl) ($Ru(bpy)_3^{2+}$) but it is expensive dye and the excited state of ruthenium complex could be quenched by the oxygen present in solution.[2] In the quest for ever-increasing sensitivities, ECL can ideally be coupled to nanotechnology to develop new systems and strategies for analyte determination also in very complex matrices.[3] In this context, various alternatives are investigated in order to increase the ECL efficiency such as dye doped silica nanoparticles and Carbon Nanodots (CNDs).[4] Here we report the ECL from CNDs functionalized with boron-dipyrromethene (Bodipy). BCNDs (Bodipy-CND) are investigated as luminophores in co-reactant ECL mechanism thanks to good CND features, like nontoxicity, chemical inertness, high resistance to photobleaching and excellent ECL properties[5]. The ECL propriety is also compared to photoluminescence (PL): divergent and interesting behaviours are observed probably due to different excited states formed in PL and ECL analysis. This feature will be used to find the surface-modified BCND that gives the best ECL response.

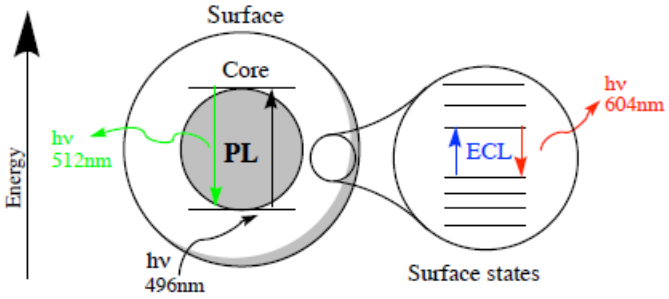

Figure 1 Scheme of BCNDs surface states and internal excitation

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DESIGN AND SYNTHESIS OF A SMALL LIBRARY OF CASHEW NUT SHELL LIQUID (CNSL) DERIVATIVES AS HDAC INHIBITORS: POTENTIALLY EPIGENETIC SUSTAINABLE TOOLS FOR THE TREATMENT OF ALZHEIMER'S DISEASE.

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ABSTRACT

Neurodegenerative diseases, such as Alzheimer's disease (AD), represent a formidable challenge for drug discovery. The lack of effective treatment and the increasing life expectancy are the reason of an ever-increasing number of people affected by AD in the world and in particular, in the developing countries. Indeed, the actual palliative treatment approved by FDA act as inhibitors of acetyl cholinesterase (donepezil, galantamine, and rivastigmine), and once as NMDA antagonist (memantine). Moreover, the cost of currently treatments is too high for the people affected in developing countries, hence the possibility to develop new drugs based on inexpensive resources has gained increasing attention. Brazil is one of the main producers of cashew nuts. During the cashew nut processing, an enormous amount of a dark viscous fluid, called cashew nut shell liquid (CNSL), is obtained as a waste material. [1] Long-chain phenolic compounds contained in the inexpensive CNSL show innate multi-target mechanisms of action, becoming innovative molecules with potential applications for the treatment of AD. Moreover, the structural homology between CNSL components (such as cardanol) and SAHA (suberoylanilidehydroxamic acid), caught our attention. Indeed, recent studies with the approved HDAC inhibitor (HDACI) SAHA showed an improvement in memory, and cognition in several AD animal models.[2]

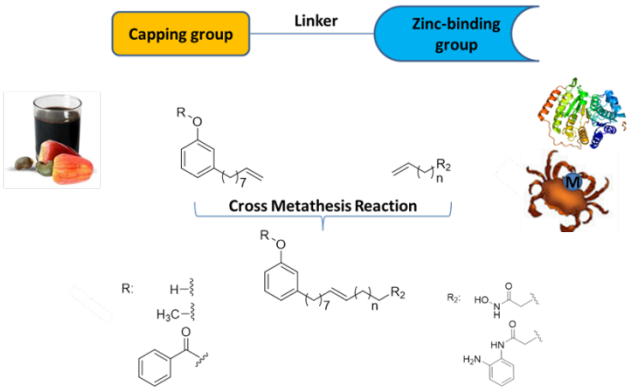

Figure 1. Design of CNSL-derivatives.

In light of this, the aim of this work is the design and synthesis of accessible and sustainable multi-target compounds obtained by combining CNSL derivatives with the well know SAHA structure. The target compounds has been synthesis using a cross metathesis synthetic strategy (Figure 1) that allowed us to obtain innovative HDACIs, and with potential metal chelating activity against iron, cupper, and zinc, responsible of the oxidative stress in the AD

I would like to acknowledge the European COST ACTION Epichembio CM1406 (Epigenetics Chemical Biology) for the opportunity to participated at the Short-Term Scientific Mission (STSM) in the Institut de Chimie des Milieux et Matériaux de Poitiers, under the supervision of Professor Philippe Bertrand.

