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DIVISIONE DI CHIMICA FARMACEUTICA

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Programma Scientifico

Divisione di Chimica Farmaceutica

Lunedì 11 Settembre 2017

Sala Saturno	
<i>Chairpersons: Gabriele Costantino, Fabrizio Giordanetto</i>	
9:00-9:30	FAR KN01 - Fabrizio Giordanetto, D E Shaw Research <i>Fragment-based discovery of AZD2716: a novel, potent secreted phospholipase A2 (sPLA2) inhibitor for the treatment of coronary artery disease</i>
9:30-9:50	FAR OR01 – Tracey Pirali, Università del Piemonte Orientale <i>Discovery of Store-Operated Calcium Entry modulators as an effective treatment for calcium-related rare genetic diseases</i>
9:50-10:10	FAR OR02 – Claudia Spatari, Università della Calabria <i>A new generation of dihydropyridines: photodegradation and photostabilization strategies</i>
10:10-10:30	FAR OR03 – Andrea Carotti, Università di Perugia <i>In Silico Approaches Supporting Pharmaceutical Analysis Enigmas</i>
10:30-11:00	Coffee Break
<i>Chairpersons: Roberto Di Santo, Maria Laura Bolognesi</i>	
11:00-11:30	FAR KN02 – Maria Laura Bolognesi, Università di Bologna <i>Sustainable drug discovery for neglected infectious diseases: the case of cardanol-based anti-trypanosomatid hybrids</i>
11:30-11:50	FAR OR04 – Rolando Cannalire, Università di Perugia <i>2,2-Dioxido-2,1-benzothiazines as new allosteric inhibitors of DENV NS5 RNA-dependent RNA polymerase</i>
11:50-12:10	FAR OR05 – Mattia Mori, Università di Siena and Istituto Italiano di Tecnologia (IIT) <i>Structure-based identification of HIV-1 nucleocapsid protein inhibitors active against wild-type and drug-resistant HIV-1 strains</i>
12:10-12:30	FAR OR06 – Tommaso Felicetti, Università di Perugia <i>Improvement of Staphylococcus aureus NorA efflux pump inhibition by methoxy group introduction on 2-phenylquinoline core</i>
12:30-12:50	FAR OR07 – Iuni Margaret Laura Trist, Università di Siena <i>Blocking PA-PB1 Protein-Protein Interaction with the Aid of Molecular Modelling to Counteract Influenza A Virus</i>
13:00-14:00	Intervallo Pranzo – Lunch Break

Sala Paestum B	
14:00-15:00	<i>Sessione Poster 1 (FAR PO01 – FAR PO21)</i>

Sala Saturno	
<i>Chairpersons: Cosimo Altomare, Ersilia De Lorenzi</i>	
15:00-15:30	FAR KN03 – Ersilia De Lorenzi, Università di Pavia <i>Development and chromatographic evaluation of Molecularly Imprinted Polymers for the selective recognition of drugs</i>
15:30-15:50	FAR OR08 – Michele Bianchi, Università del Piemonte Orientale <i>Quantitative in vivo evaluation by LC-ESI-MSn analysis of adenosine 5'-tetrphosphate (Ap4), a nucleotide related to nicotinamide phosphoribosyltransferase activities (NAMPT)</i>
15:50-16:10	FAR OR09 – Matteo Micucci, Università di Bologna <i>Thymus vulgaris L. essential oil in gastrointestinal diseases</i>

16:10-16:30	FAR OR10 – Azzurra Stefanucci, Università di Chieti-Pescara “G. D’Annunzio” <i>Structural modification of the β-sheet ARC repressor: design, conformational analysis and binding properties of linear and cyclic ARC mimetics</i>
16:30-17:00	Coffee Break
<i>Chairperson:</i>	
17:00-17:30	FAR MD01 – Claudiu T. Supuran, Università di Firenze (Pratesi DCF Medal)
17:30-17:45	FAR PZ01 – Agostino Bruno, Istituto FIRC di Oncologia Molecolare (DCF Prize)
17:45-18:00	FAR PZ02 – Sergio Valente, Sapienza Università di Roma (DCF Prize)
18:00-18:10	FAR PZ03 – Elisa Azzali, Aptuit Verona (DCF Best PhD Thesis Award)
18:10-18:20	FAR PZ04 – Bruno Cerra, Università di Perugia (DCF Best PhD Thesis Award)
18:30-20:00	<i>Assemblea della Divisione di Chimica Farmaceutica</i>

Martedì 12 Settembre 2017

<i>Sala Saturno</i>	
<i>Chairpersons: Tiziano Bandiera, Maria Menichincheri</i>	
9:00-9:30	FAR KN04 – Maria Menichincheri, Nerviano Medical Sciences <i>Discovery of Entrectinib: a novel and potent inhibitor of ALK, ROS1, and Pan-TRKs kinases active in multiple molecularly defined cancer indications</i>
9:30-9:50	FAR OR11 – Loredana Salerno, Università di Catania <i>Targeting Heme Oxygenase-1 to Overcome Imatinib Resistance in Chronic Myeloid Leukemia</i>
9:50-10:10	FAR OR12 – Marco Lucio Lolli, Università di Torino <i>Potent human dihydroorotate dehydrogenase (hDHODH) inhibitors obtained by scaffold-hopping approaches: from the theoretical design to the in vivo evaluation</i>
10:10-10:30	FAR OR13 – Emanuele Amata, Università di Catania <i>Development of Sigma Receptors Nitric Oxide Photodonor Ligands with Antiproliferative Activity</i>
10:30-11:00	Coffee Break
<i>Chairpersons: Federico Corelli, Rosaria Gitto</i>	
11:00-11:30	FAR KN05 – Rosaria Gitto, Università di Messina <i>Discovery and optimization of isoquinoline-derived inhibitors of human Carbonic Anhydrases (hCAs)</i>
11:30-11:50	FAR OR14 – Giannamaria Annunziato, Università di Parma <i>Discovery of New, Potential Anti-Infective Compound Based on Carbonic Anhydrase Inhibitors by Rational Target-Focus Repurposing Approach</i>
11:50-12:10	FAR OR15 – Francesco Saccoliti, Sapienza Università di Roma <i>Discovery of Novel Diaryl Sulfide Derivatives as Inhibitors of Trypanothione Reductase Enzyme</i>
12:10-12:30	FAR OR16 – Michele Tonelli, Università di Genova <i>Synthesis of 4,6-diamino-1,2-dihydrotriazines as influenza viruses and respiratory syncytial virus inhibitors targeting the host DHFR</i>
12:30-12:50	FAR OR17 – Carmen Cerchia, Università di Napoli “Federico II” <i>Application of a New Scaffold Concept for the Identification of Analog Series in Commercial Databases</i>
13:00-14:00	Intervallo Pranzo – Lunch Break
<i>Sala Paestum B</i>	
14:00-15:00	<i>Sessione Poster 2 (FAR PO22 – FAR PO48)</i>

Mercoledì 13 Settembre 2017

<i>Sala Paestum B</i>	
14:00-15:00	<i>Sessione Poster 3 (FAR PO49 – FAR PO82)</i>
<i>Sala Saturno</i>	
<i>Chairpersons: Vincenza Andrisano, Paolo Caliceti</i>	
15:00-15:30	FAR KN06 – Paolo Caliceti, Università di Padova <i>New drug delivery nanomachines: visionary concepts or reality</i>
15:30-15:50	FAR OR18 – Marco Paolino, Università di Siena <i>π-Stacked Polymers in Drug Delivery Applications</i>
15:50-16:10	FAR OR19 – Paola Russo, Università di Salerno <i>Clarithromycin dry powders for inhalation: A focus on drug solubility</i>
16:10-16:30	FAR OR20 – Francesco Peri, Università di Milano-Bicocca <i>Synthesis and preclinical evaluation of glycolipid-based TLR4 modulators: new therapeutics for inflammatory and autoimmune diseases</i>
16:30-17:00	Coffee Break
<i>Chairpersons: Gianluca Sbardella, Gilberto Spadoni</i>	
17:00-17:30	FAR KN07 – Gilberto Spadoni, Università di Urbino <i>Strategies to maximize therapeutic opportunities for melatonin derivatives</i>
17:30-17:50	FAR OR21 – Leonardo Pisani, Università di Bari <i>Nitrate-ester prodrugs of dual AChE-MAO B inhibitors as anti-Alzheimer Multitarget Hybrids</i>
17:50-18:10	FAR OR22 – Francesca Spyraakis, Università di Torino <i>Discovering new casein kinase 1δ inhibitors with innovative MD-integrated virtual screening</i>
18:10-18:30	FAR OR23 – Letizia Crocetti, Università di Firenze <i>Isoxazol-5(2H)-one: a new scaffold for potent human neutrophil elastase (HNE) inhibitors</i>
18:30-18:50	FAR OR24 – Angelica Mazzolari, Università di Milano <i>Modelling of Glucuronidation Reactions in the MetaQSAR Database: Successful Strategies to Handle Unbalanced Data in Metabolism Prediction</i>

Medaglie e Premi della Divisione di Chimica Farmaceutica

Medaglia Pratesi

Claudiu T. Supuran, Università di Firenze

Premi alla Ricerca

Premio della Divisione di Chimica Farmaceutica

Agostino Bruno, Istituto FIRC di Oncologia Molecolare

Sergio Valente, Sapienza Università di Roma

Premio miglior tesi di Dottorato, Divisione Chimica Farmaceutica

Elisa Azzali, Aptuit Verona

Bruno Cerra, Università di Perugia

Keynote

- **FAR KN01** – Fabrizio Giordanetto, D E Shaw Research, “*Fragment-based discovery of AZD2716: a novel, potent secreted phospholipase A2 (sPLA2) inhibitor for the treatment of coronary artery disease*”.
- **FAR KN02** – Maria Laura Bolognesi, Università di Bologna, “*Sustainable drug discovery for neglected infectious diseases: the case of cardanol-based anti-trypanosomatid hybrids*”.
- **FAR KN03** – Ersilia De Lorenzi, Università di Pavia, “*Development and chromatographic evaluation of Molecularly Imprinted Polymers for the selective recognition of drugs*”.
- **FAR KN04** – Maria Menichincheri, Nerviano Medical Sciences, “*Discovery of Entrectinib: a novel and potent inhibitor of ALK, ROS1, and Pan-TRKs kinases active in multiple molecularly defined cancer indications*”.
- **FAR KN05** – Rosaria Gitto, Università di Messina, “*Discovery and optimization of isoquinoline-derived inhibitors of human Carbonic Anhydrases (hCAs)*”.
- **FAR KN06** – Paolo Caliceti, Università di Padova, “*New drug delivery nanomachines: visionary concepts or reality*”.
- **FAR KN07** – Gilberto Spadoni, Università di Urbino, “*Strategies to maximize therapeutic opportunities for melatonin derivatives*”.

Fragment-based discovery of AZD2716: a novel, potent secreted phospholipase A2 (sPLA2) inhibitor for the treatment of coronary artery disease

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Starting from a benzamide-containing hit identified through fragment screening, a rapid medicinal chemistry campaign enabled the design of AZD2716 as a novel, potent secreted phospholipase A2 (sPLA2) inhibitor. Data-driven structure-based reasoning coupled with physicochemical parameters control resulted in the successful optimization of the efficacy, pharmacokinetic and toxicological profile of the series, culminating in the selection of AZD2716 as a clinical candidate for the treatment of coronary artery disease.

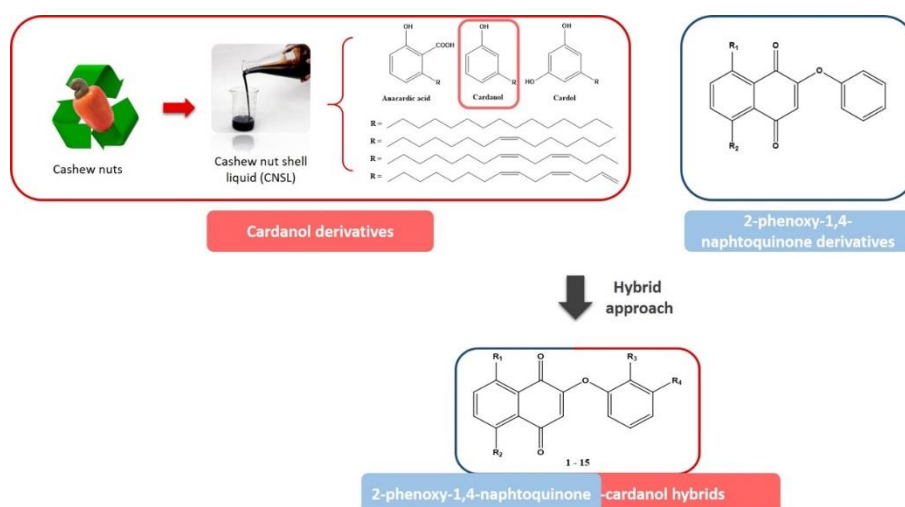
Sustainable drug discovery for neglected infectious diseases: the case of cardanol-based anti-trypanosomatid hybrids

Maria Laura Bolognesi^a

^a Department of Pharmacy and Biotechnology, Alma Mater Studiorum – University of Bologna, Via Belmeloro, 6, 40126 Bologna, Italy

Trypanosomatid infections are a group of highly debilitating and potentially fatal neglected diseases with major impacts on human health. Although they mainly affect populations living in poverty, with poor access to health services, leishmaniasis, Chagas disease and human African trypanosomiasis are increasingly becoming a concern for Europe too. Current insufficient chemotherapy regimens mostly rely on single-target drugs, which very often suffer by toxic side effects, lack of efficacy, and development of resistance. Moreover, cost of treatments is too high for the affected population, and the availability of quality medicinal agents on a sustainable basis is an increasingly appreciated public health care concept.¹ On this basis, efforts to lower the costs of therapy by developing new drugs based on inexpensive resources (e.g. food waste products) has gained growing attention.

Based on the above considerations, as well as on our continuous interest in multi-targeted compounds,² we turned our attention to cashew nut shell liquid (CNSL) as a sustainable starting material for the development of new hybrid drugs against Trypanosomatid infections. CNSL, produced in the cashew nut processing process as a waste, is a mixture of anacardic acid, cardanol, and cardol, whose structures offer opportunities for chemical derivatization. In particular, following a framework combination strategy, new hybrids have been designed by merging the naphthoquinone moiety of previously discovered anti-trypanosomatidic hits, with the phenoxy group of cardanol.



The synthesized molecules have been characterized for their anti-trypanosomal activity, both in enzyme assays and in *in vitro* parasite cultures. Given the profile of the starting hybrids, inhibition of glyceraldehyde-3-phosphate-dehydrogenase and trypanosome alternative oxidase has been studied for selected compounds. Mechanistic studies directed at elucidating the mitochondrial mechanism of action have been performed. Thanks to an effective multifaceted anti-trypanosomal profile, the current series emerge as low-cost, accessible hit compounds that deserve further characterization.

References: 1. Renslo A. R. & MacKerrow J. H. *Nat. Chem. Biol.* **2006**, 2, 701 – 710. 2. Pieretti, S. et al *PLoS Negl. Trop. Dis.* **2013**, 7, e2012; Prati, F. et al *J. Med. Chem.* **2015**, 58, 6422–34. Bruno S et al. *Chem Biol. Drug Des.* **2017**, doi: 10.1111/cbdd.12941.

Development and chromatographic evaluation of Molecularly Imprinted Polymers for the selective recognition of drugs

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By Molecular Imprinting Technology one can synthesize polymeric artificial receptors known as Molecularly Imprinted Polymers (MIPs) (1). In the non covalent approach, functional monomers are arranged around a molecular template (print molecule) in an appropriate solvent; then this assembly is copolymerized in the presence of an excess of cross-linker and free radical initiator, to obtain a polymeric rigid structure. Removal of the template leaves behind cavities which are complementary in size, shape and chemical functionality to the template molecule. Owing to their high physical stability, straightforward preparation, remarkable robustness and low cost, MIPs specifically designed to recognise bioactive molecules have received widespread attention and gained popularity in many fields, including purification by solid phase extraction, chiral separation, drug delivery, artificial antibodies and chemo/biosensing (2).

Preliminary evaluation and characterization of these materials is a key step before further selection and optimisation. It may conveniently include, along with advanced physical techniques, both zonal and frontal chromatography, by comparing results obtained on MIP and NIP-packed columns where NIP are synthesized in the same fashion but with the omission of the template. A wealth of information can be obtained on selectivity, loading capacity, aqueous compatibility, efficiency and reproducibility. In particular frontal analysis chromatography is an extremely powerful technique for a quantitative study of the interactions between solutes (template) and a stationary phase (MIP), as it affords the number of classes of sites on the polymer surface, saturation capacity as well as the binding constant of template associated to each class of sites.

The design and chromatographic characterisation of MIPs for the selective recognition of folic acid, methotrexate and structural analogues, bupivacaine as well as for the class-selective recognition of glucuronides will be presented. To overcome intrinsic weaknesses associated to MIPs (poor aqueous compatibility, non specific adsorption, slow mass transfer) special imprinting strategies have been implemented. The substructure or epitope approach and stoichiometric imprinting demonstrate the analogy between biological and synthetic receptors. Different MIP formats such as classical bulk particles, microparticles, capillary monoliths and composite silica-MIP particles will be evaluated for HPLC, capillary electrochromatography (CEC) and solid phase extraction (SPE) applications. Finally, the presentation will also include one of the first examples of MIP as a valid alternative to immunoassays for protein detection, to be used as biomarker discovery tool (3-5).

References: 1. Sellergren, B. (Ed.), Molecularly imprinted polymers. Man-made mimics of antibodies and their application in analytical chemistry (Techniques and instrumentation in analytical chemistry, vol.23), Elsevier, Amsterdam, 2001. 2. Chen, L. et al., J. Chem.Soc.Rev., 45 (2016) 2137. 3. Quaglia, M. et al., J. Am. Chem. Soc., 123 (2001) 2146. 4. Emgenbroich, M. et al., Chem. Eur. J., 14 (2008) 9516. 5. Ambrosini, S., et al., Analyst, 137 (2012) 149.

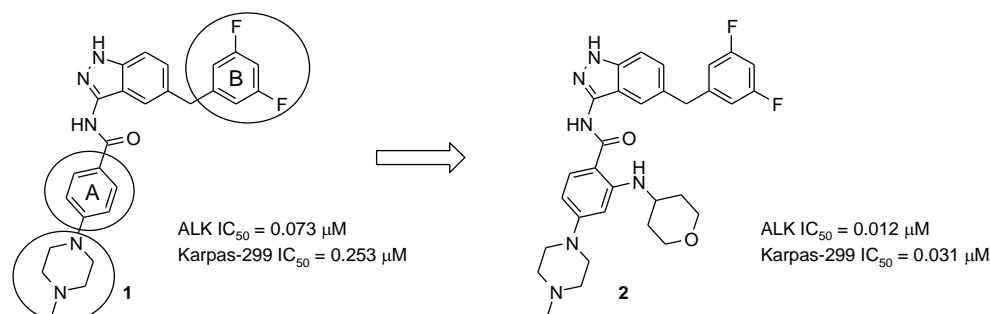
Discovery of Entrectinib: a novel and potent inhibitor of ALK, ROS1, and Pan-TRKs kinases active in multiple molecularly defined cancer indications

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The anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase that plays a key role in the development of different tumor types. For instance the oncogenic protein NPM-ALK was originally identified as responsible for a subset of Anaplastic Large Cell Lymphoma (ALCL), a rare type of non-Hodgkin lymphoma (1). Subsequently and most importantly subsets of Non-Small Cell Lung Cancer (NSCLC) have been reported to be dependent on activated forms of ALK, the most frequent being the EML4-ALK protein (2). Interestingly oncogenic forms of the strictly related c-ros Oncogene 1 kinase (ROS1), and tropomyosin receptor kinase A (TRKA) have been found in the same tumor indication (3,4). In addition TRKs fusion proteins have been also identified in subsets of colorectal carcinoma (CRC) (5) and in other tumor types (6). Despite the remarkable clinical activity of the ALK inhibitor Crizotinib, the emergence of resistance mutations and of brain metastasis often cause patient relapse (7). In the search of novel and potent ALK inhibitors, the high-throughput screening (HTS) of our corporate compound collection allowed us to identify the 3-aminoindazole compound **1** (figure 1), endowed with good biochemical potency against ALK ($IC_{50} = 0.073 \mu M$) and good antiproliferative activity on the ALK-dependent ALCL Karpas-299 cell line ($IC_{50} = 0.253 \mu M$) (8, 9). From this starting point a medicinal chemistry effort, focused on the variation of ring A and ring B substitution, led to the final candidate compound **2** (entrectinib), that potently inhibits the ALK kinase ($IC_{50} = 0.012 \mu M$), and the proliferation of the ALK-dependent Karpas-299 cell line ($IC_{50} = 0.031 \mu M$).

Figure 1



Entrectinib is characterized by good oral bioavailability in all animal species, excellent *in vivo* efficacy in ALK-driven tumor models, efficient penetration of the blood-brain barrier (BBB) and good antiproliferative activity on Ba/F3 cell line transfected with different mutated forms of EML4-ALK. Moreover compound **2** is a potent inhibitor of the closely related tyrosine kinases ROS1 and TRKs, and is highly efficacious in *in vivo* related tumor models. Entrectinib is currently undergoing Phase II Clinical Trials for the treatment of selected patients affected by ALK-, ROS1-, and TRK-positive tumors.

References: 1. Shaw, A. T.; Engelman, J. A. *J. Clin. Oncol.* **2013**, *31*, 1105-1111. 2. Soda, M. *et al. Nature* **2007**, *448*, 561-566. 3. Bergethon, K. *et al. J. Clin. Oncol.* **2012**, *30*, 863-870. 4. Vaishnavi, A. *et al. Nat. Med.* **2013**, *19*, 1469-1472. 5. Ardini, E. *et al. Mol. Oncol.* **2014**, *8*, 1495-1507. 6. Amatu, A. *et al. Esmo Open*, **2016**; *1*: e000023. 7. Gainor, J. F, *et al. J. Thor. Oncol.* **2013**, *8*, 1570-1573. 8. Menichincheri, M. *et al. J. Med. Chem.* **2016**, *59* (7), 3392-3408. 9. Ardini, E. *et al. Mol. Cancer Ther.* **2016**, *15* (4), 628-639.