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PEPTIDE NUCLEIC ACIDS PROBES FOR ADVANCED SENSORY SYSTEMS

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ABSTRACT

Modern sensor technologies allow to monitor analytes with unprecedented performances in many fields (e.g. in environmental, food and clinical analyses); genosensors can be very useful in clinical environment for the non-invasive early detection of infectious diseases and cancer. Very important biomarkers for early detection of cancer are circulating DNA and micro-RNA that can be found in peripheral blood performing a liquid biopsy with ultrasensitive techniques. Development of efficient probes able to specifically bind DNA and RNA targets, and strategy to couple these with advanced sensory systems are crucial points in this context. Peptide Nucleic Acids (PNAs), synthetic analogous of DNA, have been selected as nucleic acid capture probes for their well-known enhanced affinity to target nucleotide (necessary for detection in traces) and selectivity (crucial for single point mutation discrimination). They are very versatile molecules that can be chemically modified for enhancing their performances, at backbone, nucleobase or both[1]. The present communication describes the approaches used during PhD thesis for the development of PNA structures to be used in highly performant sensory systems; part of the work was in the context of the EU-project ULTRAPLACAD, which was aimed to the development of sensors for the early detection of colorectal cancer.
PNA probes specific for mutant DNA and miRNA, suitable to be used on Surface Plasmon Resonance (SPR) sensors, were produced (Fig.1). In particular, for detecting micro RNA associated to colorectal cancer, different types of probe geometries were tested. According to preliminary test, better results have been obtained anchoring the central region of PNA, which exploit a C5-modified monomer[2] (Fig. 1). For surface deposition of probes, different linking strategies were tested, using amino terminal spacers, azide moieties or protected thiols[3,4]. Specific single point mutations are crucial for the identification of best therapies, therefore probes that can distinguish a single mismatch are very important. For enhancing this characteristic, "Chiral Box"[5] PNAs, which have C2 modified backbones were synthesized following a novel procedure in terms of backbone synthesis (reductive amination by iridium-catalyzed hydrogen transfer[6]) and solid phase synthesis of PNA (minimally protected-submonomer strategy). Optical purity of these has been evaluated for backbone formation and PNA synthesis by GC analysis[7]. This kind of modified PNAs could be used in future clinical applications in other advanced sensory system that have been developed during PhD thesis: amperometric genosensors[8], field effect transistors and photonic crystal optical fibers[9].

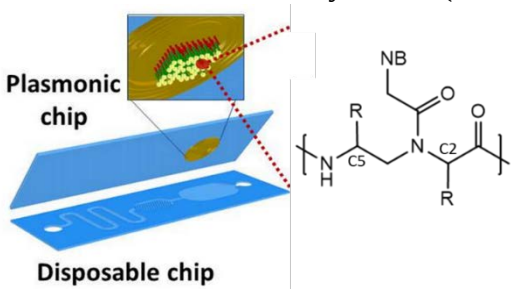

Figure 1: Different PNA-backbone modification for enhancing properties as probe on SPR sensor.

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FUNCTIONALIZATION OF GELATIN WITH A NATURAL FLAVONOID

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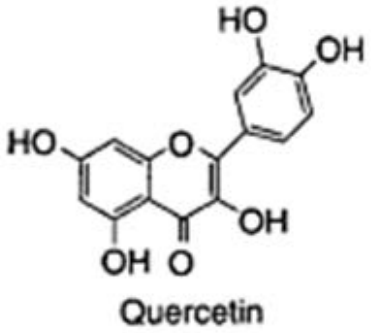
ABSTRACT

Gelatin belongs to the branch of the biodegradable polymers and it can be obtained by thermal denaturation of collagen, as well as by its physical and chemical degradation. It is a non immunogenic, biocompatible, biodegradable and relatively cheap material. These properties justify the wide use of gelatin in different applications, for example in the pharmaceutical, cosmetic, and food industries [1].
Quercetin is a flavonoid with antioxidant and antibacterial properties that is ubiquitously presents in foods including vegetables, fruit, tea and red wine [2]. In this work, this flavonoid has been utilized to functionalize gelatin, with the aim to limit problems due to its high solubility in aqueous solutions and to imbue the composite materials with the relevant properties of quercetin for possible biomedical applications.