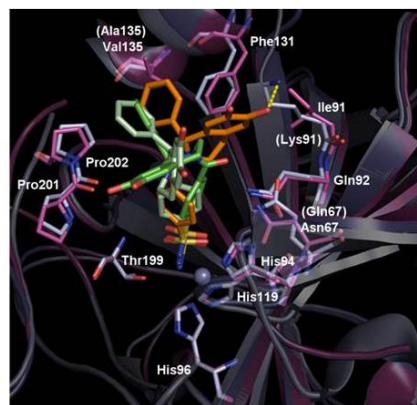
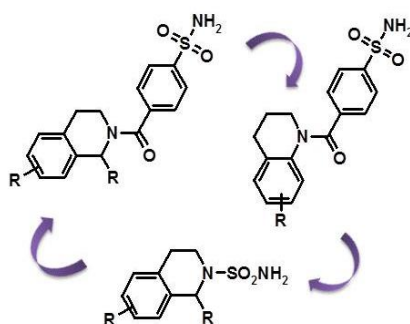
Discovery and optimization of isoquinoline-derived inhibitors of human Carbonic Anhydrases (hCAs)

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Giuseppina De Simone^c, Claudiu T. Supuran^d*

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Human Carbonic Anhydrases (hCAs, EC 4.2.1.1) catalyze the reversible hydration of carbon dioxide and are involved in various physiological processes (gluconeogenesis, lipogenesis, and ureagenesis). However, their abnormal levels or activities have been often associated with several diseases. Selected CA isoforms (hCA VII, hCA IX, hCA XII and hCA XIV) have become relevant targets for the design of inhibitors for the treatment of cancer, epilepsy, obesity, glaucoma, and so on. Although the first generation of CA inhibitors (CAIs) were able to bind druggable isoforms, they were also great inhibitors of the ubiquitous hCA I and hCA II isoforms, thus displaying many undesired side-effects. Consequently, many research efforts have been recently dedicated to design new CAIs targeting hCA VII, hCA IX, hCAXII and hCA XIV. It is well-known that the (hetero)aryl-sulfonamide-based CAIs bind the catalytic zinc ion through the deprotonated nitrogen of the sulfonamide moiety; whereas, the remaining molecular fragment interacts with hydrophobic/hydrophilic residues which delimit the CA-catalytic site thus eliciting isoform selectivity.

Starting from the first series of isoquinoline-based sulfonamides CAIs (1), we performed the hit optimization for this class of compounds thus identifying selective agents toward hCA VII, hCA IX isoforms (2,3).



On the basis of cocrystal structures of hCA II in complex with the most active/selective inhibitors we further designed and synthesized isoquinoline/quinoline sulfonamides and investigated the main structure-activity relationships (4,5). To in-depth study the CA isoform selectivity we also performed molecular studies and docked the best active inhibitors in to the catalytic pocket of druggable isoforms. These studies revealed that the isoquinoline nucleus promotes extensive interactions in the active site and tunes the isoform selectivity profile.

References: 1. Gitto, R.; Agnello, S.; Ferro, S.; De Luca, L.; Vullo, D.; Brynda, J.; Mader, P.; Supuran, C. T.; Chimirri, A. *J. Med. Chem.* **2010**, *53*, 2401-2408. 2. Gitto, R.; Agnello, S.; Ferro, S.; Vullo, D.; Supuran, C. T.; Chimirri, A. *ChemMedChem* **2010**, *5*, 823-826. 3. Gitto, R.; Damiano, F. M.; De Luca, L.; Ferro, S.; Vullo, D.; Supuran, C. T.; Chimirri, A. *Bioorg. Med. Chem.* **2011**, *19*, 7003-7007. 4. Buemi, M. R.; De Luca, L.; Ferro, S.; Bruno, E.; Ceruso, M.; Supuran, C. T.; Pospíšilová, K.; Brynda, J.; Řezáčová, P.; Gitto, R. *Eur. J. Med. Chem.* **2015**, *102*, 223-232. 5. Bruno, E.; Buemi, M.R.; Di Fiore, A.; De Luca, L.; Ferro, S.; Angeli, A.; Cirilli, R.; Sadutto, D.; Alterio, V.; Monti, S.; Supuran, C.T.; De Simone, G.; Gitto, R. *J. Med. Chem.* **2017**, *60*, 000, DOI: 10.1021/acs.jmedchem.7b00264.

New drug delivery nanomachines: visionary concepts or reality

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Over the past years, multifunctional nanotechnology has emerged as a novel approach to overcome the biopharmaceutical pitfalls of old and new drugs, including oligonucleotides and peptides, and optimize their therapeutic performance. As a result, last generation delivery nanosystems are capable of complex functions, which enable sequential overcoming of multiple biobarriers following a certain time/site determined “logic” of events. These nanocarriers provide longer drug circulation times, higher tolerability, and site specific delivery, factors that result in better patient outcomes. Cancer represents the field of medicine application to which multifunctional nanotechnology has made the most prominent contributions. Main strategies for tumour targeting involve the exploitation of the peculiarities of the cancer tissues and cells, which include the high angiogenesis and blood vessel permeability and low lymph derange (EPR effect), the expression of specific cell membrane receptors (biorecognition) and the unique local environmental physical features (temperature, pH, redox potential and enzyme composition). Natural and synthetic polymers are landmark materials for production of novel smart nanomedicines for anticancer drug delivery. Multivalent, amphiphilic and stimuli responsive polymers have been in fact exploited to produce drug bioconjugates and self-assembling colloidal systems or to bestow peculiar physicochemical and biological properties on inert colloidal scaffolds. Stimuli sensitive polyacrylates represent unique functional modules for drug delivery as they can be used to produce assemblies, namely temperature or pH sensitive micelles and polymersomes. According to their physicochemical features, these systems can be sharply designed to dispose in the tumour tissue where the specific local conditions can induce structural changes that selectively release the drug or provide for the intracellular delivery of the drug cargos.

Polyacrylate copolymers formed by A-B blocks bearing ionisable phenol pendant units (block A) and hydrophilic neutral pendant moieties (block B) have been shown to form micelles or polymersomes depending on the ionisable/hydrophilic composition. These vesicles have been shown to efficiently deliver either hydrophobic or hydrophilic drugs yielding high cell up-take under the typical conditions of the tumour tissue. Environmentally stimuli materials can be also combined with targeting agents and cell up-take enhancers to generate sophisticate supramolecular combinations with unique in vivo performance. A-B-C triblock copolymers containing ionisable polyhistidine units (block B) and neutral hydrophylic terminal blocks (block A and C) that form polymersomes in the presence of oligonucleotide drugs have been functionalized with folic acid for active cancer cell targeting. Gold nanoparticles decorated with thermosensitive polyacrylates have been found to gain switchable properties: particle aggregation and cell interaction and internalisation. The combination of the temperature and pH sensitive polyacrylate decorated nanoparticles with targeting agents has been found to bestow switchable recognition properties on the colloidal systems that can be exploited for surface recognition or cell targeting and may be used for theragnostic applications. Finally, gold nanoparticles and liposomes simultaneously decorated with pH sensitive polyacrylates and targeting agents and cell penetration enhancers have been designed to program a hide/reveal behaviour. These systems have been found to maintaining their stealth properties under physiological conditions while in the tumour tissue they reveal the cell-penetration modules that promote the cell up-take and intracellular drug delivery. In conclusion, based on a deep knowledge of biological aspects of tumours nanotechnology offers a variety of opportunities to ameliorate the selectivity and therapeutic activity of anticancer drugs. Nonetheless, despite the development of these nanomedicines for tumour targeting are carefully in silico designed their behaviour is often unpredictable.

Strategies to maximize therapeutic opportunities for melatonin derivatives

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The neurohormone melatonin (MLT) is involved in several (patho)physiological processes including sleep, depression, anxiety, pain perception, cancer and neurodegenerative diseases (1). MLT has a pleiotropic mechanism of action as it displays antioxidant effects, activates membrane receptors and interacts with intracellular mediators such as the transcription factor Nrf2 and the MT₃ binding site (quinone reductase 2). These effects have formed the basis for the rational design of different melatonin derivatives to maximize their therapeutic potential in a wide range of established and novel indications. In particular, different ligand-based techniques, such as pharmacophore models, QSAR, conformational constraints or molecular simplification, allowed to design and develop a high number of structurally diverse classes of melatonin receptor ligands, which are employed in the treatment of sleep disturbances and depression, or are under development for novel therapeutic applications.

In this presentation, we report the design of melatonin membrane receptor ligands, based on the characterization of their pharmacophore elements and of their conformational space. Different substitution patterns allowing occupation of specific regions at the binding site have led to compounds selective for each of the two *G-protein coupled melatonin receptor* subtypes, MT₁ or MT₂ (2,3). These selective MLT receptor ligands displayed interesting sleep-inducing, antinociceptive or anxiolytic properties (4,5).

Recent investigations have also illustrated the potential for drug combination strategies to widen and further enhance the therapeutic opportunities. Information gained from pharmacophore and receptor/enzyme models has been applied to the design and optimization of multi-target compounds, which combine the interesting properties of melatonin receptor ligands with other, potentially synergistic, pharmacological activities.

Melatonin has also shown receptor-independent actions, mainly related to its radical scavenging ability and enhancement of antioxidative defense systems. These effects are evaluated for many therapeutic applications, for example, in neurodegenerative pathologies, cancer treatment, or to counteract skin aging. In this context, we designed a series of melatonin derivatives linked to ROS-responsive arylboronate triggers to investigate their potential cytoprotective activities against H₂O₂-induced oxidative damage.

References: 1. Liu J, Clough SJ, Hutchinson AJ, Adamah-Biassi EB, Popovska-Gorevski M, Dubocovich ML. *Annu. Rev. Pharmacol. Toxicol.* **2016**, *56*, 361-83. 2. Rivara S, Lodola A, Mor M, Bedini A, Spadoni G, Lucini V, Pannacci M, Fraschini F, Scaglione F, Sanchez RO, Gobbi G, Tarzia G. *J. Med. Chem.* **2007**, *50*, 6618-26. 3. Spadoni G, Bedini A, Lucarini S, Mari M, Caignard DH, Boutin JA, Delagrangre P, Lucini V, Scaglione F, Lodola A, Zanardi F, Pala D, Mor M, Rivara S. *J. Med. Chem.* **2015**, *58*, 7512-25. 4. Ochoa-Sanchez R, Comai S, Lacoste B, Bambico FR, Dominguez-Lopez S, Spadoni G, Rivara S, Bedini A, Angeloni D, Fraschini F, Mor M, Tarzia G, Descarries L, Gobbi G. *J. Neurosci.* **2011**, *31*, 18439-52. 5. Lopez-Canul M, Palazzo E, Dominguez-Lopez S, Luongo L, Lacoste B, Comai S, Angeloni D, Fraschini F, Boccella S, Spadoni G, Bedini A, Tarzia G, Maione S, Granados-Soto V, Gobbi G. *Pain* **2015**, *156*, 305-17.

Comunicazioni Orali

Discovery of Store-Operated Calcium Entry modulators as an effective treatment for calcium-related rare genetic diseases

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Store Operated Calcium Entry (SOCE) is the major route of replenishment of intracellular Ca^{2+} in response to depletion of Ca^{2+} stores in the endoplasmic reticulum (ER). The key molecular components of SOCE machinery are STIM proteins, which function as endoplasmic reticulum calcium sensor, and Orai channels.⁽¹⁾

Recently, several human diseases have been associated with mutations in these two proteins: loss-of-function mutations result in SCID-like immunodeficiencies, while gain-of-function mutations cause Stormorken syndrome, York platelet syndrome and tubular aggregate myopathy (TAM).⁽²⁾ These pathologies are rare diseases with an estimated prevalence of 1 every 500 births and are currently without therapy.

Due to the recent discovery of STIM and Orai proteins, structural information is poor and only a low resolution crystal structure of Orai from *Drosophila melanogaster* has been described.⁽³⁾ Therefore, the search for SOCE modulators perfectly suited to a click chemistry approach. Starting from the structure of known pyrazole derivatives (BTP, Pyr),⁽⁴⁾ a library of candidates was designed and synthesized. Screening was performed by calcium microfluorography in wild type and mutated human embryonic kidney (HEK-293T) cells and led to the identification of both SOCE activators and inhibitors (Figure 1). Selected compounds were further evaluated by electrophysiological experiments and by *ex vivo* studies on muscle biopsies from patients affected by TAM.⁽⁵⁾

Chemical synthesis, metabolic stability profile and biological evaluation of this class of compounds will be discussed.

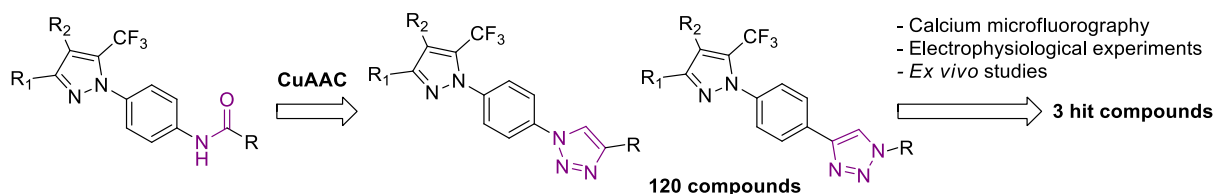


Figure 1

References: 1. A. Verkhratsky, V. Parpura, *Neurosci. Bull.* **2014**, *30*, 125. 2. R.S.Lacruz, S. Feske, *Ann. N.Y. Acad. Sci.* **2015**, *1356*, 45. 3. X. Hou, L. Pedi, M.M. Diver, S.B. Long, *Science* **2012**, *338*, 1308. 4a. S. Kyyonaka, K. Kato, M. Nichida, K. Mio, T. Numaga, Y. Sawaguchi, T. Yoshida, M. Wakamori, E. Mori, T. Numata, M. Ishii, H. Takemoto, A. Ojida, K. Watanabe, A. Uemura, H. Kurose, T. Morii, T. Kobayashi, J. Sato, C. Sato, I. Hamachi, Y. Mori, *Proc. Natl. Acad. Sci.* **2009**, *106*, 5400; 4b. H. Schleifer, B. Doleschal, M. Lichtenegger, R. Oppenrieder, I. Derler, I. Frischauf, T.N. Glasnov, C.O. Kappe, C. Romanin, K. Groschner, *Br. J. Pharmacol.* **2012**, *167*, 1712. 5a. B. Riva, A. Griglio, M. Serafini, S. Aprile, G. Grosa, M. Garibaldi, E. Bertini, G. Tasca, D. Alansary, C. Distasi, B. Niemeyer, T. Pirali, A.A. Genazzani, *Cell Chem. Biol.* Submitted. 5b. "Modulators of SOCE, compositions and use thereof"; T. Pirali, B. Riva, A.A. Genazzani; ITUA20164199.

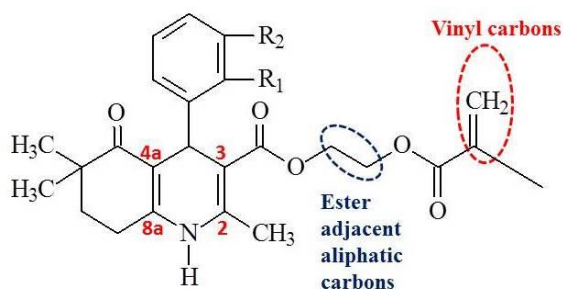
A new generation of dihydropyridines: photodegradation and photostabilization strategies

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1,4-dihydropyridine derivatives (DHPs) are used in the treatment of the hypertension and angina as L-type calcium channel blockers. Exposure of these molecules to natural or artificial light leads to a significant production of singlet oxygen, superoxide, or both of them, which in most cases are responsible of photosensitive/phototoxic effects (1). In a previous study (2), a quantitative structure-property relationships (QSPR) model, correlating the light sensitivity against theoretical molecular descriptors, was developed for a set of 1,4-dihydropyridine drugs. The influence of different substituents on both benzene and pyridinic rings was evaluated in terms of hydrophobic, electronic and steric parameters.

According to these results, a series of new condensed DHP analogues was synthesized by microwave irradiation method. The muscle relaxant activity was evaluated and compared with that of nifedipine. All the synthesized compounds were subjected to photodegradation tests, in accordance with the ICH international rules (3). Concentration of parent compounds and by-products was calculated by multivariate curve resolution - alternating least squares (MCR-ALS) applied to the spectral data. The kinetic degradation parameters of all compounds were calculated and all the DHPs photoproducts estimated by MCR-ALS (4). Because of their known instability to light, several studies have also proposed or are under investigation for producing formulations able to provide a valid photoprotection for this class of drugs. In recent years, supramolecular systems have been proposed as a means to increase the stability of drugs to light and many studies have reported significant results (5). In particular, liposomes and cyclodextrins have shown the most promising results due to their ability to improve aqueous solubility, chemical stability and bioavailability for several drug molecules by incorporating them in their core.



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References: 1. Ioele G, Oliverio F, Andreu I, De Luca M, Miranda MA, Ragno G. Different photodegradation behavior of nifedipine under natural and forced irradiation. *J. Photochem. Photobiol. A: Chem.* 215, 205-213 (2010). 2. Ioele G, De Luca M, Oliverio F, Ragno G. Prediction of photosensitivity of 1,4-dihydropyridine antihypertensives by quantitative structure-property relationship. *Talanta* 79, 1418-1424 (2009). 3. International Conference on Harmonization. ICH Q1A(R2), Stability testing of new drug substances and products, 2003, IFPMA, Geneva. 4. Ioele G, Gündüz MG, De Luca M, Simone R, Şafak C, Muzzalupo R, Ragno G. Photodegradation studies of 1,4-dihydropyridine compounds by MCR analysis on UV spectral data. *Future Med Chem.* 8 (2), 107-115 (2016). 5. Ragno G, Risoli A, Ioele G, Cione E, De Luca M. Photostabilization of 1,4-dihydropyridine antihypertensives by incorporation into β -cyclodextrin and liposomes. *J. Nanosci. Nanotech.* 6, 2979-2985 (2006).

In silico approaches supporting pharmaceutical analysis enigmas

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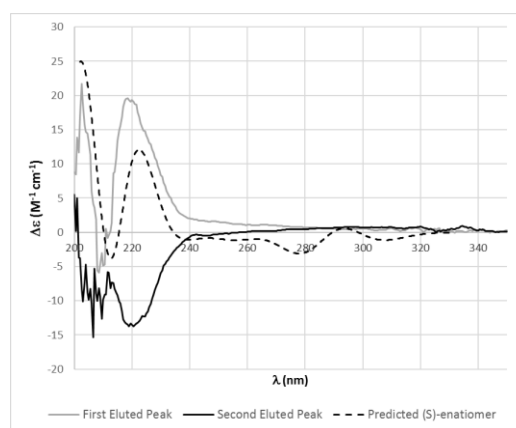
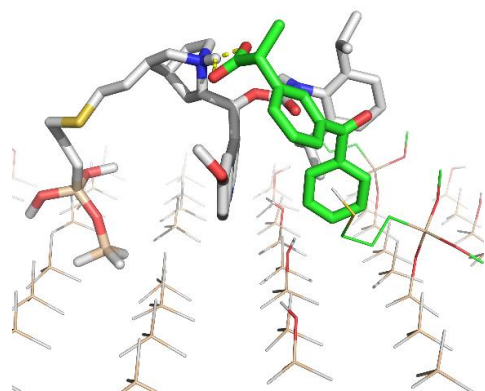
The determination of the enantiomeric elution order (EEO) is a key issue in chiral HPLC analysis. The knowledge of the absolute configuration (AC) of the more- and the less-retained enantiomer in a chiral chromatography environment is of primary importance for several reasons.

First of all, it allows organic and medicinal chemists to quickly evaluate the outcome of an enantioselective synthesis procedure (often measured in terms of enantiomeric excess value). Furthermore, in preparative chromatography applications it allows analytical and medicinal chemists to properly correlate the AC of a definite compound with one or more of its observed or measured properties (such as a specific biological activity).

Also importantly, from a theoretical point of view, understanding the fine mechanism governing the EEO means understanding the network of interactions and perturbations responsible for the stereoselective analyte (selectand, SA)-selector (SO) binding association in a definite asymmetric setting.

Cheminformatic procedures as well as molecular mechanics and quantum chemistry techniques can be successfully applied to address chirality related problems especially when enantiomerically pure reference standards are missing. (1-3)

A number of methods developed in our laboratories to explain the mechanism of enantioselective recognition and hence to rationalize and even foresee the EEO of pharmaceutically relevant compounds in chiral chromatographic settings characterized by either low- or high-molecular weight SOs will be presented.



References: 1. Carotti A., Ianni F., Camaioni E., Pucciarini L., Marinozzi M., Sardella R., Natalini B. (2017). N-Decyl-S-trityl-(R)-cysteine, a new chiral selector for "green" ligand-exchange chromatography applications. *JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS*, ISSN: 0731-7085, doi: 10.1016/j.jpba.2017.02.009 2. Carotti A., Ianni F., Sabatini S., Di Michele A., Sardella R., Kaatz G. W., Lindner W., Cecchetti V., Natalini B. (2016). The "racemic approach" in the evaluation of the enantiomeric NorA efflux pump inhibition activity of 2-phenylquinoline derivatives. *JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS*, vol. 129, p. 182-189-189, ISSN: 0731-7085, doi: 10.1016/j.jpba.2016.07.003 3. Sardella R., Carotti A., Manfroni G., Tedesco D., Martelli A., Bertucci C., Cecchetti V., Natalini B (2014). Enantioresolution, stereochemical characterization and biological activity of a chiral large-conductance calcium-activated potassium channel opener. *JOURNAL OF CHROMATOGRAPHY A*, vol. 1363, p. 162-168, ISSN: 0021-9673, doi: 10.1016/j.chroma.2014.06.020.

2,2-Dioxido-2,1-bentothiazines as new allosteric inhibitors of DENV NS5 RNA-dependent RNA polymerase

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Dengue and the other flaviviruses are (re)emerging pathogens that are rapidly spreading from tropical to other areas of the World (1). Flavivirus infections cause flu-like symptoms that may evolve toward severe and sometimes fatal conditions (1). Furthermore, no drugs are available against these viruses (2). Targeting the viral NS5 RNA-dependent RNA polymerase (RdRp) may represent an attractive strategy to find anti-flavivirus drugs (3). However, few anti-NS5 RdRp chemotypes have been reported and often they are devoid of antiviral activity in cells; moreover, no inhibitors are currently in clinical development.

With the aim to identify new NS5 RdRp inhibitors, we decided to re-task our in-house HCV NS5B inhibitors focused library (Figure 1). Representative compounds for the different chemical families were screened in vitro against Dengue 3 NS5 RdRp and the 2,2-dioxido-2,1-bentothiazines resulted promising hits with IC₅₀ ranging from 11 to >50 μM. Biochemical evaluation of the entire series led to the identification of derivatives **8** and **10** able to inhibit the enzyme with 0.6 and 0.9 μM, respectively. Structure-activity relationships highlighted a key role for the C-4 benzoyl group and as suitable a halosubstituted C-6 phenoxy group. Kinetic studies for representative hit **8** indicated an allosteric mechanism consistently with a mixed type of enzyme inhibition. In agreement with the biochemical data, the predicted binding modes of representative molecules confirmed the key contribution of the benzoyl and the phenoxy regions for the binding at the so-called N pocket of the RdRp thumb domain. Unfortunately, compounds **8** and **10** were not active against DENV and other flaviviruses in cells. Thus, we speculated that modest cell permeability coupled with an ex vivo low stability of the benzoyl ester could explain the lack of antiviral activity.