Figure 1. Molecular structure of Quercetin



Due to the insolubility of quercetin in the aqueous medium, several mixtures of solvents were tested, which could allow the dissolution of both components.
We have verified the possibility of prepare films according to three different procedures : (a) addition of quercetin in a mixture 50:50 water: ethanol to as-prepared gelatin films; (b) Films prepared from solutions containing gelatin and quercetin in DMSO; (c) Films prepared from solutions containing gelatin and quercetin in 50:50 water:ethanol (not characterized, since they were not homogeneous).
The influence of quercetin on the properties of gelatin, such as structure, morphology, thermal stability and swelling behavior, has been investigated in films at different content of the flavonoid. In particular, the results of DSC analyses show a decrease of the values of the enthalpy of denaturation of gelatin on increasing quercetin concentration of the films, which could be related to a decrease of crystallinity due to interaction between the biopolymer and the flavonoid.

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SYNTHESIS, CHARACTERIZATION AND MOLECULAR STRUCTURES OF THE NEW $[Bi@Rh_{12}(CO)_{27}]^{3-}$, $[(Bi@Rh_{12}(CO)_{26})_2Bi]^{5-}$, $[Bi@Rh_{14}(CO)_{27}Bi_2]^{3-}$ AND $[Bi@Rh_{17}(CO)_{33}Bi_2]^{4-}$ CARBONYL CLUSTERS.

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ABSTRACT

The chemistry of homo-metallic carbonyl clusters of rhodium has been widely investigated over the last four decades, [1, 2] but the limited number of characterized rhodium compounds containing post-transition elements prompted us to investigate the chemistry of hetero-metallic Rh-Bi carbonyl clusters. In fact, there are several examples in literature of metal carbonyl clusters which present bismuth, [3] although none with rhodium.
By reacting an acetonitrile solution of the precursor cluster $[Rh_7(CO)_{16}][NEt_4]_3$ [4] with a suspension of $BiCl_3$ in the same solvent, under N_2 atmosphere and at room temperature, it is possible to achieve the new hetero-metallic $[Bi@Rh_{12}(CO)_{27}]^{3-}$ cluster in high yields. The icosahedral compound is very similar to the analogous $[E@Rh_{12}(CO)_{27}]^{3/4-}$ (E=Sb, Sn) isoelectronic clusters and it has crystallized with both $[NEt_4]^+$ and $[NMe_4]^+$ counter-ions. The new carbonyl cluster is completely stable under CO atmosphere, even for a prolonged period of time, as inferred by IR spectroscopy. However, its stability is not confirmed at high temperature: when its acetone solution is heated by refluxing under N_2 atmosphere a constant lowering of the ν_{CO} absorptions occurs, proving a possible loss of some CO ligands and the formation of an unsaturated species, unfortunately not yet identified. Moreover, controlled additions of $BiCl_3$ to $[Bi@Rh_{12}(CO)_{27}]^{3-}$ result firstly in the formation of the dimeric species $[(Bi@Rh_{12}(CO)_{26})_2Bi]^{5-}$ and the $[Bi@Rh_{14}(CO)_{27}Bi_2]^{3-}$, both in low yields, and finally in $[Bi@Rh_{17}(CO)_{33}Bi_2]^{4-}$ cluster, in fairly good yield. Both reactions are conducted in acetonitrile and at room temperature and lead to the same products under either N_2 or CO atmosphere. All these compounds have been completely characterised by IR spectroscopy and ESI-MS spectrometry and their molecular structures determined by X-ray diffraction studies. [5] Notably, they represent the first examples of Bi atoms interstitially lodged in metallic cages that, in this specific case, are all based on an icosahedral geometry.

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A Safe Lithium Metal Battery Using Glyme Electrolyte

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Lithium metal is the anode of choice for cell with high energy density due to its high theoretical specific capacity and the lowest electrochemical potential (-3V vs SHE) [1]. The use of lithium as the anode material may be enabled by exploiting electrolytes of relevant safety, such as those based on polymer or solid state configurations. Among them, end-capped glymes based on $(-OCH_2CH_2-)_n$ groups demonstrated favorable properties, such as low flammability and satisfactory ionic conductivity, as well as suitable electrochemical stability window [1]. Furthermore, the addition of film forming agents may allow efficient behavior and low polarization of the lithium cell [2].