However, few anti-DENV RdRp chemotypes are known and most of them are devoid of antiviral activity in cells. Therefore, the results obtained in this work indicated the 2,2-dioxido-2,1-bentothiazine scaffold as promising anti-DENV RdRp chemotype and the information acquired will drive future chemical optimization to provide new potent non-nucleoside NS5 RdRp inhibitors effective also in cell lines.

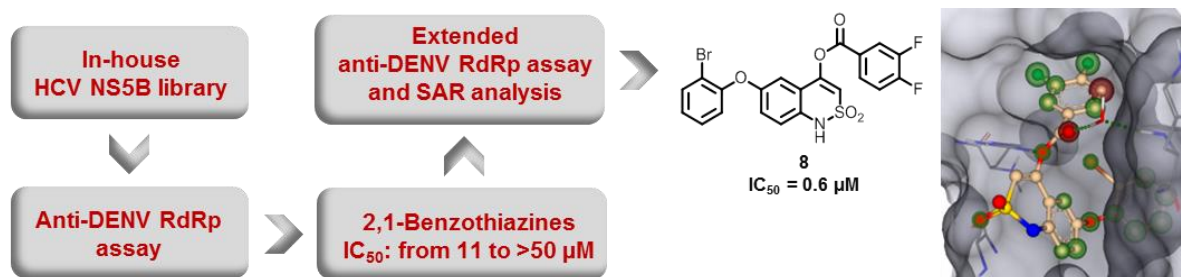


Figure 1. Workflow: from the in vitro screening of the focused library to the identification of compound 8 as potent DENV RdRp inhibitor

References: 1. Mackenzie, J.S.; *et al. Nat. Med.* **2004**, *10*, S98-S109. 2. Kok, W.M. *Expert Opin. Drug Discov.* **2016**, *11*, 433. 3. Lim, S.P.; *et al. Antiviral Res.* **2015**, *119*, 57.

Structure-based identification of HIV-1 nucleocapsid protein inhibitors active against wild-type and drug-resistant HIV-1 strains

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AIDS is still one of the leading causes of death worldwide. Current drugs that target the canonical steps of HIV-1 life cycle are efficient in blocking viral replication, but are unable to eradicate HIV-1 from infected patients.(1) Moreover, drug resistance (DR) is often associated with the clinical use of these molecules, thus raising the need for novel drug candidates as well as novel putative drug targets. In this respect, pharmacological inhibition of the highly conserved and multifunctional nucleocapsid protein (NC) of HIV-1 is considered a promising alternative to current drugs and, particularly, to overcoming DR.(2,3)

Following our research strategy, in the last eight years we devoted several efforts to targeting NC and understanding molecular determinants for its potent inhibition by different chemotypes, thus contributing to validate NC as antiretroviral target.(2,4,5,6)

Within the framework of the THINPAD project – FP7,(7) we recently established a multidisciplinary approach combining in silico screening, fluorescence-based molecular assays and cellular antiviral assays to discover non-covalent NC inhibitors. Among multiple lead compounds identified, nordihydroguaiaretic acid (NDGA) emerged as a novel natural product inhibitor of NC. By using NMR, mass spectrometry, fluorescence spectroscopy and molecular modelling, NDGA was found to act through a dual mechanism of action. First, the molecule recognizes and binds non-covalently the NC, which results in the inhibition of the nucleic acid chaperone properties of NC. In a second step, chemical oxidation of NDGA induces a potent chemical inactivation of the protein, although the binding occurs in a non-covalent manner as highlighted by mass spectrometry. Overall, the NDGA inhibits NC and the replication of wild-type and drug-resistant HIV-1 strains in the low micromolar range with moderate cytotoxicity, that makes it a profitable tool compound as well as a good starting point for the development of pharmacologically relevant NCIs.

References: 1. Olender, S. A.; Taylor, B. S.; Wong, M.; Wilkin, T. J. *CROI. Top Antivir Med* **2015**, 23, 28-45. 2. Mori, M.; Kovalenko, L.; Lyonnais, S.; Antaki, D.; Torbett, B. E.; Botta, M.; Mirambeau, G.; Mely, Y. *Curr Top Microbiol Immunol* **2015**, 389, 53-92. 3. Demene, H.; Dong, C. Z.; Ottmann, M.; Rouyez, M. C.; Jullian, N.; Morellet, N.; Mely, Y.; Darlix, J. L.; Fournie-Zaluski, M. C.; Saragosti, S.; et al. *Biochemistry* **1994**, 33, 11707-16. 4. Mori, M.; Manetti, F.; Botta, M. *J Chem Inf Model* **2011**, 51, 446-54. 5. Mori, M.; Nucci, A.; Lang, M. C.; Humbert, N.; Boudier, C.; Debaene, F.; Sanglier-Cianferani, S.; Catala, M.; Schult-Dietrich, P.; Dietrich, U.; Tisne, C.; Mely, Y.; Botta, M. *ACS Chem Biol* **2014**, 9, 1950-5. 6. Mori, M.; Schult-Dietrich, P.; Szafarowicz, B.; Humbert, N.; Debaene, F.; Sanglier-Cianferani, S.; Dietrich, U.; Mely, Y.; Botta, M. *Virus Res* **2012**, 169, 377-87. 7. <http://www.thinpad.unisi.it/>

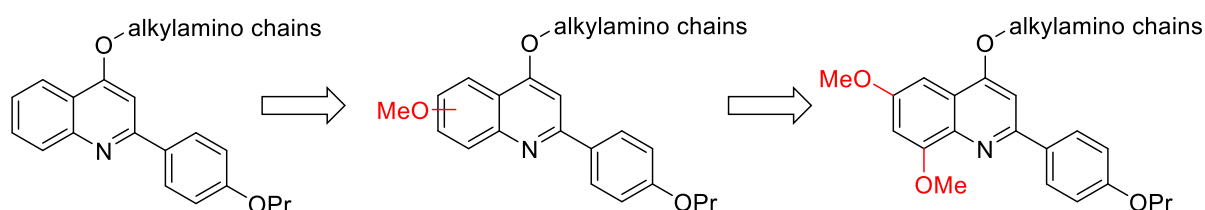
Improvement of *Staphylococcus aureus* NorA efflux pump inhibition by methoxy group introduction on 2-phenylquinoline core

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Antimicrobial resistance is nowadays a public health threat by causing several acute and chronic infections worldwide. The rapid insurgence of drug resistance in nosocomial strains is faster than the discovery of new antimicrobials having an innovative mechanism of action.(1) Thus, the strategy to sustain the antimicrobial activity of an approved antibiotic with a helper compound devoid of any antibacterial activity but having the capability to restore drug sensibility against resistant strains is taking hold. Therefore, since microbial efflux pumps are recognized as a main contributor to a basal or high level of resistance in several different microbes, to find an efflux pump inhibitor (EPI) can result an excellent strategy to restore strain sensibility to extruded antibacterials. The most expressed efflux pump in *Staphylococcus aureus* is NorA, associated with fluoroquinolone resistance and responsible for extrusion of unrelated substances out of the bacterial cell.(2)

Previously, we reported a series of 2-phenylquinoline derivatives as potent NorA EPIs.(3,4) Starting from these promising results and maintaining the best groups resulted from the preliminary SAR data, the introduction of a methoxy group, a substituent frequently recurrent in natural or synthetic NorA EPIs, was planned. Thus, new series of C-5, C-6, C-7, or C-8 (mono)methoxy-2-phenylquinoline derivatives were synthesized and tested.(5) Hence, the interesting results obtained both in terms of NorA EPI activity and synergistic activity with ciprofloxacin (CPX) against resistant *S. aureus* strains prompted us to further explore the double introduction of methoxy groups on the same core thereby affording dimethoxy-2-phenylquinoline derivatives.



Therefore, a new set of 6,8-dimethoxy-2-phenylquinoline derivatives was synthesized and tested primarily by ethidium bromide (EtBr) assays in *S. aureus* strain overexpressing *norA* gene. Finally, compounds endowed with an EtBr efflux inhibition $\geq 80\%$ and devoid of antibacterial activity were assayed in synergism with CPX against a panel of resistant *S. aureus* strains. Results of this study will be presented.

References: 1. L.J. Piddock, *Lancet Infect Dis*, **2012**, *12*, 249. 2. D. Patel, C. Kosmidis, SM. Seo, and GW. Kaatz, *Antimicrob Agents Chemother*, **2010**, *54*, 5070. 3. S. Sabatini, F. Gosetto, G. Manfroni, O. Tabarrini, GW. Kaatz, D. Patel, and V. Cecchetti, *J Med Chem*, **2011**, *54*, 5722. 4. S. Sabatini, F. Gosetto, N. Iraci, ML. Barreca, S. Massari, L. Sancineto, G. Manfroni, O. Tabarrini, M. Dimovska, GW. Kaatz, and V. Cecchetti, *J Med Chem*, **2013**, *56*, 4975. 5. Manuscript in progress.

Blocking PA-PB1 protein-protein interaction with the aid of molecular modelling to counteract Influenza A Virus

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A still worrying health burden responsible for important consequences on the global morbidity, mortality and economy is influenza, a seasonal disease commonly known as “flu”.(1) It is caused by RNA viruses that infect vertebrates and belong to either one of the three genera of the *Orthomyxoviridae* family. Among these, influenza A is accountable for severe upper respiratory diseases in humans that occur seasonally with epidemic and sometimes pandemic proportions.(2) Anti-influenza countermeasures are available, however the existing anti-influenza vaccine needs annual updating and there is a rapid emergence of viral strains resistant to available therapy, making the need for antiviral drugs that exploit novel mechanisms of action urgent.(3) The viral RNA polymerase (RdRp) is a heterotrimer essential for viral replication and less prone to mutations than current viral targets. In particular, the interaction between two of its three subunits (PA, and PB1) is essential for RdRp activity and viral infectivity, making the disruption of this protein-protein interaction a promising drug design strategy.(4)

Through a virtual screening procedure we have identified a novel class of 3-cyano-4,6-diphenylpyridines that inhibit the PA-PB1 interaction.(5) In our model, these molecules bind to PA in the site of binding of PB1, superposing very well with its N-terminal residues. We chemically modified this scaffold aiming the optimization of the compounds' activity through the enhancement of interactions with PA.(6) In this presentation, the good cytotoxicity profile of the molecules and both their ability of disrupting the PA-PB1 interaction and antiviral activity will be discussed. Furthermore, the results of the study of the mechanism of action, clarified through molecular modelling simulations, will be discussed.

References: 1. WHO. Fact Sheet 211 March 2014 <http://www.who.int/mediacentre/factsheets/fs211/en/>; 2. Palese et al, *Fields Virology 5th Ed.* Lippincott Williams and Wilkins: Philadelphia (2007); 3. Webby et al, *Science* **2003**, 302, 1519-1522; 4. Perez et al, *J Virol* **2001**, 75, 8127-8136; 5. Tintori et al, *BMCL* **2014**, 24, 280-282; 6. Trist et al, *J Med Chem* **2016**, 59, 2688-2703.

Quantitative *in vivo* evaluation by LC-ESI-MSⁿ analysis of adenosine 5'-tetrphosphate (Ap4), a nucleotide related to nicotinamide phosphoribosyltransferase activities (NAMPT)

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Nicotinamide phosphoribosyltransferase (NAMPT) is the rate-limiting enzyme in nicotinamide adenine dinucleotide (NAD) synthesis, that is an essential coenzyme for maintaining the cellular homeostasis (1,2). Adenosine 5'-tetrphosphate (Ap4) is a natural nucleotide known as the most potent vasoactive purinergic mediator in mammals (3). Preliminary *in vitro* (4) studies have shown that Ap4 production is related to NAMPT activity. However, it has never been reported whether NAMPT can catalyze the synthesis of Ap4. The main aim of the work was to develop a new bioanalytical LC-ESI-MSⁿ method to quantify Ap4 in engineered B16 Melanoma cells. Secondly, to quantify, with the same method, all the analytes (adenosine 5'-diphosphate, adenosine 5'-triphosphate, nicotinamide, nicotinamide mononucleotide and NAD) involved in NAD homeostasis to better understand the two different NAMPT activities. In order to investigate NAMPT PRTase and ATPase activities, various cells lines were analyzed which differ each other for intracellular NAMPT levels. As result, intracellular Ap4 levels were increased more than two times in cells over-expressing NAMPT (v. WT cells; $p < 0.05$) and were significantly reduced in cells silenced for the enzyme (v. WT cells; $p < 0.05$). Moreover, WT cells treated with FK866, confirmed that it is a selective inhibitor of NAMPT PRTase activity, but not of NAMPT ATPase activity. In fact, the data collected showed a significant downregulation of NAD levels but in contrast, an upregulation of intracellular Ap4 levels (v. WT cells; $p < 0.01$) (5). This indicates that both the reactions catalyzed by NAMPT should be equally considered when investigating the effect of NAMPT inhibitors. In conclusion, the study reports that Ap4 production in melanoma cells is dependent on NAMPT expression and highlights novel mechanisms by which this enzyme could exert the plethora of actions that are attributed to it.

References: 1. A. A. Grolla, et al., *Pigment Cell & Melanoma Research* **28**, 718-729 (2015). 2. U. Galli, C. Travelli, et al., *Journal of Medicinal Chemistry* **56**, 6279-6296 (2013). 3. J. Pintor, et al. *The Journal of Pharmacology and Experimental Therapeutics* **308**, 468-473 (2003). 4. E. S. Burgos. et al. *Biochemistry* **47**, 11086-11096 (2008). 5. A. Amici, A. A. Grolla, et al., *Cell Chemical Biology* **24**, pages 1-12 (2017).

***Thymus vulgaris* L. essential oil in gastrointestinal diseases**

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In the last few years an increase in the scientific interest for essential oils has been observed (1). Recent studies have proposed their multiple effects, from direct effects on autonomic nervous system to a synergic activity with antibiotic drugs, aiming at membrane structure disruption and bacterial cell permeabilisation. The increasing emergence of drug-resistant bacteria led the research also towards the use of essential oils as potential alternatives. Moreover, some essential oils showed also antifungal properties and could represent viable therapeutic strategies addressed to drug-resistant fungal strains.



Thymus vulgaris L.

Essential oil obtained from *Thymus vulgaris* L., a perennial plant belonging to Lamiaceae family, has been known since long time for its biological effects (2). The lipophilic nature of its secondary components allows them to cross cell wall, alter membrane composition and increase membrane fluidity, leading to leakage of ions and cytoplasmic molecules.

The aim of this study is the investigation of the chemical composition of *Thymus vulgaris* L. essential oil and of its biological activities towards gastrointestinal tissues and microorganisms.

An analytical chemical profiling approach with quali-quantitative purposes was exploited to study *Thymus vulgaris* L. secondary metabolites, by means of liquid chromatography and capillary electrophoresis coupled to diode array detection and mass spectrometry (LC-MS/MS and CE-DAD). *Thymus vulgaris* L. essential oil was studied towards the main pathogenic and non-pathogenic bacterial and fungal species in the gastrointestinal system. Similarly, in the guinea pig, its effects on intestinal basal and stimulated contractility were investigated. These overall preliminary results suggested that *Thymus vulgaris* L. essential oil may be useful in gastrointestinal inflammatory diseases.

References: 1. Sharifi-Rad J, Sureda A, Tenore GC, Daglia M, Sharifi-Rad M, Valussi M, Tundis R, Sharifi-Rad M, Loizzo MR, Ademiluyi AO, Sharifi-Rad R, Ayatollahi SA, Iriti M, *Biological activities of essential oils: from plant chemoecology to traditional healing systems*. *Molecules* 22 (2017) 70. 2. Sakkas H, Papadopoulou C, *Antimicrobial activity of basil, oregano, and thyme essential oils*. *J Microbiol Biotechnol* 27 (2017) 429-438.

Structural modification of the β -sheet ARC repressor: design, conformational analysis and binding properties of linear and cyclic ARC mimetics

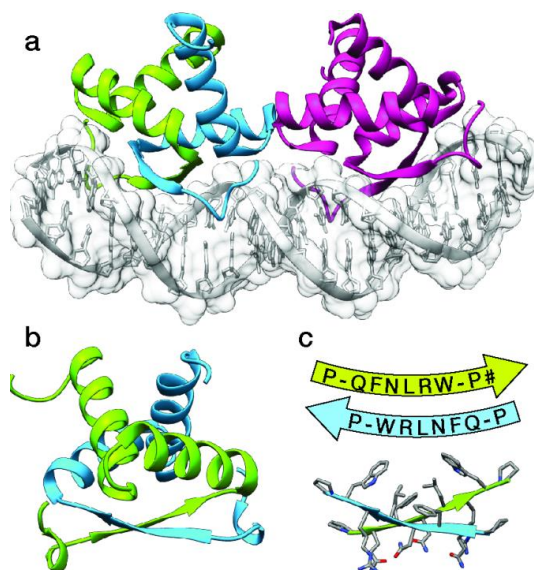
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ARC repressor (apoptosis repressor with caspase recruitment domain) is an inhibitor of apoptosis critically involved in many physiological and pathological conditions (1). In human being ARC is primarily expressed into striated muscle tissue, which normally doesn't undergo a rapid cell turnover, this suggest that it may play a protective role on the muscular fibers and possible implications in the prevention against the Duchenne Muscular Dystrophy and several tumors (2). In this work we report the synthesis and binding properties of novel β -sheet and β -hairpin ARC mimetics, based on the amino acid sequence of the native β -sheet domain (3). Our data showed unspecific interactions between the novel chemical entities and the DNA sequence, providing more insights into the biomolecular recognition process and laid the groundwork for the design of novel β -sheet folded peptides as valuable substitutes of transcription factor proteins in drug's therapy.



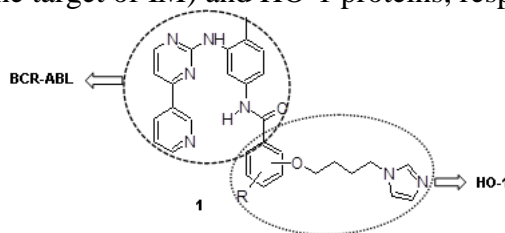
References: 1. Darnell, J. E. Transcription factors as targets for cancer therapy. *Nat. Rev. Cancer* **2002**, *2*, 740-749. 2. Look, A. T. Oncogenic transcription factors in the human acute leukemias. *Science* **1997**, *278*, 1059-1064. 3. Stefanucci, A.; Mosquera, J.; Vázquez, E.; Mascareñas, J.L.; Novellino, E.; Mollica, A. Synthesis, characterization and DNA binding profile of a macrocyclic β -Sheet analogue of ARC protein. *ACS Med. Chem. Lett.* **2015**, *6*, 1220-1224.

Targeting Heme Oxygenase-1 to Overcome Imatinib Resistance in Chronic Myeloid Leukemia

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Heme oxygenase-1 (HO-1) is the enzyme catalyzing the rate-limiting oxidative degradation of cellular heme into free iron, carbon monoxide (CO) and biliverdin, which is then rapidly converted into bilirubin (1). HO-1 is considered a survival molecule in various stress-related conditions (2). By contrast, growing evidences suggest that HO-1 is a survival-enhancing molecule also in a number of solid and blood cancers, promoting carcinogenesis, tumor progression, and chemo-resistance. Chronic myeloid leukemia (CML) is currently therapeutically well treated with tyrosine kinase inhibitors (TKIs) such as Imatinib (IM) and its congeners, nevertheless resistance to all kind of current drugs persists in a number of patients. Therefore, identification of new eligible targets that may improve CML therapy is of general interest. Recent studies provided evidence that silencing HO-1 in IM resistant CML cells by siRNA resulted in induction of apoptosis, restoring IM activity (3, 4). To support these studies, we recently discovered that two novel imidazole-based HO-1 inhibitors were able to restore IM sensitivity in IM resistant LAMA-84 R cells (5). These results confirmed that inhibition of HO-1 activity can be a viable new anticancer strategy and co-administration of a HO-1 inhibitor with IM opens up new perspectives in the management of IM resistance. An alternative approach to the co-administration of two agents would be to combine multiple activities within the same compound providing a superior therapeutic effect and side effect profile compared to the action of single molecules. In this respect, conjugation of two biologically active molecules into one hybrid compound can be beneficial for the treatment of diseases with complex etiologies such as cancer (6). On these bases, the aim of this study is the design, synthesis and evaluation of antitumor properties of a new series of hybrid compounds obtained combining IM structure with our HO-1 inhibitors (1). These hybrids contain an IM-like portion and an aryloxyalkylimidazole moiety, needed for the interaction with BCR-ABL (the target of IM) and HO-1 proteins, respectively.



Multiple biological tests are in progress, including evaluation of HO-1 enzymatic activity, quantification of BCR-ABL, and viability of sensitive and resistant CML cell lines. Finally, in order to improve pharmacokinetic properties, reduce the undesired distribution to off target tissues, concentrate the drug in the target organ, and increase the half-life, Styrene Maleic Acid (SMA) nanoparticles containing the most interesting HO-1/TKIs will be prepared. Results obtained so far will be presented at the meeting.

References: 1. Abraham N G et al, *Pharmacol. Rev.* 60 (2008) 79, 2. Gozzelino R, *Annu. Rev. Pharmacol. Toxicol.* 50 (2010) 323, 3. Mayerhofer M et al, *Blood*, 111, (2008), 2200, 4. Tibullo D et al, *Curr Pharm Des*, 19, (2013), 2765, 5. Salerno L et al, *Bioorg Med Chem*, 21, (2013), 5145, 6. Srinivasarao M et al, *Nature Rev Drug Discovery*, 14, (2015), 203.

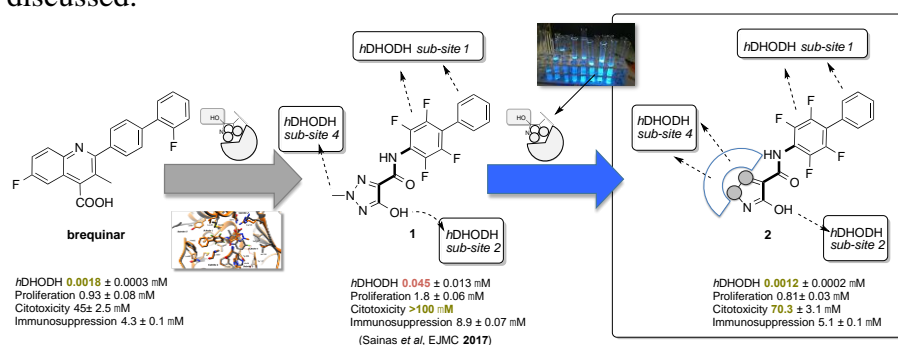
Potent human *dihydroorotate dehydrogenase* (*hDHODH*) inhibitors obtained by scaffold-hopping approaches: from the theoretical design to the *in vivo* evaluation.

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Human dihydroorotate dehydrogenase (*hDHODH*) catalyzes the rate-limiting step in the *de novo* pyrimidine biosynthesis where dihydroorotate (DHO) is converted to orotate (ORO). Being already validated as therapeutic target for the treatment of autoimmune diseases,[1] as *rheumatoid arthritis* or *multiple sclerosis*, in the fall 2016[2] *hDHODH* was associated to *acute myelogenous leukemia* (AML), a disease that has not seen a new therapies in four decades being *cytarabine* still representing the last significant advance.[3] This discovery opened a totally new prospective in *hDHODH* field. Starting from *brequinar*, one of the most potent known *hDHODH* inhibitors, and by applying innovative *scaffold-hopping* replacement, we recently designed a new generation of potent and selective *hDHODH* inhibitors.[4] Their general structure is characterized by a biphenyl moiety joined through an amide bridge with an acidic hydroxyazole scaffold (*hydroxylated thiadiazole*, *pyrazole*, *triazole* and *furazan*). All the compounds presented nano-molar activity on the isolated *hDHODH*, just one digit from the *lead* *brequinar*. The best compound the series, the hydroxytriazole (**1**), also showed *in vitro* better drug-like properties.

In this occasion, we move ahead presenting a second generation of inhibitors designed by using as hydroxyazole a novel fluorescent isostere of carboxylic acid. Using a combination of *structural*- and *ligand*- optimization strategies we obtained compound **2** (see Figure), this latter able to reach *brequinar* *hDHODH* potency levels although using a different scaffold. Theoretical design, modeling, synthesis, SAR, fluorescent properties, X-ray crystallographic poses, biological assays (cell viability, proliferation, cytotoxicity, immunosuppression), ADME and *in vivo* preliminary experiments are here presented and discussed.



References: 1. Lolli, M.L., et al., *Use of human Dihydroorotate Dehydrogenase (hDHODH) inhibitors in autoimmune diseases and new perspective in cancer therapy*. Recent Patents on Anti-Cancer Drug Discovery, 2017. **Committed review (submitted)**. 2. Sykes, D.B., et al., *Inhibition of Dihydroorotate Dehydrogenase Overcomes Differentiation Blockade in Acute Myeloid Leukemia*. Cell, 2016. **167**(1): p. 171-186.e15. 3. Tzelepis, K., et al., *A CRISPR Dropout Screen Identifies Genetic Vulnerabilities and Therapeutic Targets in Acute Myeloid Leukemia*. Cell Reports, 2016. **17**(4): p. 1193-1205. 4. Sainas, S., et al., *Design, synthesis, biological evaluation and X-ray structural studies of potent human dihydroorotate dehydrogenase inhibitors based on hydroxylated azole scaffolds*. European Journal of Medicinal Chemistry, 2017. **129**: p. 287-302.

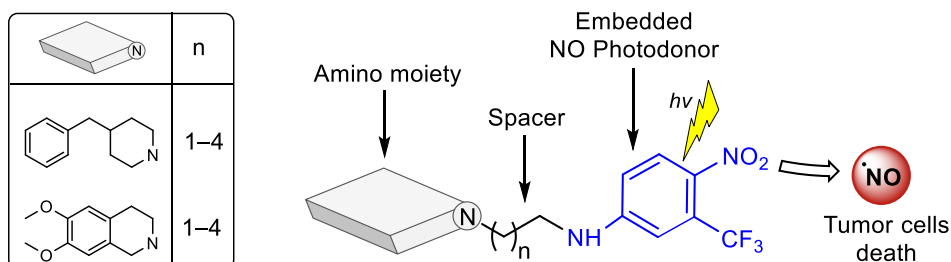
Development of Sigma Receptors Nitric Oxide Photodonor Ligands with Antiproliferative Activity

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Nitric oxide (NO) is a short-lived gas with recognized important roles in various biological and physiological processes (1). Modulation of NO levels seems to have benefits in the treatment of cancer. However, due to its reactive and unstable gaseous nature, the spatiotemporally well-controlled NO exposition to cancer sites is challenging. For selective and effective delivery of cytotoxic NO, the use of photo-controllable NO donors is useful to induce a NO-dependent cellular response under light irradiation (2).

Additionally, one of the major issues of conventional anticancer drugs is the high toxicity towards proliferating cells, including normal cells (3). A strategy for minimizing this toxicity may result by conjugating the therapeutic agent with a tumor-cell-specific ligand, selectively recognized by a biological target overexpressed in cancer cells (4). Sigma (σ) receptors represent a class of proteins useful for cancer cells targeted drug delivery, being highly overexpressed in cancer cells (5).



In light of the aforementioned, we turned our interest to the combination of σ receptors chemical moieties with a NO photodonor scaffold, developing a new series of hybrid ligands. The novel compounds are made of a portion able to bind to the overexpressed σ receptors, the 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline or 4-benzylpiperidine amino moieties, linked to a NO photodonor scaffold, a 4-nitro-3-(trifluoromethyl)aniline, and separated by two to five methylene unit spacers. The new synthesized compounds have been evaluated in *in vitro* σ receptor binding assays and tested for their ability to release NO under appropriate light irradiation. Based on these previous findings, best compounds were selected for dark/light *in vitro* studies on tumorigenic and non-tumorigenic cell lines variously expressing σ receptors. Preminent results showed a significant antiproliferative activity on tumorigenic cells when photoactivated while no activity was observed in dark condition and in non-tumorigenic cells at chosen concentrations.

References 1. Fukumura, D. *Nature reviews* **2006**, 6, 521-534. 2. Carpenter, A. W. *Chemical Society reviews* **2012**, 41, 3742-3752. 3. Chari, R. V. *Accounts of chemical research* **2008**, 41, 98-107. 4. Jaracz, S. *Bioorganic & medicinal chemistry* **2005**, 13, 5043-5054. 5. Spitzer, D. *Cancer research* **2012**, 72, 201-209.

Discovery Of New, Potential Anti-Infective Compound Based On Carbonic Anhydrase Inhibitors By Rational Target-Focus Repurposing Approach

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Drug-repurposing or repositioning (DR) denotes an ensemble of tasks aimed to the identification of new drug indications for existing drugs, and is an alternative strategy in drug discovery program, both in pharma and academia. In academia, DR can be also translated into compound-recycling (CR) that is the repurposing of compound library collections already available in-house. Indeed, small molecules already synthesized, that resulted inactive against a target of interest, can be tested on other targets, leading to a new-purpose for an old molecule.¹

We embarked in a project aimed at the repurposing of the compound libraries available in-house, looking for a new potential applications for our compounds. In this scenario a rational target-based drug repurposing approach was applied.² The analysis of the data available in literature, for similar classes of chemical structures, allowed us to identify the Carbonic Anhydrase (CA, EC 4.2.1.1) metalloenzyme family as potential target of some of our compound series.

We proceed to the analysis of the fragments and chemotypes present in our library by applying the Maximum Common Substructure (MCS) decomposition approach. A thoroughly validated docking screenings protocol was combined with chemical synthesis³ and *in vitro* assays to disclose new potential CA inhibitors. Such a method allowed us to identify eleven compounds as potential CA inhibitors (CAIs).

The compounds were, therefore, tested *in vitro* for their ability to inhibits different classes and isoforms of CA superfamily, leading to the discovery of a CAIs active in the low μM range, but characterized by: (i) two unprecedented chemotypes CAIs inhibitors; (ii) an unprecedented selectivity profile for this class of molecules, with the ability to preferentially bind microbial CAs over the human ones; (iii) good Ligand Efficiency and Binding Efficiency Indexes (BEI) with respect to that marketed CAIs. Modelling studies together with *in vitro* assays allowed us to identify new CAI chemotypes, which are characterized by a low μM affinity for microbial CA.⁴ Even if, the activity profile of the compounds needs to be improved, the identified molecules can represent excellent hits to be further optimized in hits-to-lead campaigns.

References [1] M. Mori, Y. Cau, G. Vignaroli, I. Laurenzana, A. Caivano, D. Vullo, C. T. Supuran, M. Botta, *ACS Chem. Biol.* **2015**, *10*, 1964–1969; [2] J. Langedijk, A. K. Mantel-Teeuwisse, D. S. Slijkerman, M.-H. D. B. Schutjens, *Drug Discov. Today* **2015**, *20*, 1027–1034; [3] G. P. Vallerini, L. Amori, C. Beato, M. Tararina, X.-D. Wang, R. Schwarcz, G. Costantino, *J. Med. Chem.* **2013**, *56*, 9482–9495. [4] G. Annunziato, A. Angeli, F. D'Alba, A. Bruno, M. Pieroni, D. Vullo, V. De Luca, C. Capasso, C. T. Supuran, G. Costantino. *Chemmedchem*, **2016**, *17*, 1904-1914.

Discovery of novel diaryl sulfide derivatives as inhibitors of Trypanothione Reductase enzyme

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Trypanosomatidae protozoa are the causative agents of several tropical diseases, such as African sleeping sickness, Chagas's disease and various forms of leishmaniasis, causing millions of deaths every year mainly in the developing world.(1) Nowadays, no safe and efficacious drugs are available for the treatment of most of these neglected tropical diseases, and, furthermore, high costs and increasing number of drug-resistant pathogens render the treatment even difficult.(2,3) Therefore, there is a strong need to develop more efficient and affordable antiprotozoal compounds and identify new promising targets. In this context an innovative approach is targeting protein essential for the parasite survival but absent in the human host. Instead of the mammalian redox defense machinery based on glutathione, the trypanosomatid parasites possess trypanothione as the main defending system against oxidative damage.(4,5,6) Trypanothione (TSH₂) is kept in its reduced state by trypanothione reductase (TR), a NADPH dependent flavoprotein which acts as key enzyme of the trypanothione pathway, being critical for the protozoan survival, thus representing an attractive and promising target for the development of new potential drugs.(2,3) Furthermore, due to structural differences between the protozoan enzyme and the human homolog glutathione reductase (GR), a selective therapeutic approach might be possible. Following the discovery of some related compounds described in literature as TR inhibitors,(7) we evaluate the antiprotozoal activities of our in-house diaryl sulfide derivatives and some of the them proved to be active in whole cell assays, showing inhibitory activities within the micromolar range on different protozoa. Moreover, we found that our derivative **RDS 777** was able to inhibit TR of *L. infantum* (*Li*TR) with good efficiency, showing a Ki of 0.25 μM that is six times lower than that of Sb(III), the active form of antimonials being the most used drug against leishmaniasis.(8) Thus, we solved the X-ray structure of *Li*TR in its oxidized state in complex with **RDS 777** at 3.5 Å resolution, disclosing its mechanism of action. Indeed, this structure shows that the compound localizes at the catalytic site, engaging interactions with the residues more involved in the catalysis namely: Glu466', Cys57, Cys52 and Tyr110 thereby inhibiting the trypanothione binding. These data provide important insight that could be very helpful for future development of this class of inhibitors endowed with focused structural modifications in order to increase affinity and potency against protozoan target.

References: 1. Gelb, M. H.; Hol, W. G., *Science* **2002**, 297, 343-344. 2. Krauth-Siegel, R. L.; et al., *Angew. Chem.* **2005**, 44, 690-715. 3. Krauth-Siegel, R. L.; et al., *Parasitol. Res.* **2003**, 90, 77-85. 4. Comini, M.; et al., *Free Radic. Biol. Med.* **2014**, 73, 229. 5. Colotti, G.; et al., *Future Med. Chem.* **2013**, 15, 1861-75. 6. Fiorillo, A.; et al., *PLoS Negl. Trop. Dis.* **2012**, 6, e1781. 7. Stump, B.; et al., *Org. Biomol. Chem.* **2008**, 6, 3935-3947. 8. Saccoliti, F.; et al., *J. Enzyme Inhib. Med. Chem.* **2017**, 32, 304-310.

Synthesis of 4,6-diamino-1,2-dihydrotriazines as influenza viruses and respiratory syncytial virus inhibitors targeting the host DHFR

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The *Orthomyxoviridae* and *Paramyxoviridae* families comprise important respiratory pathogens, such as, influenza viruses and respiratory syncytial virus (RSV). The acute respiratory illnesses caused by these viruses represent a major medical need (1,2). Currently used antiviral drugs preferentially inhibit virus-specific replication factors. Host-targeting antivirals represent an alternative and emerging strategy to address host proteins involved in virus life cycle. Herein, we have identified a series of cycloguanil-like derivatives able to inhibit influenza A and B virus and RSV replication targeting the host dihydrofolate reductase (DHFR) enzyme (3). The 1-aryl-4,6-diamino-1,2-dihydrotriazines (**2-28**) were designed by exploring the effect on biological activity as a result of the chemical variation of the *para*-Cl substituent on the phenyl ring and/or of the two methyl groups at C(2) of cycloguanil (**1**) with smaller/bulkier alkyl groups. They proved active against influenza B virus in the low micromolar range, reaching for the best compounds (**11**, **13**, **14** and **16**) the sub-micromolar potency of zanamivir (EC₅₀= 0.060 μM), and markedly exceeded (up to 327 times) the antiviral efficacy of ribavirin. Besides inhibiting two influenza A strains, more importantly the compounds displayed nanomolar activity against RSV with a SI (CC₅₀/EC₅₀) >10,000 for compounds **11**, **14** and **16** (EC₅₀ ~0.008 μM), far surpassing the potency and safety profile of the licensed drug ribavirin (EC₅₀= 5.8 μM, SI>43). The interesting dual activity of these cycloguanil analogues against influenza and RSV viruses, *via* inhibition of the cellular hDHFR enzyme, points to this host factor as a new therapeutic target for these two respiratory viruses. In fact, reversal effect on antiviral activity has been demonstrated in RSV-infected HeLa cells, exposed to compound **14**, in combination with different concentrations of dihydrofolic acid, such as natural DHFR substrate. These compounds, tested against the recombinant protein of the hDHFR, also confirmed to bind this enzyme in the sub-micromolar range. Kinetic inhibition studies showed a competitive inhibition behavior, and docking studies disclosed the most probable binding mode for this class of hDHFR ligands. The possibility to suppress influenza viruses by interfering with the purine or pyrimidine pathway was proposed for a few other enzymes (4), but our study is the first to identify the relevance of host hDHFR in antiviral therapy. Therefore, we deemed interesting to further investigate the SAR of this class of compounds, exploring a novel azaspiro-4,6-diamino-1,2-dihydrotriazine scaffold different from the previous one. It was obtained by exploiting in a synthetic step the 4-piperidone, as useful building block, which allowed through its nitrogen atom to introduce an additional reactive center of molecular diversification. Within the new series, interesting hit compounds have been identified, warranting further investigations of their chemical space for the design of improved host-targeting antiviral agents.

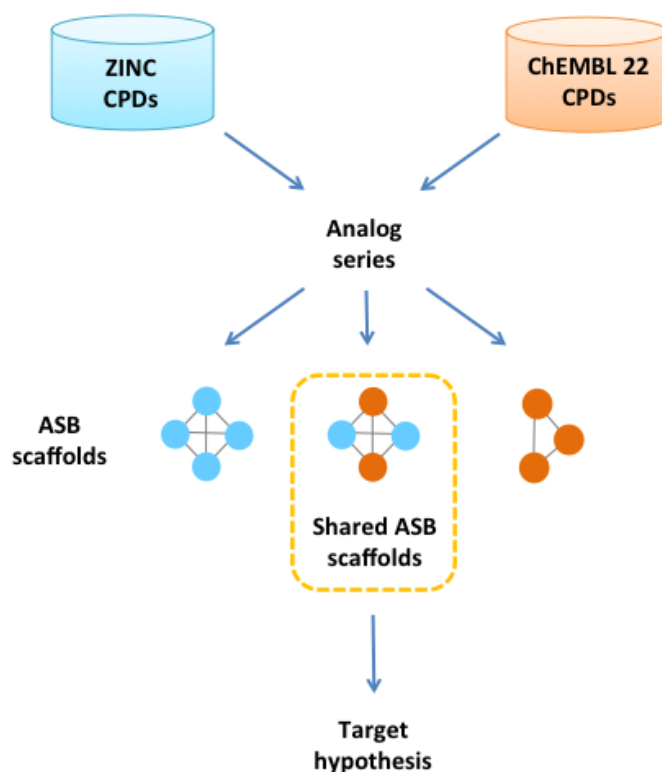
References: 1. A.C. Hurt et al Overview of the 3rd isirv-Antiviral Group Conference--advances in clinical management, *Influenza Other Respir. Viruses* 2015, 9, 20-31. 2. M. Tonelli et al *Curr. Med. Chem.* 2016, 23, 1802-1817. 3. M. Tonelli et al, *Eur. J. Med. Chem.* 2017, 135, 467-478. 4. A. Stevaert et al *Med. Res. Rev.* 2016, 36, 1127-1173.

Application of a New Scaffold Concept for the Identification of Analog Series in Commercial Databases

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In medicinal chemistry scaffolds are used to represent core structures of compounds. (1,2) Scaffolds are intensely explored in computer-aided drug design: of particular interest is the association of core structure motifs with specific biological activities. We hereby describe our analysis to globally view accessible analog space and systematically search for analog series in large compound repositories. The analysis was focused on a recently introduced molecular scaffold definition, termed analog series-based (ASB) scaffold. (3) ASB scaffolds were designed to further increase the medicinal chemistry relevance of scaffolds by incorporating chemical reaction information. Therefore, analog series were systematically extracted from the ZINC drug-like database as well as ChEMBL 22, and the resulting ASB scaffolds were collected. Then, the ASB scaffolds shared by ZINC and ChEMBL compounds were prioritized. In this way, target annotations from ChEMBL can provide novel compound-target hypothesis. (4)



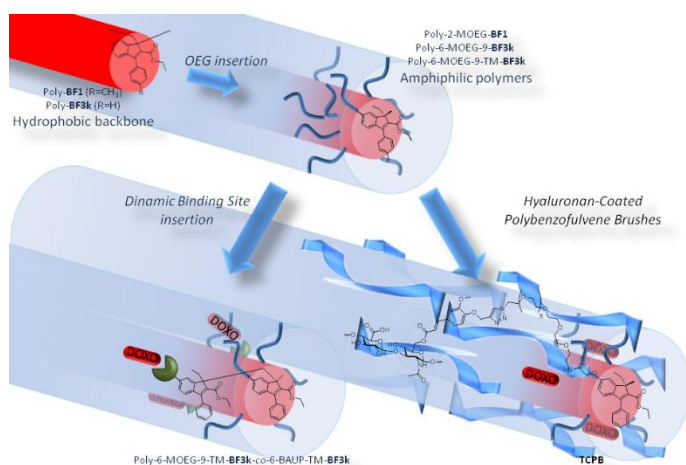
References: 1. Hu Y. *et al. J. Chem. Inf. Model.* **2011**, 51, 1742-1753. 2. Hu Y. *et al. J. Med. Chem.* **2016**, 59, 4062-4076. 3. Dimova D. *et al. Future Sci. OA* **2016**, 2, FSO149. 4. Lavecchia A. *et al. Drug Discov. Today* **2015**, 21, 288-298.

π -Stacked Polymers in Drug Delivery Applications

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In parallel with the discovery of new bioactive compounds, research in the pharmaceutical field has targeted to the development of new formulations able to control the amount and release speed of the drugs into the organism in order to improve their therapeutic action. For this purpose, non-conventional dosage forms, commonly called drug delivery systems (DDS), have been developed. Over the last 15 years, our research group has been involved in the discovery and the application of a new class of π -stacked polymers: the polybenzofulvenes. A large variety of benzofulvene derivatives were synthesized and allowed to polymerize spontaneously by solvent removal in the apparent absence of catalysts or initiators. The polybenzofulvene derivatives are characterized by interesting features including tunable solubility in different solvents and aggregation behavior in water, and propensity to generate nanostructured aggregates. Among the large variety of structure manipulations, we explored the insertion of oligo(ethylene glycol) (OEG) side chains on the polymer backbone through different synthetic strategies to obtain polybenzofulvene molecular brushes (PBFMBs) capable to interact with the water.(1,2,3) PBFMBs have been employed to complex and release bioactive molecules, such as immunoglobulin G (IgG) from a strong physical hydrogel obtained with poly-2-MOEG-9-BF1(4) or the anticancer peptide leuprolide from nanogel obtained with poly-6-MOEG-9-BF3k(5) through non specific protein–polymer interactions.



In a subsequently strategic step, PBFMBs have been engineered with a synthetic dynamic receptors capable of interacting with the anticancer drug doxorubicin (DOXO) and delivering it to cancer cells.(6) Recently, a PBFMB has been functionalized with low molecular weight hyaluronic acid (HA) macromolecules in a tri-component polymer brush (TCPB) to develop a new advanced biomimetic functional material.(7) TCPB has been employed in the preparation of a nanostructured drug delivery system capable of deliver DOXO to cancer cells exploiting

the selective interaction of the HA with the CD44 receptors.

References: 1. A. Cappelli, M. Paolino, et al. *J. Polym. Sci., Part A: Polym. Chem.*, **2010**, *48*, 2446–2461. 2. A. Cappelli, M. Paolino, et al. *Polym. Chem.*, **2011**, *2*, 2518–2527. 3. A. Cappelli, G. Grisci, et al. *Chem. – Eur. J.*, **2013**, *19*, 9710–9721. 4. M. Licciardi, M. Grassi, et al. *Int. J. Pharm.*, **2010**, *390*, 183–190. 5. M. Licciardi, G. Amato, et al. *Int. J. Pharm.*, **2012**, *438*, 279–286. 6. A. Cappelli, G. Grisci, et al. *J. Mater. Chem. B*, **2015**, *3*, 361–374. 7. A. Cappelli, M. Paolino, et al. *Polym. Chem.*, **2016**, *7*, 6529–6544.

Clarithromycin dry powders for inhalation: A focus on drug solubility.

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Introduction:

Apart from deposition, the success of an inhalation therapy is related to the ability of the deposited drug to dissolve in the fluids lining the lung. In the case of cystic fibrosis, the thick mucus acts as a physical barrier to the dissolution of the drug, weakening the drug effectiveness. Among antibiotic therapy, macrolides are not commonly used in CF to treat infections caused by mucoid strains of *Pseudomonas aeruginosa*. Notably, several studies described a clinical benefit when macrolides were administered, with a decrease of the bacterial ability to adhere to airways epithelial cells (1). Thus, our research was focused on the design and development of a stable and effective Dry Powder Inhaler (DPI) containing an association of a macrolide antibiotic (clarithromycin, CLA) and a mucolytic agent (N-acetylcysteine, NAC).