Accordingly, we report herein a glyme electrolyte designed as a safe electrolyte for an efficient lithium metal battery using an olivine based $LiFePO_4$ cathode. The viscous end-capped glyme solvent has an excellent thermal stability, and actually a low flammability. The electrochemical impedance spectroscopy study of the electrolyte demonstrates a Li^+ transference number of 0.65, a conductivity of the order of 10^{-2} S cm^{-1} (Figure 1), and a high interphase stability with the lithium metal. Linear sweep voltammetry indicates an electrochemical stability window extending up to 4.3 V vs. Li/Li^+. Furthermore, promising electrochemical performances in terms of reversibility, cycling stability and low charge-discharge polarization are observed using the lithium iron phosphate (LFP) cathode (Figure 2).

Hence, the electrolyte is considered a promising candidate for applications in safe, high performance lithium metal battery.

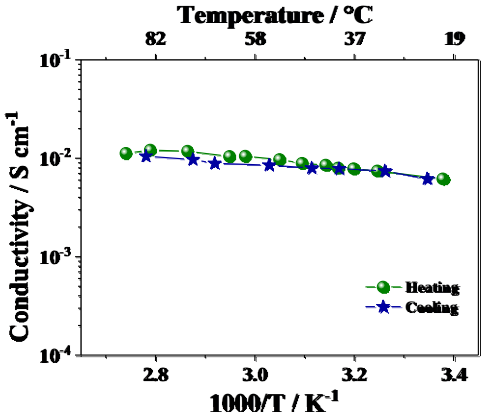

Figure. 1 Temperature dependence of the ionic conductivity.

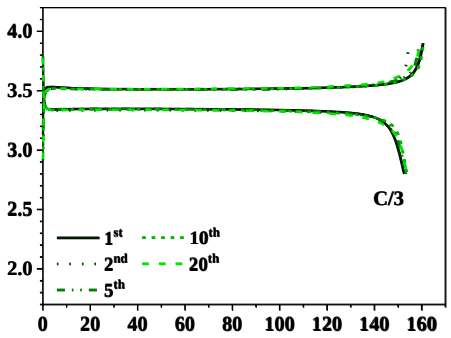

Figure 2 Voltage profiles of lithium cell.

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SYNTHESIS OF BENZISOXAZOLES AND STUDY ON HEMOPROTEINS-CATALYZED KEMP ELIMINATION

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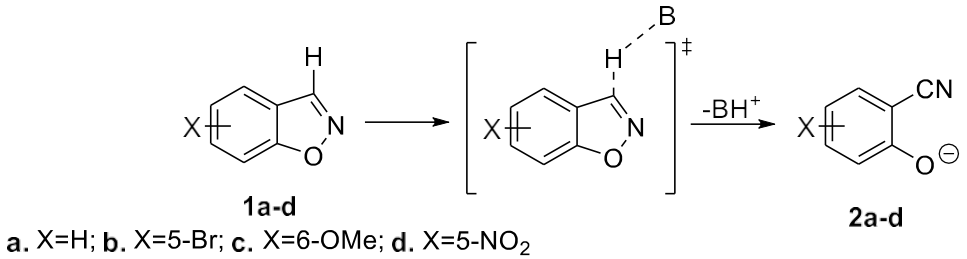
ABSTRACT

The base-catalyzed decomposition of benzisoxazole to yield 2-cyanophenol is called Kemp elimination (**Scheme 1**), a well-studied benchmark for catalysts design and a model for enzymatic C-H bond abstraction [1,2].



Scheme 1. Kemp reaction.

This reaction involves a N-O bond cleavage on the benzisoxazole ring, through a concerted E2 mechanism, as a consequence of the deprotonation of CH bond, adjacent to nitrogen atom, by a base. The benzisoxazoles **1a-d** were obtained through a multistep synthesis in good yields. Formylation of a phenol derivative, nucleophilic addition of hydroxylamine and a final cyclization are the three key steps which afforded the desired fused isoxazole rings.
The base-catalyzed decomposition of synthesized substrates was monitored through UV/Vis spectrophotometry, in order to study the catalytic effect of three hemoproteins, i.e. cytochrome c, myoglobin and hemoglobin. Cytochrome c, myoglobin and hemoglobin catalyze the Kemp elimination after reduction of Fe (III), present in the heme group of all three enzymes, by the ascorbate. The catalysis is influenced by the kind of substituent bonded to benzene ring of benzisoxazole: the deprotonation rate decreases in the order 5-NO_2BI>5-BrBI>6-OMe, ongoing from more to less electron-withdrawing substituents.
Unlike cytochrome c, which catalyzes the Kemp reaction faster than myoglobin and hemoglobin, these latter are deactivated over time: myoglobin is deactivated due to the production of hydrogen peroxide by ascorbate; instead the hemoglobin is deactivated due to interaction with oxygen.
The findings from this study suggest that the hemoproteins herein studied catalyze the Kemp reaction through an oxidation-reducing mechanism that implies the presence of Fe (II) in the heme group.