Methods

Micronized powders were obtained from different hydro-alcoholic solutions containing 2-Propanol from 30% to 50% (v/v) and CLA and NAC in equimolar ratio, with a total powder concentration of 3% (w/v). All liquid feeds were dried using a Buchi Mini Spray Dryer B-191. Particle size of spray-dried particles was determined using a light-scattering laser granulometer equipped with a tornado powder dispersing system. The *in vitro* aerodynamic properties of the *Spray-Dried* (SD) powders were assessed by a *Single Stage Glass Impinger* (SSGI) using the monodose DPI RS01 model 7 as device to aerosolize the powders (*Eur. Phar.* 8). To study and compare the behavior of different Spray Dried (SD) powders when in contact with small amount of fluids (closer to *in vivo* conditions), a vertical diffusion cell equipment (Franz-type cells) was used.

Results and Discussion

The process yield increased with the 2-PrOH content, thanks to the reduction of the energy heat of the solvent mixture. Particle diameter (d_{50}) of the SD particles ranged between 2.6 μm and 3.3 μm , suitable values for inhalation. Morphology studies evidenced that the increase in 2-PrOH concentration caused the formation of spherical particles together with corrugated ones, in a blend not very homogenous. As to the aerodynamic behaviour, the produced powders showed all excellent flow and aerodynamic properties as evidenced by the very high emitted doses and fine particle fractions. Finally, compared to CLA batches (drug in non-salt form), higher dissolution profiles were obtained with CLA-NAC powders. These results confirmed that the spray drying process together with drug salification enhanced both powder solubility and wettability, with no need of potentially toxic excipients.

Conclusions

Co-spray dried powders of CLA and NAC showed good technological and aerodynamic properties, appearing as a valid pharmacological support for a better management the CF respiratory disease.

Acknowledgments

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Reference: 1. Wozniak DJ, Keyser R. Effects of subinhibitory concentrations of macrolide antibiotics on *Pseudomonas aeruginosa*. *CHEST Journal*. 2004;125(2_suppl):62S-9S.

Synthesis and preclinical evaluation of glycolipid-based TLR4 modulators: new therapeutics for inflammatory and autoimmune diseases

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Toll-like Receptor 4 (TLR4) activation by bacterial lipopolysaccharide (LPS) is the basis of inflammatory and innate immune response to invading pathogens in humans. However, excessive TLR4 activation by bacterial and endogenous ligands causes a large array of inflammatory and autoimmune pathologies. High-affinity TLR4 agonists and antagonists are therefore drug candidates to target a large array of diseases, some of which are still lacking specific pharmacological treatment. Recent achievements in the rational design, synthesis, and biological characterization of new, glycolipid-based Toll-like Receptor 4 (TLR4) modulators are reported. In the frame of the MSCA-ETN European project TOLLerant (www.tollerant.eu) we are studying the TLR4 activity of synthetic glycolipids mimicking the structure of lipid A, in the perspective to develop new TLR4-based small-molecule therapeutics (1). We are using the same molecules as high-affinity ligands of the MD-2 and CD14 co-receptors that are important players of the TLR4 activation process. With these synthetic probes we aim to dissect and study the molecular mechanisms of TLR4 activation and signaling. In particular we report on recent findings in the activity of such drug candidates to block influenza virus lethality (2), amyotrophic lateral sclerosis (ALS)(3), inflammatory bowel diseases (IBDs), aortic aneurysm (4) and other inflammatory diseases. Very recent achievements in the synthesis of non-toxic TLR4 antagonists based on different biocompatible scaffolds will be presented. NMR binding studies, biochemical experiments with purified MD-2 co-receptor, and microscopy imaging will be presented. These recent data give new insights into the mechanism of action of synthetic, glycolipid-based TLR4 modulators.

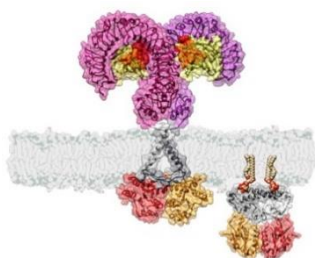


Figure 1. The TLR4/MD-2 activated heterodimer (pink and yellow) on cellular membrane.

References: 1. F. Peri, V. Calabrese, *Journal of Medicinal Chemistry* 2014, 57(9), 3612-3622. 2. De Paola M.; Sestito S. E.; Mariani A.; Memo C.; Fanelli, R.; Freschi, M.; Bendotti C.; Calabrese V.; Peri F., *Pharm. Res.* 2016, 103, 180-187. 3. Perrin-Cocon L.; Aublin-Gex A.; Sestito S.E.; Shirey K.A.; Patel M.C.; André P.; Blanco J.C.; Vogel S., Peri F.; Lotteau V., *Sci. Rep.* 2017, 7, 40791. 4. 84.F. Peri, G. Pirianov, *Atherosclerosis* 2015, 242, 563-570.

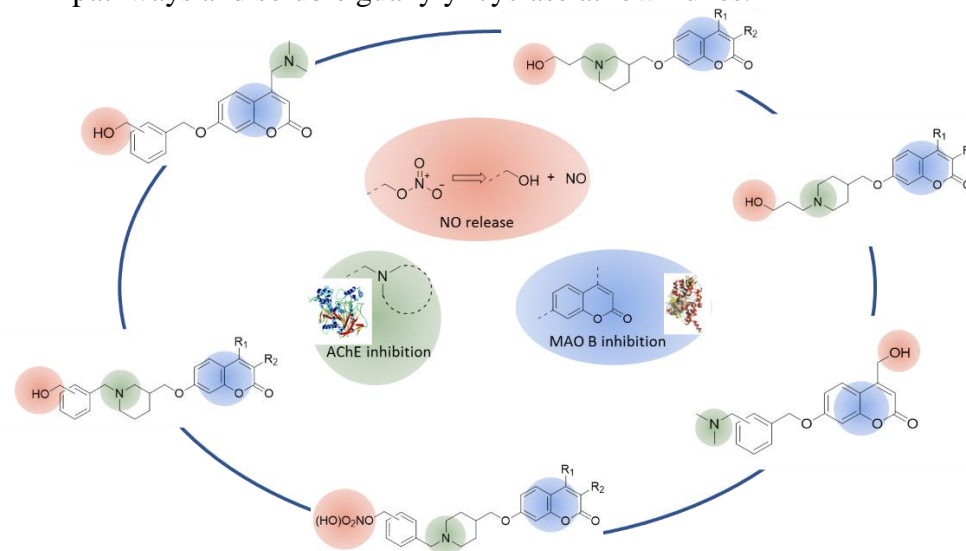
Nitrate-ester prodrugs of dual AChE-MAO B inhibitors as anti-Alzheimer Multitarget Hybrids

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The discovery of disease-modifying agents to treat Alzheimer's disease (AD) is a challenging research topic due to the multifactorial etiopathogenesis.(1) An innovative multitarget strategy aims at identifying drugs able to modulate simultaneously two or more relevant targets in the search for additive effects ultimately curative.(2) Along this idea, herein we propose the development of compounds able to promote synergistic activities against AD as follows:

- inhibition of acetylcholinesterase (AChE), for counteracting cholinergic depletion at the synaptic level;
- inhibition of monoamine oxidase B (MAO B) in reactive astrocytes, for reducing oxidative stress arising from hydrogen peroxide activity;
- release of nitric oxide (NO), for exerting neuroprotective and precognitive actions via ERK-CREB pathways and soluble guanylyl cyclase at low fluxes.



Among the possible NO-donors, alkyl nitrate esters were chosen to investigate the potential release of alcohol-based active metabolites upon hydrolysis. In order to exploit this bioactivation reaction, different dual AChE-MAO B inhibitors bearing an hydroxymethyl group (3) were developed before being transformed into the corresponding nitrate prodrugs in the case of the most active alcohol derivatives. By following a fragment-merging approach three diverse pharmacophore features, each potentially promoting a relevant activity, were joined in multifunctional compounds, while changing the linkage pattern.(4) To this aim, a planar coumarin backbone, selected to attain MAO B affinity, was decorated through a tertiary protonatable basic head to improve AChE binding affinity and a hydroxymethyl-masking nitrate group eligible for NO release.

References: 1. Querfurth, H. W.; LaFerla, F. M. *N. Engl. J. Med.* 2010, 362, 329-344. 2. Morphy, R.; Kay, C.; Rankovic, Z. *Drug Discov Today*. 2004, 9, 641-651. 3. Pisani, L.; Farina, R. et al. *J. Med. Chem.* 2016, 59, 6791–6806. 4. Nikiforov, P.; Surade, S. et al. *Org. Biomol. Chem.* 2016, 14, 2318–2326.

Discovering new casein kinase 1d inhibitors with innovative MD-integrated virtual screening

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The value of including protein flexibility in structure-based drug design and, in particular, in structure-based virtual screening is widely documented and recognized. Molecular Dynamics represents one of the most powerful tools to investigate and simulate protein dynamics, yet the inclusion of MD-derived information is still far from trivial. The huge amount of information in terms of conformations generated by MD has to be filtered to reduce noise and redundancy. In SBVS this generally corresponds to a significant minimal set of conformations to be used in *in silico* screening experiments.

We developed an integrated approach for enhancing accuracy, efficacy, and for conformation selection in VS campaigns, by combining in a pipeline MD, Clustering and the Linear Discriminant Analysis implemented in FLAP (1,2). MD trajectories were clustered according to the Molecular Interaction Fields variation, in order to catch the most representative binding site images, then the LDA chose the best performing conformations, for identifying active ligands among thousands of decoys, thus combining an unsupervised (clustering) with a supervised pre-filtering (LDA). Retrospective analyses on different pharmacological relevant cases recognized the MD-FLAP approach to be a valuable tool for improving VS performances, and confirmed that ensemble receptor protocols outperform single rigid receptor ones (3).

On the basis of these promising results we applied the same procedure on a real case, looking for new possible scaffolds able to target casein kinase 1d. CK1 kinases participate to various cellular processes as DNA repair, cell cycle progression, differentiation and apoptosis, and their deregulation contributes to the pathogenesis of a number of diseases like cancer, neurodegenerative diseases and inflammatory disorders (4). By applying the aforementioned pipeline we obtained a VS model able to separate known actives from inactives on an in-house Pfizer library of about 17000 kinase inhibitors, with a global AUC of 0.9 and a partial ROC enrichment at 0.5% of 0.18, with respect to the 0.77 and 0.036 obtained with a single structure approach. The model was then used in a real VS campaign, screening the internal Pfizer database. The best performing 1000 molecules were filtered according to their structural similarity with known CK1d inhibitors present in the ChEMBL database, looking for new scaffolds. Two new structures were identified and different derivatives analyzed. The best binder showed an IC₅₀ of 134 nM. The results supported once more the potential of the integrated MD-FLAP approach in real screening campaigns and the importance of including receptor flexibility for the detection of new ligand scaffolds.

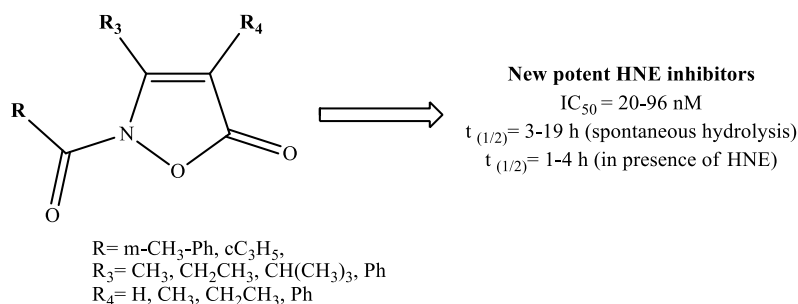
References: 1. Baroni M., Cruciani G., Sciabola S., Perruccio F., Mason J.S. *J. Chem. Inf. Model.*, 2007, 47, 279-294. 2. <http://www.moldiscovery.com>. 3. Spyraakis F., Benedetti P., Decherchi S., Rocchia W., Cavalli A., Alcaro S., Ortuso F., Baroni M., Cruciani G. *J. Comput. Inf. Model.*, 2015, 55, 2256-2274. 4. Knippschild U., Kruger M., Richter J., Xu P., Garcia-Reyes B., Peifer C., Halekotte J., Bakulev V., Bischof J. *Front. Oncol.* 2014, 4, 96

Isoxazol-5(2H)-one: a new scaffold for potent human neutrophil elastase (HNE) inhibitors

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Human neutrophil elastase (HNE) is a serine protease belonging to the chymotrypsin family. It is stored in the azurophil granules of polymorphonuclear neutrophils (PMNs), where it participates in non-oxidative intracellular and extracellular pathogen destruction. HNE plays an important role in many processes, such as blood coagulation, apoptosis and inflammation and exhibits proteolytic activity against a variety of extracellular matrix proteins, like elastin, fibronectin, collagen, proteoglycans and laminin (1). In physiological conditions, the action of HNE is regulated by its endogenous inhibitors (α 1-PI, α -2 macroglobulin, SLPI and elafin) but if the balance between proteases and anti-proteases disappears, the excess of HNE activity can cause tissue damage (2). Among the respiratory system pathologies associated with increased HNE are COPD (3), CF (4), ALI and ARDS, but also for rheumatoid arthritis, cancer (5) and neuropathic pain (6) an involvement of HNE was demonstrated. Our interest in the design and synthesis of new non-peptide HNE inhibitors led to the discovery of a potent class of HNE inhibitors with a N-benzoylindazole scaffold (7,8), with IC₅₀ values in the low nanomolar range. These compounds are competitive and pseudo-irreversible HNE inhibitors with good selectivity for HNE versus other serine protease and an appreciable chemical stability in aqueous buffer. One of these compound has been also tested in vivo in painful rat models of rheumatoid arthritis (9), osteoarthritis and neuropathic pain. We investigated other scaffold such as cinnoline (10), indole (11) and 7-azaindole and now we have shifted our attention in the design and synthesis of monocyclic nucleous such as isoxazol-5(2H)-one which demonstrated to be a suitable scaffold for HNE inhibitors.



References: 1. Korkmaz B et al. (2010) *Pharmacol Rev* 62: 726. 2. Stockley RA. (1999) *Am J Respir Crit Care Med* 160: 49-52. 3. O'Donnell R et al. (2004) *Thorax* 59: 837-842. 4. Gifford AM et al. (2014) *Curr Opin Hematol* 21: 16-22. 5. Moroy G et al. (2012) *Anticancer Agents Med Chem* 12: 565-579. 6. Muley M et al. (2016) *Br J Pharmacol* 173(4): 766-777. 7. Crocetti L et al. (2011) *Bioorg Med Chem* 19: 4460-4472. 8. Crocetti L et al. (2013) *J Med Chem* 56: 6259-6272. 9. Di Cesare Manelli L et al. (2016) *Rheumatology (Oxford)* 55: 1285. 10. Giovannoni MP et al. (2016) *J Enz Inhib Med Chem* 31(4): 628-639. 11. Crocetti L et al. (2016) *Drug Dev Res* 77: 285-299.

Modelling of Glucuronidation Reactions in the MetaQSAR Database: Successful Strategies to Handle Unbalanced Data in Metabolism Prediction

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Drug metabolism consists of a variety of transformations directly affecting the structure and reactivity of bioactive compounds, and it has a crucial impact on both the efficacy and the safety of drugs. The ability to anticipate such biotransformations is one of the major challenges along the road to producing lead compounds, and computational approaches play a central role in that effort.

Among the classes of metabolic reactions, glucuronidations are unanimously considered the most important reaction type for phase II metabolism, both in qualitative and in quantitative terms (1); however, despite their important contribution, they have been rarely investigated by computational methods. Attempting to make a step towards filling this gap, we are focusing our research on the UDP-glucuronosyltransferase enzymes (UGT) and have developed new integrated predictive models of their activity, exploiting both ligand- and structure-based strategies.

The source of data for our studies is the MetaQSAR metabolic database (2), internally developed and critically collected, which represents a crucial advance over the previous state of the art thanks to the high level of data curation, and provides a reliable data source for model building (3). As expected when dealing with the specific prediction of a single metabolic reaction class (local methods), the dataset collected from MetaQSAR unavoidably includes unbalanced data (399 molecules are UGT substrates and 1421 molecules are not UGT substrates), and this can affect the predictive power of models.

In order to handle this common issue, we present here two different strategies as applied to the prediction of the glucuronidation reactions. The first is based on a machine learning binary classification model, implemented as in the proteochemometric technique, for which we fruitfully exploited the random under-sampling procedure, affording a balanced accuracy of 0.80 (4). The second strategy involves a virtual screening method based on the 3D-structure for the human UGT2B7 isoform (5), recently optimized in our laboratory. This method affords outstanding results, as assessed by enrichment factor analyses (e.g. 100% of substrates ranked in the top 1% and 80% ranked in the top 5%)

Although based on completely different approaches, both models provide very encouraging results and prove successful in addressing the critical issues deriving from unbalanced datasets, which typically challenge metabolic predictive algorithms.

References: 1. Testa B, Pedretti A, Vistoli G. Reactions and enzymes in the metabolism of drugs and other xenobiotics. *Drug Discov Today*; 2012;17(11–12):549–60. 2. Pedretti A., Mazzolari A., Vistoli G., Testa B. MetaQSAR: An Integrated Database Engine to Manage and Analyze Metabolic Data. Submitted. 3. Karp P.D. Can we replace curation with information extraction software? *Database (Oxford)*. 2016, 1-44. Mazzolari A., Afzal A., Pedretti A., Vistoli G., Testa B., Bender A. Prediction of UGT metabolism using a proteochemometric approach. Poster presentation, Lhasa, Leeds, January 2017 5. Lewis BC, Mackenzie PI, Miners JO. Homodimerization of UDP-glucuronosyltransferase 2B7 (UGT2B7) and identification of a putative dimerization domain by protein homology modeling. *Biochem Pharmacol.*; 2011;82(12):1–8.

Comunicazioni Poster

Identification of new KDM4 inhibitors through a HTS and hit refinement strategy

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JHDMs (JmjC-domain-containing histone demethylases) are the largest class of demethylase enzymes, contain a Jumonji C (JmjC) domain and catalyze lysine demethylation of histones through an oxidative reaction that requires Fe(II) ion and α -ketoglutarate (α kG) as cofactors. The misregulation of these enzymes, in particular JMJD2 subfamily, has been significantly implicated in cancer initiation and progression. (1) Potent and specific inhibitors of these enzymes have not been identified yet. Moreover, most of the reported ones show a good affinity to many other Fe(II)/ α kG dependent oxygenases, are non-specific for the different isoforms or are affected by undesirable characteristics. (2) By means of a high throughput screening (HTS) campaign, we selected a pool of interesting hit compounds and then, to refine the results, filtered out poor quality scaffolds not suitable for future optimization. The use of a multiple combined approach of different in vitro techniques led us to select EML586 as scaffold for further derivatization. From a series of EML586 analogues we were able to derive a pharmacophore hypothesis and structure-activity relationships (hit-to-lead), and to select 3-hydroxy-2,3-dihydroquinazolinone moiety as starting point for the development of novel optimized derivatives. The substitution of quinoxaline ring with more aliphatic portions gave derivatives such as EML678 and EML684, which demonstrate a better activity against hKDM4A compared to the starting hit compound (Figure 1). Furthermore, they induced a marked reduction in methylation of lysines H3K9 and H3K27 in a cell-based assay together with an arrest in the S-phase of cell cycle.

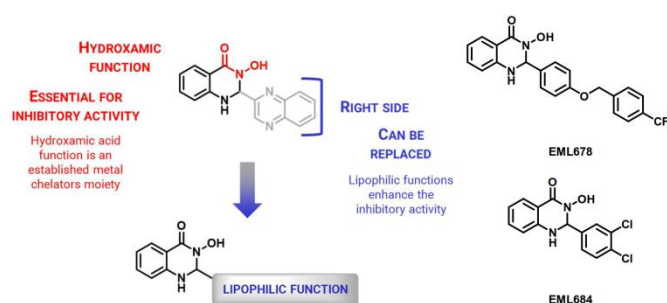


Figure 1. General scheme of our hit derivatization.

References: 1. Rotili, D., Mai, A., *Genes & Cancer* **2011**, 2, 663-679. 2. Leurs, U., Clausen, R. P., Kristensen, J. L., Lohse, B., *Bioorganic & Medicinal Chemistry Letters*, **2012**, 22, 5811-5813.

Triazolo quinolone derivatives: a new frontier for the treatment of multi-drug resistant Mycobacterium Tuberculosis strains.

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Tuberculosis (TB) is one of the most common infectious diseases worldwide, with about one-third of world population infected with Mycobacterium tuberculosis (M.Tb.). More frightening is the recent emergence of multi-drug and extensively drug resistant M.Tb. strains (MDR-M.Tb. and XDR-M.Tb., respectively). In the setting of drug resistance or intolerance to first-line agents (e.g. isoniazid, rifampin...), second-line agents may be used. Indeed, fluoroquinolones have been classified as second-line antituberculous drugs since they are active on isolated M. Tb. expressing resistance to both isoniazid and rifampin. Recently we demonstrated that [1,2,3]triazolo[4,5-h]quinolones (TQs) were endowed with a good anti-mycobacterial activity, paired to absence of cytotoxicity (CC₅₀ > 100 µg/mL against MT-4 cells). Some of them stood out for their potency against H37Rv and H37Ra and further clinical isolates of MDR-TB/XDR-TB strains (1,4).

Here we present the preliminary development of an interdisciplinary project (5) with the aim to improve knowledge concerning triazolo quinolone derivative scaffold structure-activity relationship (SAR), to identify a pharmacophoric map and enhance the biological activity. New triazolo quinolone derivatives bearing fluorine substitution on the classical quinolone moiety were designed and synthesized to obtain compounds able to inhibit replication in H37Rv and clinically isolated M.Tb. strains bearing different resistance patterns.

All tested derivatives resulted able to inhibit replication in M. Tb. wild type and resistant strains, and no activity resulted when tested on bacterial and fungal strains. The selectivity of action demonstrated by these compounds was investigated through the analysis of their biological target, the M. Tb. DNA-gyrase (wild type and mutated form), which binding site would diverge from classical quinolones.

All data collected, indicating for the compounds a new action mechanism compared to classical quinolones, will be used to create an innovative treatment plan able to reduce possible pharmacological resistances.

References: 1. A. Carta, M. Palomba, G. Paglietti, P. Molicotti, B. Paglietti, S. Cannas, S. Zanetti. *Bioorg. Med. Chem. Lett.* (2007), 17, 4791–4794. 2. A. Carta, S. Piras, M. Palomba, D. Jabes, P. Molicotti, S. Zanetti. *Anti-Infective Agents*, (2008), 7, 134-147. 3. A. Carta, M. Palomba, I. Briguglio, P. Corona, S. Piras, D. Jabes, P. Gugliera, P. Molicotti, S. Zanetti. *Eur. J. Med. Chem.* (2011), 46, 320-326. 4. I. Briguglio, S. Piras, P. Corona, M.A. Pirisi, D. Jabes, A. Carta. *Anti-Infective Agents*, (2013), 11, 75-89. 5. Progetti di Ricerca di Interesse Nazionale (PRIN) 2015, prot. 2015C7PCYZ. New designed Triazoloquinolones in combination with Pgp inhibitors as useful chemical probe to investigate quinolone resistance in Mycobacterium Tuberculosis: an approach to face an old re-emerging disease with new tools.

Developing new antimicrobial weapons by combination of Temporin-L with cyclodextrins

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Concern over antibiotic resistance is growing, and new classes of antibiotics, particularly against Gram-negative bacteria, are needed (1). In fact, a lack of new antibiotics for the treatment of Gram-negative infections combined with emerging multi-drug resistance issues demands for the development of new antimicrobial strategies. With an understanding of the pivotal role that cationic host defense (antimicrobial) peptides play in preventing infections by microbial pathogens in many organisms, it has been proposed that these peptides might form the foundation for a new class of clinically useful antimicrobials (2). The therapeutic application of antimicrobial peptides (AMPs) is accompanied by challenges now being resolved owing to an increased understanding of how peptide structure influences mechanism of action. With the aim of overcoming some of the main drawbacks preventing the widespread clinical use of this class of antibacterial therapeutics, i.e. toxicity and unfavorable pharmacokinetics profile, we are designing new formulations combining AMPs with different types of cyclodextrins (CDs) for modulating their hydrophobicity, amphipathicity and degree of α -helicity. Those variations could reduce peptide toxicity as evaluated by measuring their effect on mammalian cell lines. At the same time, peptides-CDs adducts could be more resistant to enzymatic degradation.

We started this project considering the peptide Temporin L (TL), an AMP belonging to the family of temporins. Among AMPs of natural origin, the amphibian temporins represent one of the largest families (more than 100 members) and are among the smallest-sized AMPs (10–14 amino acids) found in nature to date (3). Generally speaking, temporins are known to be active particularly against Gram-positive bacteria. TL is the only exception as it is strongly active also against Gram-negative bacteria and yeast strains, while being strongly hemolytic against human erythrocytes (4).

Here, TL-CDs adducts are evaluated for their antimicrobial activity, toxicity, stability and conformational properties.

References: 1. Tischendorf J. et al, Risk of infection following colonization with carbapenem-resistant Enterobacteriaceae: A systematic review. *Am. J. Infect. Control.* 2016, 44, 539. 2. Hancock R.E. et al. Antimicrobial and host-defense peptides as new anti-infective therapeutic strategies. *Nat. Biotechnol.* 2006, 24, 1551. 3. Mangoni M.L. Temporins, anti-infective peptides with expanding properties. *Cell. Mol. Life Sci.* 2006, 63, 1060. 4. Rinaldi A.C. et al. Temporin L: antimicrobial, haemolytic and cytotoxic activities, and effects on membrane permeabilization in lipid vesicles. *Biochem. J.* 2002, 368, 91-100.

Design, synthesis and in vitro evaluation of bivalent chemical probes for bromo and extra-terminal domain (BET) proteins

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Bromodomains (BRDs) are epigenetic readers that specifically recognize the acetyl-lysine residues of histones. The role in chromatin remodeling and transcriptional regulation correlate these proteins to several disease states such cancer, inflammation, and viral infection, making them an excellent therapeutic target (1). The most studied and druggable family of BRD-containing proteins is the bromo and extra C-terminal domain (BET), whose members (BRD2, BRD3, BRD4, and BRDT) contain two highly homologous bromodomains: BD1 and BD2. Several reports have suggested that these domains have different functions and their selective inhibition could be beneficial in treating diseases or mitigating unwanted effects (2, 3). To date, despite the extensive efforts, there is still a lack of powerful and selective inhibitors of bromodomain proteins, mainly due to the high homology not only between BET proteins but also between BD1 and BD2 domains. Here we describe the design, synthesis and preliminary biochemical evaluation of a new class of bivalent chemical probes of BET proteins (Figure 1). Using different spacers, we linked two different scaffolds: the RVX-208, a selective inhibitor of BD2 domain and a triazolobenzotriazepine-based compound, an inhibitor of BD1 domain. These compounds, simultaneously binding either BD1 or BD2 domains, will help clarify the differences between BD1 and BD2, allowing to get additional details on how these portions recognize the acetylated lysine residues of histones and other proteins.

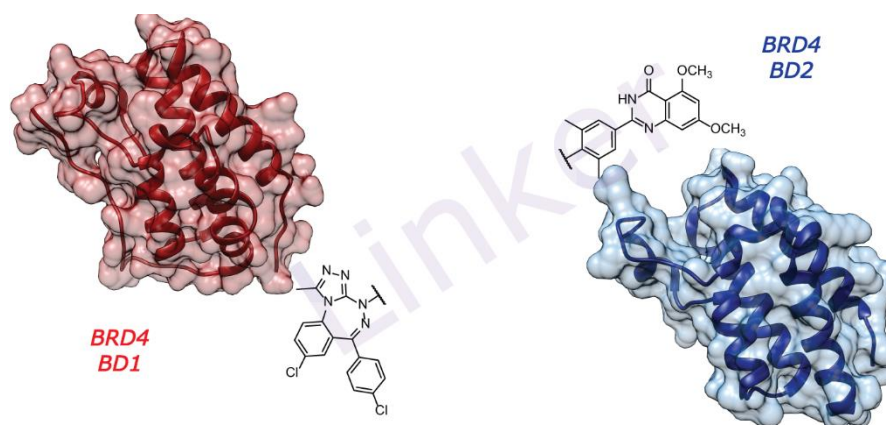


Figure 1 Development of selective and powerful class of BET chemical probes

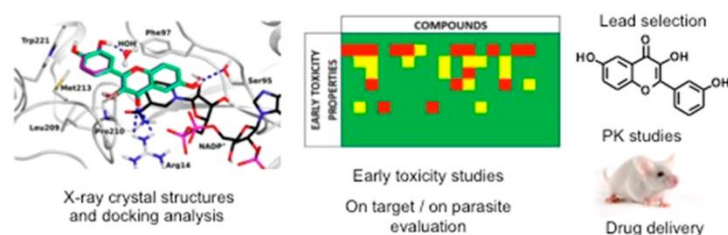
References: 1. Filippakopoulos et al; Targeting bromodomains: epigenetic readers of lysine acetylation. *Nat. Rev. Drug Discovery* **2014**, *13* (5), 337-356. 2. Gacias et al; Selective Chemical Modulation of Gene Transcription Favors Oligodendrocyte Lineage Progression. *Chem. Biol. (Oxford, U. K.)* **2014**, *21* (7), 841-854. 3. Picaud et al; RVX-208, an inhibitor of BET transcriptional regulators with selectivity for the second bromodomain. *Proc Natl Acad Sci U S A* **2013**, *110* (49), 19754-9.

Flavonol-like compounds identification as antileishmania agents: chemistry, biology and target studies.

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Protozoan parasites of the Trypanosomatidae family are the etiological agents of several significant neglected tropical diseases including human African trypanosomiasis (HAT) Chagas' disease, and leishmaniasis, which collectively affect nearly 10 million people worldwide. *Leishmania spp.* infect macrophages and cause a wide spectrum of symptoms ranging from cutaneous lesions to potentially fatal visceral infections (1). Current drugs in therapy show limited efficacy and drug resistance effects, therefore new drugs are urgently needed. A phenotypic approach was applied as a useful tool for drug discovery with the advantage of identifying compounds, which are active against the whole cell. Among a library of natural products, flavonols such as fisetin and quercetin turned out to be potent antiparasitic compounds. Recently, we reported the antiparasitic activity of a library of classical flavonols (2). Thus, the chromen-4-one moiety was confirmed a promising scaffold for the development of antiparasitic compounds. In the present work, we identified a serie of flavonol-like compounds and studied the biological profile against *Leishmania spp.* and targets.



Compound CB80 showed an antileishmanial activity comparable to that of miltefosine (EC₅₀ vs *L. infantum* H80 = 1.9 μM, Milte = 3.2 μM). We have then evaluated the compound early toxicity profile, the most of the compounds showed low toxicity towards 5 cytochrome P450 (CYPX), human ERG channel and A549 human cells. The best compound, CB80, was selected for pharmacokinetic studies. Snapshot PK studies were performed CB80 showed low stability, therefore cyclodextrin were employed to improve the compound stability. CB80 was tested in mice and hamsters. No animal toxicity was observed, however poor pharmacokinetic and short half-life suggested the need for improving the synthesis of optimized compounds. Drug resistance studies were performed through a genomic approach on sensible and miltefosine resistant *Leishmania* parasite. The drug resistance profile was different from the one observed with miltefosine. This suggests that the compound can be active on miltefosine resistant strains. Target identification studies using differential Mass Spectrometry approaches combined with gel-filtration electrophoresis studies were performed. A comparison was performed between the proteome of cell treated with CB80 with respect to the untreated one. A protein set of differentially expressed proteins was identified and the results were compared with those obtained through genomic studies. From the genomic and proteomic studies we are able to identify those proteins that are relevant for CB80 targeting. The project was developed within the NMTrypI FP7 European project.

References: 1. Castillo, E. *Curr. Med. Chem.* 2010, 17, 4027–4051; 2. Borsari C. et al *JMedChem.*2016.

New inhibitors of Dengue and Zika Virus Protease

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Infections with flaviviruses, such as dengue, and the recently re-emerging Zika virus, are an increasing and probably lasting global risk.

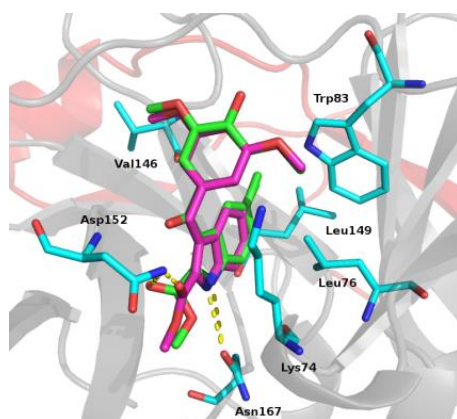
Dengue virus (DENV) is the causative agent of dengue fever, a *Aedes* mosquito-transmitted tropical illness characterized by high fever, severe headache, pain and rash. Currently no licensed vaccines or effective drugs are available, and vector control efforts have not successfully stopped the spread of the infection. There is an unmet need for effective drugs in the treatment of DENV infection. Zika virus (ZIKV) is a mosquito borne pathogen, belongs currently known for causing large epidemics in Brazil. The recent outbreak of ZIKV demands an enhanced surveillance and a need to develop novel drugs against ZIKV.

In search for new DENV protease inhibitors we carried out virtual screening (VS) studies on the NS2B/NS3 protease. Thanks to our virtual screening we were able to identify some derivatives showing promising inhibitory activity against the DENV protease at one digit micromolar concentration (Chart 1A).¹ Due to the close relationship between ZIKV and DENV, we tested if highly active anti-DENV compounds could be used as an advanced starting point for the discovery of ZIKV NS2B/NS3 protease inhibitors.

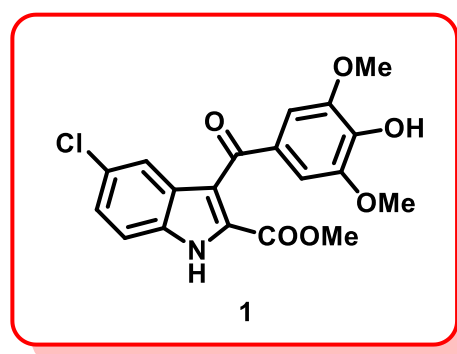
In particular, compound **1** (Chart 1B) proved to be a valuable inhibitor against ZIKV protease and paved the way for design on new more potent dual inhibitors.

Chart 1. New DENV and ZIKV protease inhibitor

A



B



References: 1 Pelliccia, S. *et al.* Inhibition of Dengue Virus Replication by Novel Inhibitors of RNA-dependent RNA Polymerase and Protease Activities. *JEIMC*, submitted.

Biomolecular and biophysical approaches for the identification of chemical probes for the PHF20 Tudor2 methyllysine reader domain

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Among epigenetic enzymes, writer and eraser proteins have been the main focus of therapeutic development but over the past few years a relatively underexplored group of proteins, the readers, have emerged as promising targets operating at the interface of translating histone marks. While their importance in several biological processes is evident, there is a strong need to identify new modulators to be used as chemical probes to better understand the role of these proteins in physiological and pathological states.

Plant homeodomain finger protein 20 (PHF20) is a multidomain protein mainly involved in the activation of p53 and in the prevention of its ubiquitylation (1). Furthermore, it uses the second Tudor domain to read dimethyl lysine residues and it plays a role in the cross-talk between lysine methylation and histone acetylation (2).

With the aim to identify chemical probes for different methyllysine reader domains (3), we synthesized a library of compounds that were used to challenge a microarray of reader proteins. This approach allowed us to identify very promising hits (4). We herein describe the development of a robust combined biochemical and biophysical screening platform for the validation of the identified hits for the Tudor domain 2 of PHF20 and their full characterization. In order to deeply characterize the key elements for the interaction of the modulators with the target protein, we used different protein sequences and we evaluated the influence of the presence of different tags. This combined approach represents a powerful method for measuring readers activity and it allowed us to identify new chemical probes, very useful for the study of the activity of this reader and its implications in physiological and/or pathological processes.

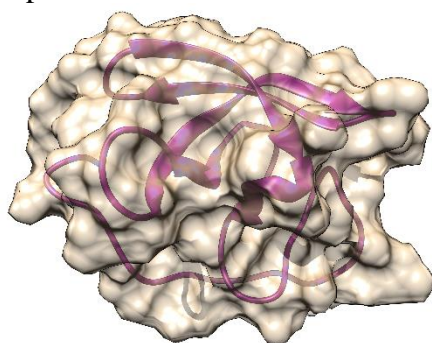


Figure 1. *Plant homeodomain finger protein 20 (PHF20)*

References: 1. Cui, G. et Al. PHF20 is an effector protein of p53 double lysine methylation that stabilizes and activates p53. *Nature Structure Molecular Biology* **2012**, 19(9), 916-924. 2. Badeaux, A.I. et Al. Loss of the Methyl Lysine Effector Protein PHF20 Impacts the Expression of Genes Regulated by the Lysine Acetyltransferase MOF. *Journal of Biological Chemistry* **2012**, 287(1), 429-437. 3. James, L. I. et Al. Discovery of a chemical probe for the L3MBTL3 methyl-lysine reader domain. *Nature Chemical Biology* **2012**, 9, 184-191. 4. Bae, N. et Al. Developing Spindlin1 small-molecule inhibitors by using protein microarrays. *Nature Chemical Biology* **2017**, (doi:10.1038/nchembio.2377).

Quinoxaline derivatives as new leads against Picornavirus

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Picornaviruses are viral agents which cause a wider range of illnesses than most other, if not all, virus families. The Picornaviridae family comprises five genera, namely Enterovirus, Rhinovirus, Hepatovirus, Cardiovirus, and Aphthovirus. Infection with various Picornaviruses may be asymptomatic or may cause from mild illnesses (the common cold, febrile rash illnesses, conjunctivitis...) to serious conditions affecting the central nervous system (encephalitis), heart (myocarditis), skeletal muscles (myositis), and liver (hepatitis). (1)

Human Enteroviruses (EVs) are relevant pathogens circulating commonly in the environment, with a seasonal peak during early fall. Cocksackievirus belong to this genus and are noted to cause systemic disease after ingestion and replication in the gastrointestinal tract (2). Actually, no specific antiviral agent is approved by the US Food and Drug Administration for the treatment of Enterovirus infections.

In this poster, we report the synthesis and the *in vitro* and *in silico* antiviral activity of a series of new quinoxaline derivatives. All compounds were tested for cytotoxicity and biological activity against a wide panel of representative ssRNA, dsRNA and dsDNA viruses. From all compounds, three quinoxaline derivatives stood out for their very potent and selective activity against Cocksackievirus B5, with EC₅₀ values in the sub-micromolar range (0.3 - 0.06 μM). The most active, selective and not cytotoxic compound, 2-[6-(2,3-dimethoxyquinoxalin-6-ylmethylthio)pyridine-3-carboxamido]-L-glutamic acid (**7a**) was widely evaluated using a combination of experimental techniques (i.e., virucidal activity, time of drug addiction, and adsorption assays) and preliminary data are here reported. These data were finally used to hypothesize the antiviral mechanism of action, and since activity of **7a** towards CVB-5 is only 10 times higher (EC₅₀ = 0.09 μM) than the one measured for the same cell line treated with pleconaril (EC₅₀ = 0.005 μM), we hypothesized that these two compounds might exert a similar mechanism of action as viral capsid protein binders. To confute *mechanicistically* the hypothesis, molecular modelling studies were further performed.

References: 1. Murphy M, Almond JW. Picornaviruses. In: Baron S, editor. Medical Microbiology. 4th edition. Galveston (TX): University of Texas Medical Branch at Galveston; 1996. Chapter 53. 2. Woodruff, J. F. Viral myocarditis. A review. Am. J. Pathol., 101 (2), 1980, 425-484.

Pyrrolyl non-dka derivatives as novel inhibitors of hiv-1 reverse transcriptase-associated ribonuclease h function

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The AIDS is a complex of pathological manifestations characterized by progressive degeneration of the immune system caused by the HIV virus. An essential enzyme for the retroviral life cycle is reverse transcriptase (RT), an heterodimeric enzyme with two associated activities: the DNA polymerase activity and the ribonuclease H (RNase H) activity that selectively degrades the RNA strand of the hybrid RNA/DNA formed during the synthesis of the minus (-) strand DNA that uses (+) RNA as a template.(1)

Despite such a large armamentarium, both acute and chronic toxicities limit the prolonged use of several antiretroviral agents, and this is even more a concern because of the life-long character of the therapy. In addition, the selection of drug-resistant strains and the spreading of such strains in newly infected patients is also an increasing concern, underscoring the pressing demand of novel anti-HIV agents, with a better therapeutic index and a very broad spectrum of activity against the mutants, possibly targeting viral functions not yet explored.(2)

In such a scenario, an attractive target turns out to be the RNase H function of HIV-1 reverse transcriptase (RT), which has been little explored although it could be potentially vulnerable to a specific inhibition. (3,4,5,6)

Although RT is a multifunctional enzyme, all RT inhibitors currently approved for the treatment of HIV infection target only the RT-associated polymerase function, while none of them block the RT RNase H activity. Nevertheless, several studies have demonstrated that the abolition of the HIV-1 RNase H function stops the virus replication, proving to be, therefore, a validated and attractive target for the development of new anti-retroviral agents, in order to enhance the anti-HIV-1 drug armamentarium effectiveness. Despite this, it has been little explored and it needs to be further developed through the support of new HIV/AIDS drug discovery programs, in order to identify more efficient anti-HIV drugs that could be used for therapy.(7,8)

To date, only few compounds have been described to inhibit the HIV-1 RNase H function. Among them, aryldiketo acid derivatives proven to inhibit both integrase enzyme and RNase H function of the RT.(9,10) Pursuing our studies on pyrrolyl DKA derivatives as dual inhibitors of IN and RNase H we developed non DKA scaffold and found a new class of compounds that selectively inhibited the RNase H. The data coming from the biological assays will be shown and discussed.

References: 1. Hu, W. S.; Hughes, S.H., *Cold Spring Harb Perspect Med.* **2012**, *2*, 1-22. 2. Moore, J. P.; et al., *Nature Rev. Mol. Cell Biol.* **2000**, *1*, 40-49. 3. Klumpp, K.; et al., *Nucleic Acids Res.* **2003**, *31*, 6852-6859. 4. Budihhas, S.R.; et al., *Nucleic Acids Res.* **2005**, *33*, 1249-1256. 5. De Clercq, E.; et al., *J. Med. Chem.* **2005**, *48*, 1297-1313. 6. Tramontano, E., *Mini Rev. Med. Chem.* **2006**, *6*, 727-737. 7. Tramontano, E.; Esposito, F.; Badas, R.; Di Santo, R.; Costi, R.; La Colla, P. *Antiv. Res.* **2005**, *65*, 117-124. 8. Tramontano, E.; et al., *Antiviral Res.* **2005**, *65*, 117-124. 9. Corona, A.; et al., *Antimicrob. Agents Chemother.* **2014**, *58*, 6101-6110. 10. Pescatori, L.; et al., *J. Med. Chem.* **2015**, *58(11)*, 4610-4623.

StOASS inhibitors as putative new antibacterial agents

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Multidrug resistant (MDR) bacteria are challenging the efficacy of the available antibiotics to treat common infections and minor injuries both in the community and hospitals. Statistical data have estimated that around 23,000 - 25,000 people die each year as a result of a superbug infection.(1,2) *De novo* cysteine biosynthetic machinery, which is exclusive in prokaryotes, has been associated with the growth, survival and pathogenicity of several bacterial species. (3,4) Therefore, inhibition of the cysteine synthase complex, the result of the association between O-acetylserine sulfhydrylase (OASS) and serine acetyltransferase (SAT) enzymes, may provide a new therapeutically relevant target against MDR strains.

To obtain the first inhibitors of OASS, several peptides were assayed on the recombinant enzyme from *Salmonella typhimurium*. (5) However since peptides present major drawbacks as chemotherapeutical tools a campaign aimed to obtain the first small molecule inhibitors of OASS was started.(6,7) Compounds with low nanomolar activity were obtained and then assayed on bacteria. Nevertheless, despite the high inhibitory activity the most promising compound wasn't able to interfere with bacterial growth. Further investigation presented permeability as the main cause of the lack of antibacterial activity. Therefore, starting from the structure of the most promising compound and with the aim of improving its pharmacokinetic properties, we herein present the synthesis and biochemical evaluation of a new series of StOASS inhibitors.

References: 1. Centers for Disease Control and Prevention, 2016. 2. World Health Organization, Fact Sheet 194, 2015. 3. Mazumder et al, *Curr Top Med Chem*. 2016;16(9):948-59. 4. Campanini et al, *Curr Med Chem*. 2015;22(2):187-213. 5. Salsi et al, *J Med Chem* 2010, 53, 345-356. 6. Amori et al, *Med Chem Commun*, 2012, 3, 1111-1116. 7. Pieroni M., Annunziato G. et al, *J. Med Chem* 2016.

Modulation of cell differentiation through HDAC inhibitors

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The induction of pluripotency to produce embryonic-like stem cells as well as the modulation of cell differentiation pathways through small molecules are major topics in stem cell research. Reprogramming of somatic cells has been attempted using different methods: somatic cell nuclear transfer, transduction of pluripotent genes into somatic cells, somatic cell fusion with pluripotent cells, and pluripotent cell extract mediated de-differentiation. The reprogramming processes of somatic cells are however still unrewarding and counteracted by the use of viral vectors eventually leading to permanent host genomic integration of foreign genetic materials. Recently, small molecules able to modulate specific targets in receptor signaling and epigenetic machinery have been used to improve the reprogramming process and/or replace some transcriptional factors, thus partially or totally avoiding the host genome involvement (1). In this context, histone deacetylase inhibitors (HDACi), such as valproic acid (VPA), thricostatin A (TSA), and suberoylanilide hydroxamic acid (SAHA), induce the hyperacetylation of histones thus modifying chromatin moiety and affecting gene expression (2). Although they are mainly used in anticancer therapy, these compounds have been successfully tested as reprogramming agents.