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RAGE IN DIABETES MELLITUS: A MULTIMETHODOLOGICAL STRATEGY TO STUDY GLYCATED HSA-RAGE INTERACTION

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ABSTRACT

The human receptor for advanced glycation end-products (RAGE) is a transmembrane glycoprotein which plays a role in innate immunity and in the inflammatory response. Nevertheless, it is also involved in a growing number of important diseases characterized by persistent inflammatory state and oxidative stress, including diabetes and its complications, Alzheimer's disease and cancer [1]. Among RAGE binders, the so-called advanced glycation end products (AGEs), a heterogeneous class of products resulting from the non-enzymatic glycation of proteins, have been identified as a direct cause of severe diabetic complications [2]. Despite a significant progress in the knowledge of AGE-RAGE axis, the pathological role of specific AGEs as well as AGEs structural requirements for AGE-RAGE interaction and RAGE activation still remain to be clarified. The lack of a clear picture is partially related to AGEs heterogenicity. Moreover, *in vitro* studies of AGE-RAGE interaction are most commonly performed using as reference ligands human/bovine serum albumin (HSA/BSA) derived AGEs, prepared in house by *in vitro* glycation and not fully characterized. The use of AGEs mixture for binding studies hampers the comprehension of biorecognition phenomenon, inhibiting the rational design of new RAGE antagonists. Based on these premises, the present study has the purpose to investigate the binding between RAGE ectodomain, i.e. VC1, and a form of marketed glycated HSA (HSAgly) by a tailored multimethodological strategy in order to obtain further insights into AGE-RAGE interaction. Initially, the structure of HSAgly was investigated by both top-down and bottom-up approaches to characterize the product in terms of glycation extent and specific aminoacid residues involved in glycation. Surface plasmon resonance technology (SPR) was exploited to confirm the ability of HSAgly to interact with VC1 and to quantify the complex affinity (K_D) which was assessed to be in the micromolar range. Moreover, an affinity chromatography coupled with mass spectrometry (affinity-MS) approach [3] was developed in order to obtain further details on the structural motives involved in binding. In particular, the combination of epitope extraction method, involving the use of a designedly developed VC1-affinity column, with the LC-MS/MS analysis of the retained protein or peptides allowed the identification of the regions of HSAgly involved in the binding. Preliminary findings highlighted a possible involvement of the subdomain IA of HSA in VC1 biorecognition.
Outcomes of this study showed that the proposed multimethodological strategy can be a suitable approach to shed light on requirements for VC1 biorecognition and it may be further employed to investigate the interaction with different glycated interactants, including glycated albumins most commonly abundant in the blood of diabetic patients.

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DISCOVERY OF NOVEL 1,3,8-TRIAZASPIRO[4.5]DECANE DERIVATIVES THAT TARGET THE C SUBUNIT OF F1/FO-ATP SYNTHASE FOR THE TREATMENT OF REPERFUSION DAMAGE IN MYOCARDIAL INFARCTION.

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ABSTRACT

Recent cardiology research studies have reported the role, function, and structure of the mitochondrial permeability transition pore (mPTP) and have shown that its opening plays a key role in the progression of myocardial cell death secondary to reperfusion. In this manuscript, we validated a new pharmacological approach as an adjunct to reperfusion in myocardial infarction (MI) treatment and describe the discovery, optimization, and structure−activity relationship (SAR) studies of the first small-molecule mPTP opening inhibitors based on a 1,3,8-triazaspiro[4.5]decane scaffold that targets the c subunit of the F1/FO-ATP synthase complex[1]. We identified three potential compounds with good mPTP inhibitory activity and beneficial effects in a model of MI, including a decreased apoptotic rate in the whole heart and overall improvement of cardiac function upon administration during reperfusion.

Oligomycin A is classified as a mPTP opening inhibitor that targets the c subunit of F1/FO-ATP synthase[2], therefore, it was selected as the reference compound for this project. Indeed, oligomycin A is known to establish several Van der Waals interactions with c subunits, in particular with Glu[59] and Leu[63] (Figure 1A)[3]. Moreover, the southern part of oligomycin A is closely engaged by the binding cavity of the c ring[3]. Considering this information and the need to simplify this natural compound to facilitate accessible and easy synthesis, we explored the activity of a series of small molecules mimicking the southern 1,7-dioxaspiro[5.5]-undecane moiety of oligomycin A. To test the hypothesis that the spiro bicyclic fragment may be mandatory for mPTP inhibition, we initially screened a small internal library of spiro derivatives that resulted in the identification of 1-phenyl-1,3,8-triaza-spiro-[4,5]decan-4-one derivative (PP11, Figure 1B). To assess the efficacy of PP11 in inhibiting Ca^{2+}-mediated mPTP opening, we first measured its biological activity in HeLa cells by calcein−cobalt assay.