To evaluate the ability of HDAC inhibitors (HDACi) in reprogramming cell differentiative potential (3), we have designed and synthesized new hydroxamic acids. The compounds have been tested on primary human fibroblasts cultured *under standard conditions (control samples) or induced into adipogenesis, myogenesis and neurogenesis with known differentiative inducers (treated samples)*. The cellular response has been evaluated by immunofluorescence (vimentin, leptin), Real-time PCR analysis (RT-PCR) (myogenic differentiation factor 1, myogenin, tropomyosin, brain-derived neurotrophic factor, nerve growth factor, tubulin β 3, synaptophysin SYP) and western blot (matrix metalloproteinases 2, 9, 13) of specific cell lineage markers. In parallel, the morphology and functionality of exosomes and microvesicles (4) from HDACi-treated samples and controls have been characterized by scanning electron microscopy and RT-PCR (pluripotent transcription factor mRNAs, growth factors, cytokines, immune regulators).

The present work has been carried out with the financial support of University of Padova (CPDA120753/12)

References: 1. Milutinovic S et al, Carcinogenesis, 2007, 28, 560. 2. Huangfu D et al, Nat Biotechnol, 2008, 26,795. 3. González F et al, Nat Rev Genet. 2011, 12, 231. 4. Zhou J et al, Sci Rep. 2016, 6, 19743

Drug design and synthesis of new indolylarylsulfones as HIV-1 non-nucleoside reverse transcriptase inhibitors

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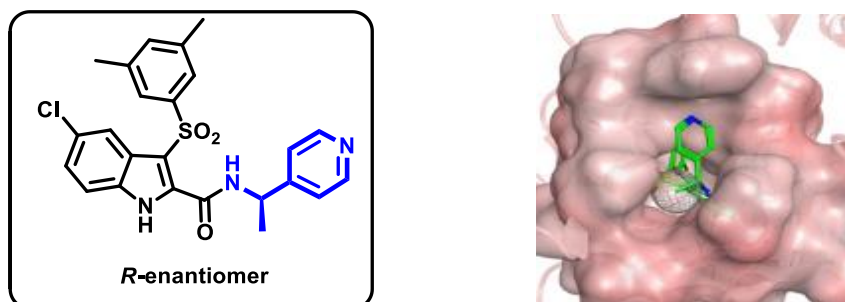
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HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) are key drugs of highly active antiretroviral therapy (HAART) in the clinical management of AIDS/HIV-1 infection. Our recent studies showed that indolylarylsulfones (IASs) bearing a cyclic moiety at the 2-carboxamide nitrogen linked through a short spacer group were endowed with potent antiretroviral activity.^{1,2}

Based on the results previously obtained, we aimed to expand the SAR studies by the introduction of new aryl or heteroaryl portions to the indole nucleus.

Interestingly, for the first time IASs endowed with asymmetric centre have shown significant differences in term of antiretroviral potency. In particular, the *R*-enantiomer proved to be exceptionally potent and uniformly superior to the *S*-enantiomer against the whole viral panel. Docking studies showed that the methyl group of the *R*-enantiomer (Figure 1) pointed toward the cleft created by the K103N mutation, differently from the corresponding group of (*S*) counterpart. By calculating the solvent accessible surface, we observed that the exposed area of the RT in complex with *S*-enantiomer was larger than the area of the (*R*) complex.³

Figure 1.



References: 1) La Regina, G., Coluccia A. *et al.* *J. Med. Chem.* **2012**, *55*, 6634–6638. 2) Famigliani, V., La Regina, G. *et al.* *Eur. J. Med. Chem.* **2014**, *80*, 101-111. 3) Famigliani, V., La Regina, G. *et al.* *J. Med. Chem.* **2014**, *57*, 9945-57.

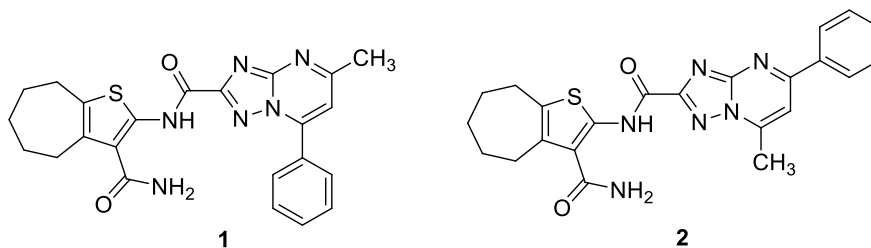
Thiophene-3-carboxamides and triazolopyrimidine-2-carboxamides as precious scaffolds to disrupt influenza polymerase PA-PB1 subunits heterodimerization.

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The limited therapeutic options against the influenza virus (flu) along with drug resistance issue make imperative the search for next-generation agents. In this context, heterotrimeric viral RNA-dependent-RNA-polymerase (RdRp) is a valuable target for a challenging but strategic protein-protein interaction inhibition approach. Since 2012, the inhibition of the RdRp PA-PB1 subunits interface has become an active field of research, following the publication of PA-PB1 crystal structures (1).

Our group has identified many of the PA-PB1 complex formation inhibitors reported to date, thanks to an initial SBVS that led to identify five hit compounds, followed by their optimization (2-4). The most enthusiastic result was achieved with the identification of two hybrid molecules (compounds **1** and **2**) obtained by merging the triazolopyrimidine and cycloheptathiophene scaffolds characterizing two of the hit compounds. Indeed, compound **1** emerged as the most potent PA-PB1 small molecule inhibitor developed thus far (4).



To further optimize compounds **1** and **2**, two efficient and region-selective one-pot synthesis were developed to prepare 7-aryl-5-methyl- and 5-aryl-7-methyl-2-amino[1,2,4]triazolo[1,5-a]pyrimidine derivatives, as key intermediates in the synthesis of an enlarged series of hybrid analogues.

In this work, their design, synthesis, and biological evaluation will be presented.

References: 1. Massari, S.; Goracci, L.; Desantis, J.; Tabarrini, O. *J. Med. Chem.* **2016**, *59*, 7699-7718. 2. Muratore, G.; Goracci, L.; Mercorelli, B.; Foeglein, Á.; Digard, P.; Cruciani, G.; Palù, G.; Loregian, A. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 6247-6252. 3. Massari, S.; Nannetti, G.; Goracci, L.; Sancineto, L.; Muratore, G.; Sabatini, S.; Manfroni, G.; Mercorelli, B.; Cecchetti, V.; Facchini, M.; Palù, G.; Cruciani, G.; Loregian, A.; Tabarrini, O. *J. Med. Chem.* **2013**, *56*, 10118-10131. 4. Massari, S.; Nannetti, G.; Desantis, J.; Muratore, G.; Sabatini, S.; Manfroni, G.; Mercorelli, B.; Cecchetti, V.; Palù, G.; Cruciani, G.; Loregian, A.; Goracci, L.; Tabarrini, O. *J. Med. Chem.* **2015**, *58*, 3830-3842.

Identification of new inhibitors of PRMTs by a multi-substrate-adduct approach

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The methylation of arginine residues is a prevalent posttranslational modification found in both nuclear and cytoplasmic proteins, which is involved in a number of different cellular processes, including transcriptional regulation, RNA metabolism, and DNA damage repair. Enzymes of the protein arginine *N*-methyltransferase (PRMTs) family catalyze the transfer of a methyl group from the donor *S*-adenosyl-*l*-methionine (SAM or AdoMet) to the guanidinium side chain of arginine residues in the target protein. Despite extensive research aimed at better understand the role of PRMTs in physiological and pathological pathways, there have been only a few publications to date describing small-molecule chemical modulators of the PRMTs. A few years ago, starting from **AMI-1** (the first selective inhibitor of PRMTs) (1) we identified **EML108**, which was characterized by an improved selectivity profile among methyltransferases and a good cellular activity (2). Moreover, docking studies clearly showed that **EML108** bind SAM and arginine pocket without fully occupying them. Starting from this evidence, we herein report the design and the synthesis of new PRMTs inhibitors based on the naphthalene scaffold of **EML108**. Firstly, we prepared some derivatives bearing a guanidine moiety connected to the naphthalene scaffold *via* a variable linker. After optimization, we further functionalized this scaffold with an adenosine moiety (Figure 1). This multi-substrate-adduct approach lead to the identification of new sub-micromolar inhibitors of PRMTs.

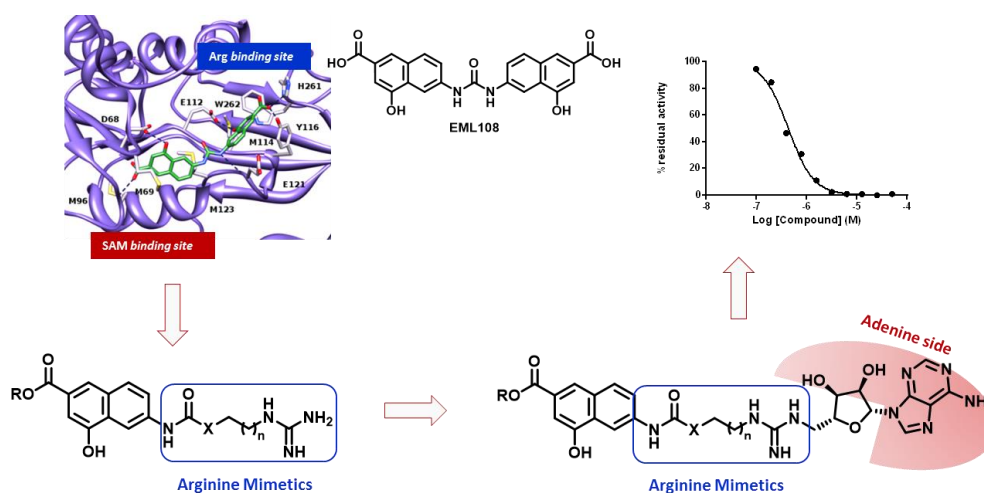


Figure 1: Multi-substrate-adduct approach to the discovery of new inhibitors of PRMTs

References: 1. Cheng, D. et Al. *The Journal of Biological Chemistry*, **2004**, 279(23), 23892–23899. 2. Castellano, S. et Al. *ChemMedChem*, **2010**, 5(3), 398-414.

Design and synthesis of a new anti-Chitinase compound

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In the last ten years, we identified and developed a new therapeutic class of antifungal agents, the macrocyclic amidinoureas (**1**). These compounds act on various *Candida* species, including clinical isolates resistant to currently available antifungal drugs (**2**). The mode of action of these molecules is still unknown. Therefore, we developed an *in-silico* target fishing procedure to identify a possible target for this class of compounds. Chitinase enzyme emerged as possible target. To confirm this hypothesis a novel macrocyclic derivative, compound **2**, has been synthesized (Fig. 1). This compound has been specifically designed to increase the inhibition of the Chitinase; to achieve this, we thought to merge **1** with Argifin (a natural compound known to be a good Chitinase inhibitor) (**3**) that assumes a similar pose and shape to **1** when docked against Chitinase. The aim of this step is to test if an increase in the enzymatic activity is reflected in the antifungal activity.

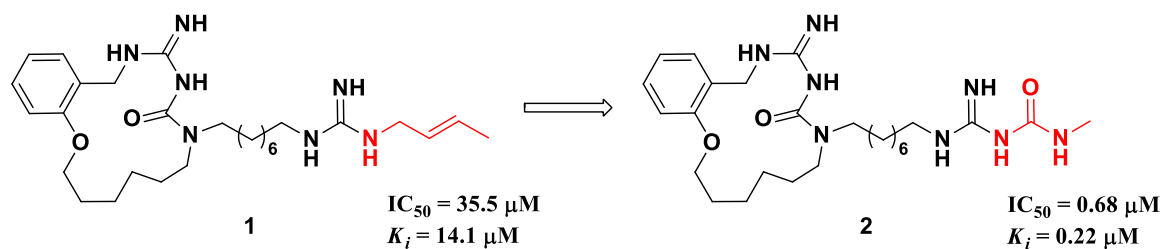


Figure 1: Compound **1** and **2**

The optimized derivative was tested against *T. viride* Chitinase and it exhibited a potent enzymatic inhibition, almost 50-fold lower than compound **1**. This confirmed the robustness of our computational model. Its antifungal activity, though, is lower than the parental compound. This could be due to the poor membrane penetration of **2**, due to the transformation of the positive-charged terminal guanidinium ($pK_a \approx 12$) to a neutral amidinourea ($pK_a \approx 6$). It is also possible that chitinase represents only one of the targets for this class of compounds, and these modifications reduced the affinity for the other targets. More investigations on this aspect need to be done.

References: 1. M. Sanguinetti, S. Sanfilippo, D. Castagnolo, D. Sanglard, B. Posteraro, G. Donzellini and M. Botta, *ACS Med. Chem. Lett.* **4** (2013) 852-857; 2. F.C. Bizerra, C. Jimenez-Ortigosa, A. C. Souza, G. Breda, F. Queiroz-Telles, D. S. Perlin and A. L. Colombo, *Antimicrob. Agents Chemother.* **58** (2014) 2438–2440; 3. Arai, N.; Shiomi, K.; Iwai, Y.; Omura, S., Argifin, a new chitinase inhibitor, produced by *Gliocladium* sp FTD-0668 - II. Isolation, physico-chemical properties, and structure elucidation. *J Antibiot* **2000**, *53* (6), 609-614

From a serendipitous discovery to new alkyl-guanidine oligomers as perspective antibacterial agents

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The rapid emergence of resistant bacteria is occurring worldwide and nowadays it is one of the major threat to human health, leading to the loss of the efficacy in the treatment of infectious diseases. (1) Thus, new chemical classes with innovative mode of action are required to prevent this crisis. (2) Our research group recently reported the identification of a series of linear guanidine derivatives and their antibacterial properties. (3) A batch of a promising candidate for optimization studies (compound **1**) turned out to be a mixture containing two unknown species and surprisingly it showed a better biological activity than the pure compound (MIC = 64 $\mu\text{g/mL}$). After this serendipitous discovery, we put efforts into the investigation about the chemical nature of the unknown components of the mixture and by means of MS analysis interfaced with the synthesis we found that the components were oligomeric derivatives of compound **1**.

Eventually, we identified a new family of compounds endowed with broad-spectrum antibacterial activity on both Gram positive and Gram negative strains. Among the synthesized compounds, the symmetric dimeric derivative **2** exhibited the best profile (MIC values ranging from 1 to 8 $\mu\text{g/mL}$) and it has been highlighted as a perspective lead compound for further studies. (**Figure 1**).

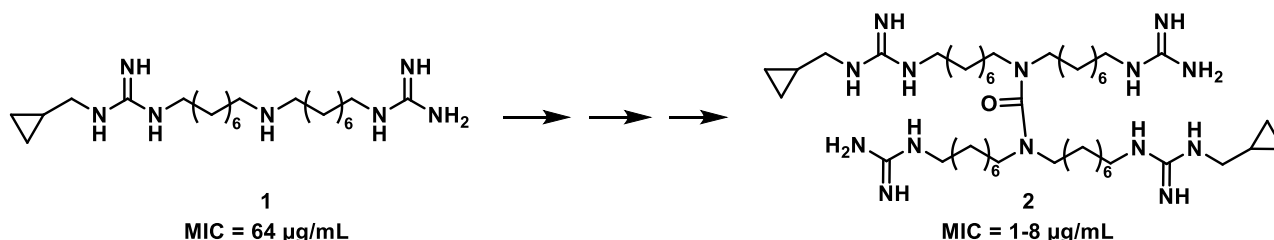


Figure 1. Compound **1** and its symmetric dimeric derivative **2**. MIC values in $\mu\text{g/mL}$ are shown for both compounds.

References: 1. Wang, B.; Pachaiyappan, B.; Gruber, J. D.; Schmidt, M. G.; Zhang, Y-M.; Woster, P. M. Antibacterial Diamines Targeting Bacterial Membranes. *J. Med. Chem.* 2016 (59), 3140–3151. 2. Chellat, M. F.; Raguz, L.; Reidl, R. Targeting Antibiotic Resistance. *Angew. Chem. Int. Ed.* 2016 (55), 6600–6626. 3. Maccari, G.; Sanfilippo, S.; De Luca, F.; Deodato, D.; Casian, A.; Dasso Lang, M. C.; Zamperini, C.; Dreassi, E.; Rossolini, G. M.; Docquier, J. D.; Botta, M. Synthesis of Linear and Cyclic Guazatine Derivatives Endowed with Antibacterial Activity. *Bioorganic Med. Chem. Lett.* 2014, 24 (23), 5525–5529.

Evolution of N-phenyl-5-(2-(phenylamino)thiazol-4-yl)isoxazole-3-carboxamides as valuable antitubercular candidates

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Tuberculosis remains one of the deadliest infectious diseases in the world, and the increased number of multidrug-resistant and extremely drug-resistant bacterial strains is a significant reason of concern.(1,2) This makes the discovery of novel antitubercular agents a cogent priority. We have previously addressed this need by reporting a series of substituted 2-aminothiazoles capable to inhibit the growth of actively replicating, non-replicating persistent, and resistant *Mycobacterium tuberculosis* strains.(3) Clues from the structure–activity relationships lining up the antitubercular activity were used for the rational design of improved analogues. Two compounds, in which the 2-aminothiazole core is linked to an *N*-substituted isoxazole-3-carboxamide, were found to possess high inhibitory activity toward susceptible and resistant *M. tuberculosis* strains, along with other favorable pharmacological characteristics such as metabolic stability, selectivity, and lack of toxicity toward macrophage cell lines.(4) Based on the structure of these interesting leads, different derivatives were synthesized in order to improve activity, define structure-activity relationships and refine drug-likeness. The preparation of such molecules was based on traditional organic chemistry combined with microwave heating. All of the synthesized compounds were preliminarily evaluated through a MABA assay: some of them were shown to possess very good activity against MTb, in some cases better than the lead compounds, and all showed a lack of toxicity when tested toward VeroCells. These results, since the detailed SAR and drug-like characteristics, encourage pursuing further efforts toward the rational synthesis of new derivatives.

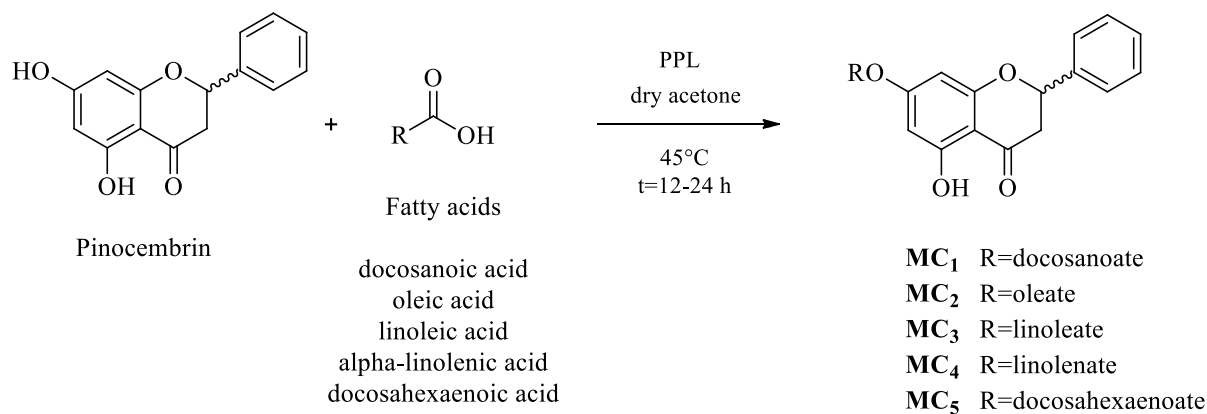
References: 1. WHO | The top 10 causes of death <http://www.who.int/mediacentre/factsheets/fs310/en/> (accessed Feb 16, 2017). 2. WHO | Global tuberculosis report 2016 http://www.who.int/tb/publications/global_report/en/ (accessed Feb 16, 2017). 3. Pieroni, M. *et al. Eur. J. Med. Chem.* **2014**, 72, 26–34. 4. Manuscript under preparation.

Lipase-catalyzed synthesis of pinocembrin derivatives as potential antibacterial agents

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Antibiotics are typically antibacterial drugs that interfere with some structures or processes which are essential to bacterial growth or survival. Antibiotic-treatment failure is generally attributed to resistance. Nowadays antibiotic resistance has spread at an alarming rate. Many resistance mechanisms have been identified, including mutations that decrease the binding of the drug to its target and increase expression of efflux pumps. The effect of such mutations is measured by the minimum inhibitory concentration (MIC), the lowest drug concentration needed to prevent the visible growth of the microorganism (1). Since the abuse and the inappropriate use of antibiotics have caused an increase of this phenomenon, scientific research aims at detecting new antibacterial agents. In this work we describe the synthesis of new molecules derived from a chemical modification of pinocembrin, one of the most abundant natural compound isolated from *Glycyrrhiza glabra* L. leaf. After a classical maceration extraction, GC-MS analysis of the organic layer (n-hexane) have revealed the presence of several fatty acids showing an interesting antibacterial activity. We merged pinocembrin, mainly present in the methanol layer and already reported for its antibacterial activity, with a series of fatty acids by a lipase-catalyzed esterification (2). We chose both saturated and unsaturated fatty acids, with a different length, to highlight differences in antibacterial power according to the chemical structure.



The obtained results have proved that MC₃ is the derivative with the best antibacterial activity.

References: 1. I. Levin-Reisman, I. Ronin, O. Gefen, I. Braniss, N. Shores, N.Q. Balaban, *Science*. 2017, DOI:10.1126/science.aaj2191. 2. Ziaullah, K.S. Bhullar, S.N. Warnakulasuriya, H.P.V. Rupasinghe, *Bioorg. Med. Chem.* 2013, 21(3), 684-692.

Design, synthesis and biological evaluation of novel G9a inhibitors with improved brain permeability from a scaffold hopping approach

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The lysine methyltransferase G9a (also known as EHMT2) catalyses the addition two methyl groups to lysine 9 of histone H3. Due to its central role in epigenetic control, the aberrant activity of this enzyme is associated to several diseases including cancer. In particular, recent evidences revealed G9a involvement in the progression of REST-expressing (repressor element (RE)-1 silencing transcription factor) medulloblastomas. (1) Only a few among the selective inhibitors of G9a reported to date are useful chemical probes for cell-based and animal studies. (2)

Starting from the inhibitor UNC0638, (3) we applied a scaffold hopping approach to develop novel chemical entities endowed with high affinity towards G9a. In particular, we replaced the quinazoline core, common to most of the reported inhibitors, with 1,4-benzodiazepine nucleus, known to be a privileged structure. We chose the 3,4-dihydro-5H-benzo[e][1,4]diazepin-5-one scaffold, that can be obtained through an efficient and gram-scale continuous-flow protocol, previously optimized by our group. (4) Moreover, this scaffold could be easily decorated to provide a number of highly functionalized potential ligands (Figure 1). To validate our approach, we designed and synthesized a small library of UNC0638 analogues. The UNC0638 benzodiazepine analogue (EML741) showed a good activity in a peptide-based AlphaLISA, together with a promising membrane permeability profile (PAMPA-BBB).