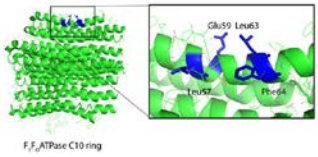

Figure 1A. Interaction between oligomycin A and c-ring

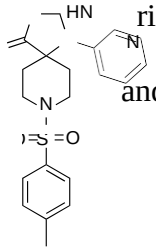

Figure 1B. PP11

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MERCURY IN BOTTLED WATER FROM EMILIA-ROMAGNA AND VENETO: ULTRA-TRACE AMOUNT DETERMINATION AND EVALUATION OF INTAKE USING A HEALTH RISK ASSESSMENT APPROACH

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ABSTRACT

Mercury (Hg) is a toxic element and a ubiquitous pollutant. Natural sources and processes (e.g. forest fires, volcanic and geothermal activities, rock weathering) and human activities (e.g. power plants, artisanal and small-scale gold and mercury mining) are both responsible for its presence in all environmental matrices (air, water and soil). Even at very low levels in both aquatic and terrestrial ecosystems, all mercury compounds are toxic and can be dangerous to humans and biota. Once in the environment, Hg can enter and accumulate in the food chain causing harmful effects on human health depending on its chemical form (elemental form, inorganic mercury and organic mercury), route, dose and duration of exposure. The most toxic organo-mercurial compound found frequently in the environment is methyl-mercury (MeHg) taken by eating fish, shellfish and fish-derived products through diet [1]. Drinking water is a minor source of mercury (as inorganic, mainly Hg^{2+}) exposure. European and Italian legislation set for drinking water (tap and botted natural mineral) the maximum admitted concentration limit of 1 microgram per litre. A total of 17 bottled water samples from 10 brands, representing 8 still, 7 sparkling and 2 lightly sparkling waters respectively. They were analysed for total mercury (Hg_T) using cold vapour atomic fluorescence spectrometry following US-EPA1631 version E method. For the first-time, mercury was detected at ultra-trace levels (sub nanogram per litre) in bottled waters from Emilia-Romagna and Veneto regions. Hg_T analyses were carried out whilst following quality assurance and quality control procedures by analyzing laboratory blanks, initial (IPR) and ongoing (OPR) precision recovery standards, matrix spikes (MSs) and three certified reference materials (CRMs). The results were corroborated by the fruitful participation in an interlaboratory comparison study for total mercury determination in freshwater samples [2,3]. In addition, through the laboratory results obtained, it was possible to carry out the evaluation of the risk of exposure to mercury through the intake of bottled water evaluated on three age groups of consumers. The daily and weekly exposure assessment will be illustrated, as well as the risk characterization through the hazard quotient (HQ) calculated with respect to the reference dose for mercury (RfD).

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CONTAMINATION OF ORGANOTIN COMPOUNDS IN THE NORTHERN ADRIATIC SEA

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ABSTRACT

The aim of this study was to monitor organotin compounds (tributyltin TBT, dibutyltin DBT, monobutyltin MTB) concentrations, in biotic and abiotic marine samples. In particular, samples of sediments, fishes and filter-feeding organisms, collected in the North-Est area of Adriatic Sea were analysed.
Organotin compounds (OTCs) are well known global pollutants. Depending on the nature and the number of the organic groups bound to the Sn cation, some organotins show specific toxic effects to different organisms, even at very low concentration levels. They are considered endocrine disruptors, as responsible for genetic, reproductive and metabolic disorders[1] and because of their persistence, OTCs presence and bioaccumulation in living organisms is still a current issue[2]. The Ministerial Decree n°260/2010 sets the environmental quality standard EQS for TBT compounds in marine sediments at 5µg/kg dw. Therefore, analytical methods in compliance with the EQS proposed to protect the aquatic environment and human beings are needed.
HPLC-inductively coupled plasma mass spectrometer (HPLC-ICP-MS) is a promising technique to satisfy these requirements. In addition, methods based on HPLC-ICP-MS can significantly simplify sample preparation step avoiding derivatization, moreover they allow for speciation of organotin compounds[3]. In order to evaluate the performance of HPLC-ICP-MS method, the results have to be compared to those obtained from current methodology adopted by national and international protection agencies.
In this study, after sample lyophilization and homogenization, the analytical procedure consisted in different sequential steps, such as extraction, derivatisation, clean up and, finally, GC/MS determination. Samples were extracted in an ultrasonic bath using a solution of tropolone 0.05% w/v in methanol, after acidification with hydrochloric acid. The supernatant was separated by centrifugation and then extracted with dichloromethane. After filtration on anhydrous sodium sulphate, the extract was concentrated, taken up in hexane and then derivatized with Grignard reagent. Clean up was performed on columns filled with silica gel and anhydrous sodium sulphate. The eluate was concentrated and injected into GC/MS.
Since low yields of derivatization and losses of analytes can easily occur during all this complex sample preparation procedure, leading to an underestimation of OTCs content in environmental samples, more accurate and sensitive analytical methods need to be improved in order to be able to detect these compounds in complex matrices such as sediments and biota.

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TEREPHTHALIC ACID FROM RENEWABLE SOURCES: EARLY STAGE SUSTAINABILITY ANALYSIS OF A BIO-PET PRECURSOR

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ABSTRACT

The scope of the present study is to investigate the environmental sustainability of different routes of terephthalic acid (PTA) production, comparing the results achieved for the traditional way with those of three bio-based routes. The aim of the work is to perform a first investigation of alternative pathways on an industrial scale, trying to identify what could guarantee the lowest environment load. Commercially, the main source of production for TPA is p-xylene (PX), an aromatic hydrocarbon compound far from being definable as "green" because it is derived from crude oil. Its oxidation through the Amoco® process lead to the synthesis of PTA. However, the importance given by *green chemistry* to the use of renewable resources has increased the interest towards new routes to produce PX and/or TPA from biomass. The comparison is between four different production processes (Figure 1):

- Scenario A: it is the traditional way, PX is obtained from catalytic reforming of crude oil as part of extracted BTX (benzene, toluene and xylenes isomers);
- Scenario B: isobutanol from the fermentation of sweet corn is converted into hydrocarbons, iso-octene and PX through the GEVO process [1];
- Scenario C: it involves the production of HMF (5-hydroxymethylfurfural) from sugar beet and its subsequent Diels-Alder reaction with bio-ethylene to obtain PX [2];
- Scenario D: it consists in the oxidation, using O_2 in the presence of a catalyst, of p-cymene (derived from orange peels) to obtain bio-PTA [3].

The first two routes are already set at industrial level, while the others are still in the development phase. In order to estimate the energy requirements of the scenarios, a simulation of the chemical processes was carried out using ChemCad software. Among those investigated, the first three ways are based on the production of PX, subsequently oxidized to PTA, while the latter directly converts limonene into TPA.

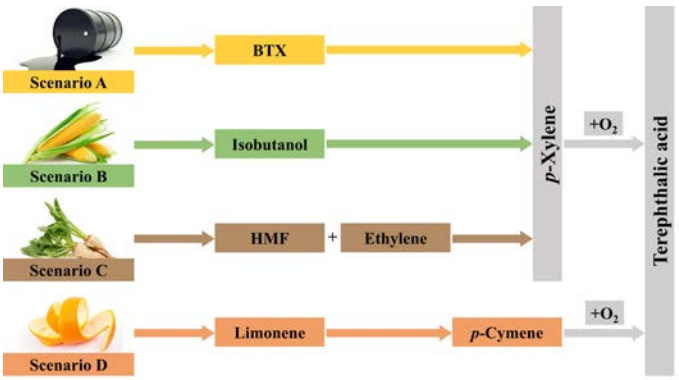

Figure 1. Different routes for terephthalic acid synthesis from biomass.

The scientific tool with which impacts are assessed and the processes are compared is the Life Cycle Assessment (LCA) methodology. SimaPro 8.5 software and the Ecoinvent 3.4 database were used for the data modelling and impact quantification phases of the scenarios. Two analysis method was selected to conduct the assessment: CED (Cumulative Energy Demand) and ReCiPe. The first one, which analyses the need for direct and indirect resources expressing the result in energy terms (e.g. equivalent GJ), highlights that the greatest consumption of resources is related to non-renewable fossils. This category is primarily responsible for the resource needs of all processes, in particular, fossil consumption is mainly due to the fuel used for the heating

3-PHENYLALLYLAMINES IN SYNTHESIS OF BENZO[*F*]ISOINDOLES

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ASTRACT

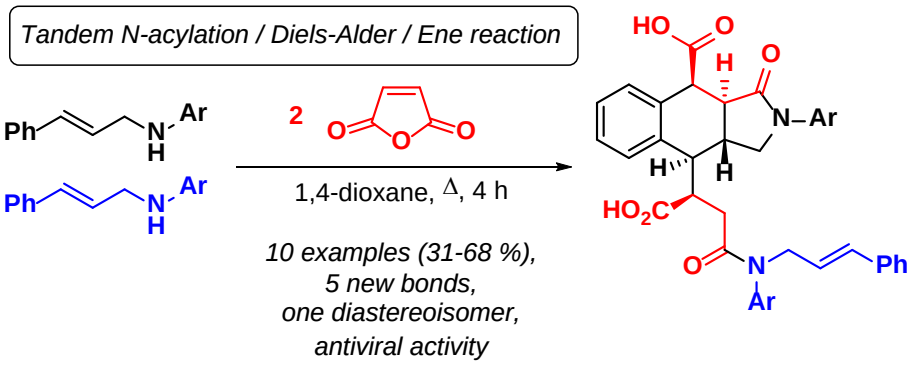

Figure 1. The selected approach to benzo[*f*]isoindole-4-carboxylic acids

The intramolecular Diels-Alder reaction of vinylarenes (IMDAV reaction) and dienes,[1] particularly styrenes represents a useful transformation for the synthesis of annulated carbo- and heterocycles. Despite the fact that the transition state of the cycloaddition includes dearomatization of the benzene ring and requires relatively harsh conditions, this methodology is widely adopted in organic synthesis due to the ready availability of the styrene starting material, and the simplicity of the experimental procedure. More interesting features of the IMDAV reaction are usually exhibited if the reaction is involved in a cascade of consecutive transformations. For example, the tandem IMDAV / Alder-ene reaction[2] proceeding through nonaromatic intermediates can serve as a pathway towards polyfunctional condensed arenes.

During the course of the investigation it revealed that the reaction between readily accessible *N*-aryl-3-phenylallylamines and maleic anhydride leads to unexpected products – polysubstituted hydrogenated benzo[*f*]isoindole-4-carboxylic acids. This transformation proceeds through a previously unknown sequence of steps: *N*-acylation of the allylamine with maleic anhydride, intramolecular Diels-Alder reaction of the vinylarene in the intermediate *N*-maleamide, and final Alder-ene reaction of the products of the previous two steps. Selected benzo[*f*]isoindoles displayed antiviral activity against the influenza virus H1N1.

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ELECTROCHEMICAL SENSOR FOR NADH DETECTION BASED ON ELECTROCHEMICALLY EXFOLIATED GRAPHENE OXIDE

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ABSTRACT

Graphene is one of the materials most studied nowadays for many applications, including energy storage and sensing. Outstanding performance of this nanosized material comes from peculiar properties, such as high surface area (>2600 m^2/g for single-layer graphene), excellent thermal and electric conductivity and high mechanical strength.
In the case of mass production, graphene is generally obtained by chemical oxidation of graphite to graphite oxide and subsequent exfoliation to graphene oxide (GO). This is considered the only process that can give quantitative exfoliation down to single layers.
Thanks to the combination of electrochemical, spectroscopic and morphologic results, we could state that the electrocatalytic performance of the material toward the oxidation of β-nicotinamide adenine dinucleotide (NADH) is strongly dependent of the different oxygenated functional groups present on GO. In particular, we could observe that hydroxyl moieties directly connected to the carbon aromatic structure impart the material peculiar electrocatalytic properties, at the basis of the development of quite efficient amperometric sensors. Similar performance is only achieved after chemical or electrochemical reduction of GO, which increase the conductivity of the material.
We could quite recently demonstrate that similar characteristics are also proper of electrochemically exfoliated graphene oxide (EGO). On the basis of electrochemical and spectroscopic results, we could observe that EGO possesses density of oxidized functional groups on the surface of the nanosheets suitable to be conductive without the need of any reduction pre-treatment and, at the same time, to activate electrocatalytic NADH oxidation.
We also exploited the carboxylic moieties present on carbon nanosheets to suitably functionalized EGO with organic residues bearing terminal alcoholic moieties. Both a chemical and an electrochemical approach were exploited to this purpose, confirming, in any case, the better performance of the functionalized material with respect to pristine EGO.
Due to the better performance of the chemically functionalized EGO, the physico-chemical properties of this material were studied in detail by combining results deriving from electrochemical, spectroscopic and UV-Vis spectroelectrochemical measurements. The analytical performance of the material was also defined and discussed in comparison with the pristine EGO material.