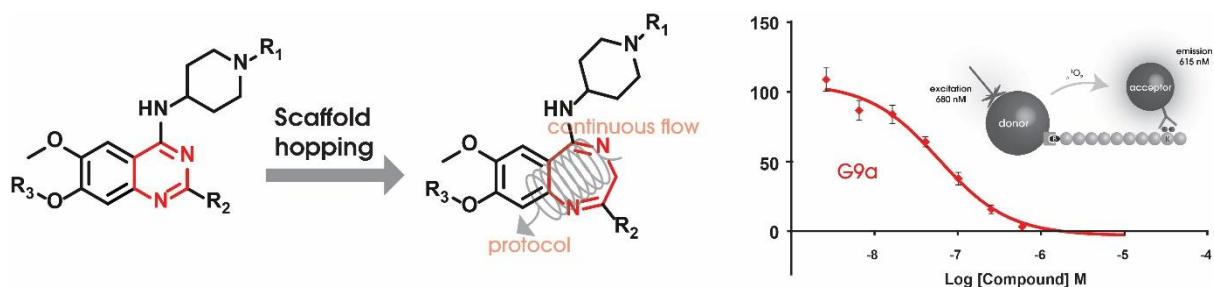


Figure 1. General scheme of our scaffold hopping approach

References: 1. Dobson, T.; Hatcher, R. J.; Swaminathan, J.; Das, C. M.; Shaik, S.; Tao, R.-H.; Milite, C.; Castellano, S.; Taylor, P.; Sbardella, G.; Gopalakrishnan, V., *Molecular Cancer Research* **2017**, *in press*, 10.1158/1541-7786.MCR-16-0424 2. Kaniskan, H. Ü. and Jin J., *ACS Chemical Biology* **2015**, *10*, 40-50. 3. Vedadi, M., Barseyte-Lovejoy, D., Liu, F., Rival-Gervier, S., Allali-Hassani, A., Labrie, V., Wigle, T. J., DiMaggio, P. A., Wasney, G. A., Siarheyeva, A., Dong, A., Tempel, W., Wang, S.-C., Chen, X., Chau, I., Mangano, T. J., Huang, X.-p., Simpson, C. D., Pattenden, S. G., Norris, J. L., Kireev, D. B., Tripathy, A., Edwards, A., Roth, B. L., Janzen, W. P., Garcia, B. A., Petronis, A., Ellis, J., Brown, P. J., Frye, S. V., Arrowsmith, C. H., Jin, J., *Nat. Chem. Biol.* **2011**, *7*, 566-574. 4. Viviano, M., Milite C., Rescigno D., Castellano S. and Sbardella G., *RSC Adv.* **2015**, *5*, 1268-1273.

Derivatives of 2-amino-6-fluorobenzoic acid as inhibitors of *Mycobacterium tuberculosis* Tryptophan biosynthetic pathway

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In spite of the enormous efforts that have been made in the hunt for new drugs, tuberculosis (TB) still remains the leading bacterial cause of mortality worldwide, causing an estimated 10.4 million new cases and 1.8 million deaths in 2015 (1). Recent studies have demonstrated that *Mycobacterium tuberculosis* (*Mtb*) survives host CD4-generated stress by production of tryptophan (Trp), thus avoiding starvation and rendering the host immune response ineffective (2). Thus, molecules that can inhibit Trp biosynthetic pathway could synergize with the host immune response to eradicate *Mtb* infection. Moreover, Trp is an essential amino acid for humans, so anti-Trp synthetic drugs should have limited mammalian toxicity. Therefore, Trp biosynthetic pathway is a valuable target for anti-TB drug development.

A 2-amino-6-fluorobenzoic acid (6-FABA) (Fig. 1) has been recently identified, whose bactericidal activity against *Mtb* was observed only in the absence of Trp, consistent with this compound acting by targeting tryptophan biosynthesis (2).

Herein we present a series of 6-FABA new analogues synthesized for optimizing the antimycobacterial activity and to improve both the drug-like properties and the pharmacokinetic profile of the parent compound (FABAs 1-37, 39-43, Fig. 1). Among the newly synthesized compounds the hydrazides FABA 14, 16, 24, 26, 27, 29-31, 34, 37, 40 and 41 have shown an outstanding antimycobacterial activity.

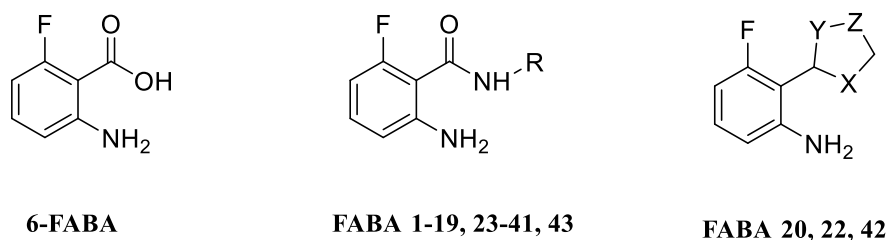


Figure 1. Chemical structure of 6-FABA and FABAs 1-37, 39-43.

References: 1. "WHO/ Global Tuberculosis Report **2015**." 2. Y. J. Zhang, M. C. Reddy, T. R. Ioerger, A. C. Rothchild, V. Dartois, B. M. Schuster, A. Trauner, D. Wallis, S. Galaviz, C. Huttenhower, J. C. Sacchettini, S. M. Behar, and E. J. Rubin, *Cell* **2013**, 155, 1296–308.

Identification of novel small-molecule ligands of methyl-lysine binding protein PHF20

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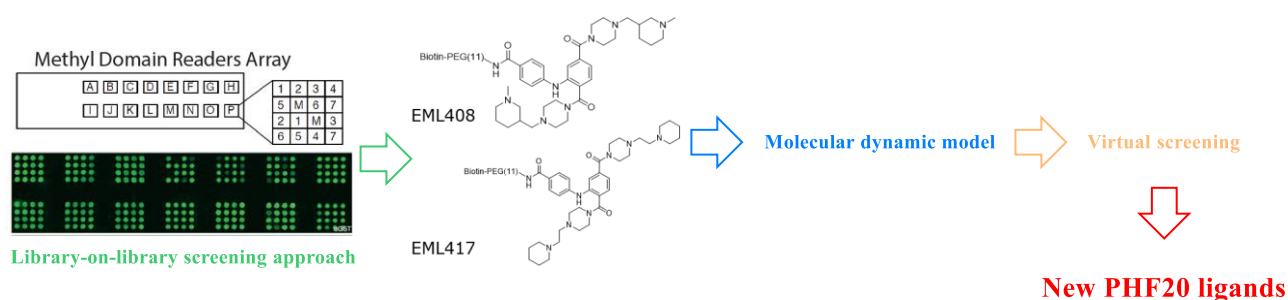
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Methylation of histone tails influences overall chromatin structure and the accessibility of DNA segments, thus representing a crucial post-translational modification involved in gene regulation. Recognition of these methyl marks has been attributed to the “Royal Family” of proteins, which includes the Tudor domain subfamily. The ability of these enzymes in binding lysine-methylated protein substrate has been well documented (1, 2). However, much remains to be elucidated with regard to precise mechanisms by which such interactions influence the processes of transcription, translation and RNA splicing.

Among the “readers”, the Plant Homeodomain Finger protein 20 (PHF20) is a transcription factor, which was originally identified in glioma patients (3). While little is known about its cognate cellular role, PHF20 is prevalent in hepatocellular tumors of stage I (4) and is also abundantly expressed in both advanced small-cell lung cancer and advanced adenocarcinoma, indicating that PHF20 might be tumor-associated antigen and could play a role in cancer progression.

Starting from a ‘library-on-library’ screening approach, compounds that selectively bound the Tudor domains of PHF20 were identified (**EML408** and **EML417**, Figure 1). A molecular dynamic model was also used to understand the right length to allow optimal interactions of the new ligands with the two cages of PHF20 dimer.

Prompted by our interest in the discovery of small molecule modulators of epigenetic targets, after structural optimization as well as virtual screening studies, here we report the identification of a series of inhibitors of PHF20, that might represent new opportunities to investigate the role of this protein in chromatin biology and drug discovery.



References: 1. Adams-Cioaba, M. A.; Min, J. Structure and function of histone methylation binding proteins. *Biochem. Cell Biol.* **2009**, 87, 93–105. 2. Rister, J.; Desplan, C. Deciphering the genome’s regulatory code: the many languages of DNA. *Bioessays* **2010**, 32, 381–384. 3. Heisel, S. M.; Ketter, R.; Keller, A.; Klein, V.; Pallasch, C. P.; Lenhof, H. P.; Meese, E. Increased seroreactivity to glioma-expressed antigen 2 in brain tumor patients under radiation. *PLoS One* **2008**, 3, e2164. 4. Bankovic, J.; Stojic, J.; Jovanovic, D.; Andjelkovic, T.; Milinkovic, V.; Ruzdijic, S.; Tanic, N. Identification of genes associated with non-small-cell lung cancer promotion and progression. *Lung Cancer* **2010**, 67, 151–159.

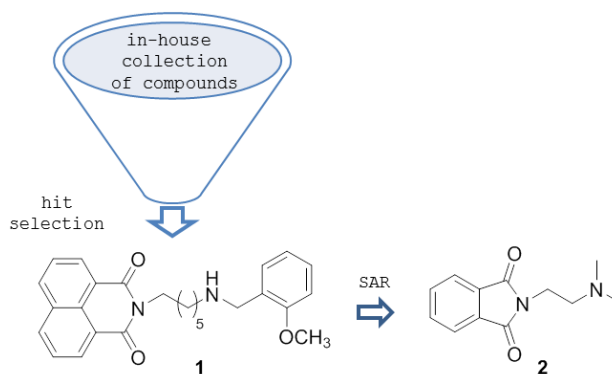
Discovery of naphthalimide-based non-ATP competitive GSK-3 β inhibitors by an ESI-Q-TOF method

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Glycogen synthase kinase-3 β (GSK-3 β) is a serine/threonine kinase largely expressed in the central nervous system (CNS), which proved to play a significant role in regulating tau phosphorylation under both physiological and pathological conditions, being implicated in the formation of amyloid beta (A β) plaques and neurofibrillary tangles (NFTs). In particular, GSK-3 β dysregulation is assumed to contribute to the aetiology of chronic conditions such as cancer, and Alzheimer's disease (AD).¹ However, most of the available GSK-3 β inhibitors binds to the ATP-binding site which is highly conserved in all the human kinome²; therefore, such agents are endowed with low selectivity. Nowadays, only few non-ATP competitive GSK-3 β inhibitors are available and, in light of these considerations, the discovery of agents acting through this mechanism of action is highly desirable.

Aim of the present investigation was the design of new low molecular weight non-ATP competitive GSK-3 β inhibitors. To reach this goal, a straightforward ESI-QTOF method, enabling fast hit selection and detailed kinetic characterization of GSK-3 inhibitors, was developed.³ Taking advantage of this new methodology, an in-house collection of compounds was screened towards GSK-3 β , leading to the discovery of **1**, a prototype of a new class of hits able to inhibit GSK-3 β . Following Structure-Activity Relationships campaign, we discovered compound **2** characterized by a K_i value of 3.49 μ M. The kinetic analysis carried out by this new spectrometric method revealed compound **2** as a nonATP-competitive mechanism of action.⁴



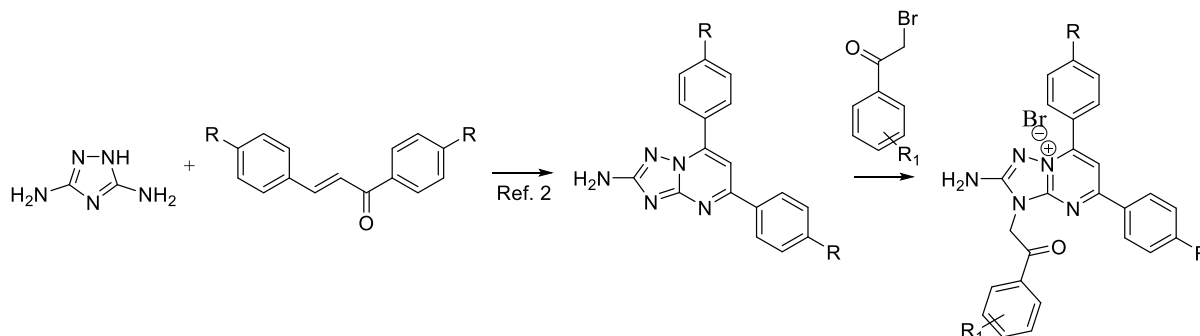
References: 1. M. Llorens-Marítin, J. Jurado, F. Hernández, J. Ávila, GSK-3 β , a pivotal kinase in Alzheimer disease. *Front. Mol. Neurosci.* 7 (2014) 1–11. 2. R.M. Eglén, T. Reisine, The current status of drug discovery against the human kinome. *Assay Drug Dev. Technol.* 7 (2009) 22–43. 3. A. De Simone, J. Fiori, M. Naldi, A. D'Urzo, V. Tumiatti, A. Milelli, V. Andrisano, Application of an ESI-QTOF method for the detailed characterization of GSK-3 β inhibitors. *J Pharm Biomed Anal.* (2017) online. 4. A. De Simone. et al. *manuscript in preparation*

Design, synthesis and biological evaluation of triazolopyrimidinium salts as novel antiproliferative agents

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Nowadays, cancer is one of the most common diseases in the world, associated with the highest mortality rate. According to the cancer statistics from National Cancer Institute (NCI), more than a million and a half of new cases of cancer have been estimated in 2017 and almost a third of diagnosed people will die. In general, the lack of evident or specific signs or symptoms makes cancer difficult to detect. Moreover, treatments for this deadly disease, including chemotherapy, radiation therapy and surgery when possible, depend on the type and the stage of cancer and most of times they are not completely successful and effective (1). Taken together, these statistics show how urgent is the discovery of new drugs to treat cancer. With this purpose, we identified the triazolopyrimidine nucleus as scaffold for the design of new antitumor agents. The salts were obtained from the triazolopyrimidine nucleus, firstly synthesized following the procedure described by Desenko et al. (2), by N-alkylation with bromoacetophenone, bearing various substituents on the aromatic ring.



The amino group was also subject of alkylation and acylation to enlarge our library of compounds. A primary screening against several different tumor cell lines showed that the new synthesized salts have a good antiproliferative effect, particularly against pancreatic cancer cells. Preliminary study showed that some derivatives may induce ROS production. Further mechanistic assays are ongoing to establish the pathway by which they cause cell death.

References: 1. <http://seer.cancer.gov/> 2. S. M. Desenko, N. N. Kolos, M. Tuéni, and V. D. Orlov, (1990) *Khimiya Geterotsiklicheskih Soedinenii*, vol. 7, pp. 938-941.

Discovery and characterization of potent F508del-CFTR correctors

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Cystic fibrosis (CF) is a fatal genetic disease affecting approximately 1 in circa 2500 live births in the Caucasian population. The disease is caused by mutations in the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) gene that result in loss-of-function of the CFTR protein, an ion channel involved in Cl⁻ and HCO₃⁻ transport in multiple organs. The most frequent mutation among patients with CF, the deletion of phenylalanine at position 508 (F508del), causes a defective maturation and impaired gating of the CFTR protein. The maturation defect can be treated with compounds known as correctors, whereas the gating defect can be overcome by compounds called potentiators (1). Only one corrector has been approved, in combination with a potentiator, for the treatment of CF patients bearing the F508del-CFTR mutation, i.e. lumacaftor (VX-809), but the therapeutic benefit of the combination is limited. There is therefore the need of new, more effective correctors.

To discover new correctors, the D3's compound collection, containing around 15,000 maximally diverse commercial compounds, was screened in two different cell types, FRT and CFBE41o- stably expressing F508del-CFTR and the Halide-Sensitive Yellow Fluorescent Protein (HS-YFP) (2). Primary hits from the high throughput screening were tested at 6 different concentrations in the same cell types and those showing dose-dependent activity were confirmed in secondary assays. Two confirmed hits, belonging to two different chemical classes, were selected for investigation of the Structure-Activity Relationships (SARs).

The medicinal chemistry work led to compounds with improved potency and efficacy with respect to the confirmed hits. A set of correctors showed high efficacy and potency in the low nanomolar range when tested in the HS-YFP assays. Further characterization of those compounds in the Trans-Epithelial Electrical Conductance (TEEC) assay, run on F508del-CFTR FRT cells, confirmed their high efficacy and potency. Finally, the most interesting correctors were tested in primary bronchial epithelial cells from CF patients homozygous for the F508del mutation. A number of compounds showed efficacy comparable or superior to that of the VX-809. Most interestingly, a few compounds retained very good efficacy at a concentration as low as 10 nM, a concentration at which no activity was observed for VX-809. The modifications of the confirmed hits to increase their activity were also accompanied by an improvement of their drug-like properties. The data generated on the most promising correctors will be presented and discussed.

This work was supported by the Italian Foundation for Cystic Fibrosis (FFC) as part of the "Task Force for Cystic Fibrosis" project.

References: 1. Lukacs et al., Trends Mol. Med., 2012, 18, 81-91. 2. Galiotta et al., Am. J. Physiol., 2001, 281, C1734–C1742

The kinase inhibitor pyrazolyl-urea GeGe3 inhibits angiogenesis and reveals dystrophin myotonic protein kinase (DMPK)1 as a novel angiogenesis target

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Activation of alternative receptor tyrosine kinases by compensatory angiogenic factors was implicated in the failure of targeting VEGF/VEGFR2 signalling in cancer therapy. Targeting MAPK and PI3K signaling pathways, commonly induced by angiogenic factors, may be an alternative approach. In previous studies, we developed several chemical libraries able to block activation of ERK1/2, p38MAPK and AKT in neutrophils stimulated by IL-8 or formyl-methyl-leucyl-phenylalanine (fMLP) peptide and inhibit neutrophil migration (1,2 and references therein cited). More recently we designed and synthesized a large series of pyrazolyl-ureas and imidazo-pyrazole-carboxamides and found them to differently modulate the activity of ERK1/2, p38MAPK and AKT in human umbilical vein endothelial cells (HUVEC) stimulated by VEGF (3). Our library revealed the ethyl 1-(2-hydroxypentyl)-5-(3-(3-(trifluoromethyl)phenyl)ureido)-1*H*-pyrazole-4-carboxylate (named GeGe3, Fig. 1) to be an inhibitor of HUVEC migration. This suggested that GeGe3 may be a potential blocker of angiogenesis.

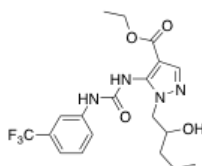


Figure 1. Compound GeGe3 structure

GeGe3 was further analysed *in vitro* on proliferation of HUVEC and cancer cell lines, and *in vivo* on physiological angiogenesis in Tg(fli1a:EGFP)y1 zebrafish embryos as well as pathological angiogenesis in Lewis Lung carcinoma LLC1 tumors in C57BL/6 mice. GeGe3 targets were identified by using Pamgene[®]12 arrays. The candidate kinases were further characterized biochemically and their relevance in angiogenesis was challenged.

Results: GeGe3 blocked ERK1/2 and AKT activation and inhibited the migration and proliferation of HUVEC, but showed no effect on proliferation of human and mouse cancer cell lines *in vitro*. Accordingly, GeGe3 impaired intersegmental angiogenesis during development of zebrafish embryos. In mice, GeGe3 blocked angiogenesis and tumor growth in transplanted subcutaneous Lewis Lung Carcinomas (LLC1). Screening for GeGe3-targeted kinases revealed Aurora B, Aurora C, NEK10, polo-like kinase (PLK)2, PLK3, DMPK1 and CAMK1 as candidate targets. In-depth examination revealed DMPK1 as a new mediator of angiogenesis through controlling the full activation of MAPK signaling pathways. GeGe3 alters angiogenesis by targeting DMPK in tumor endothelial cells and pericytes. **Conclusion:** The pyrazolyl-urea GeGe3, a blocker of MAPK and PI3K pathways, strongly inhibits physiological and tumor angiogenesis. In addition, we identified direct targets of GeGe3 including DMPK1, a new angiogenesis target. Synthesis and complete biological data will be reported in poster session.

References: 1. Bruno O, Brullo C, Bondavalli F, *et al.* *Bioorg Med Chem* 17, 3379-3387 (2009). 2. Brullo C, Spisani S, Selvatici R, Bruno O. *Eur J Med Chem* 47, 573-579, (2012). 3. Selvatici R, Brullo C, Bruno O. and Spisani S. *Eur J Pharmacol* 718, 428-434, (2013). 4. Meta E, Brullo C, Sidibé A, Imhof BA and Bruno O. *Eur J Med Chem* 133, 24-35 (2017).

Structural and functional characterization of the GEBR library: selective targeting of PDE4D for cognitive improvement in neurodegenerative diseases

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The inhibition of human phosphodiesterase-4 (PDE4) has been proposed as a strategy for the treatment of several neurodegenerative and inflammatory pathologies (1,2,3,4). Over the last few years, the design of compounds that are selective for specific PDE4 isoforms (mostly PDE4D and PDE4B) has been explored as a way to limit the side effects (emesis and diarrhea) that are associated with unspecific PDE4 inhibition (5,6,7,8). In particular, the so-called GEBR library has been developed in an effort to selectively inhibit PDE4D for cognitive amelioration in Alzheimer's disease (AD) patients. Indeed, some compounds of this library have been shown to have interesting pro-cognitive and memory enhancement properties in AD transgenic mice (5, 6, 7); however, to date no structural data describing their interactions with the enzyme has been made available in the literature. Using a combination of structural biology (X-ray crystallography), biochemistry (enzymatic assays) and *in silico* modelling (molecular dynamics), we set out to address the biochemical behavior of the large GEBR library in order to gain a mechanistic insight into the action of these compounds and pave the way to the rational design of the next generation of inhibitors.

So far, we have solved several high resolution crystal structures of the complex between the PDE4D catalytic domain and the most active GEBR molecules, thus allowing for the detailed identification of the binding mode of each ligand and the precise chemical features that influence its interaction with the target. Among these, the nature of the central moiety plays a crucial role in the conformational freedom of the inhibitor. Based on the different conformations of the ligands, we hypothesize an involvement of the regulatory domains of the enzyme (not present in our crystal structure) as possible interactors. Therefore, we are now investigating the differential inhibition properties of the library between the catalytic domain and the full length enzyme. Moreover, owing to the difficulty in crystallizing the full length version of the enzyme, we are also addressing this issue by simulating the behavior of the whole system by molecular dynamics (MD).

Structure analysis results will be discussed during the poster session.

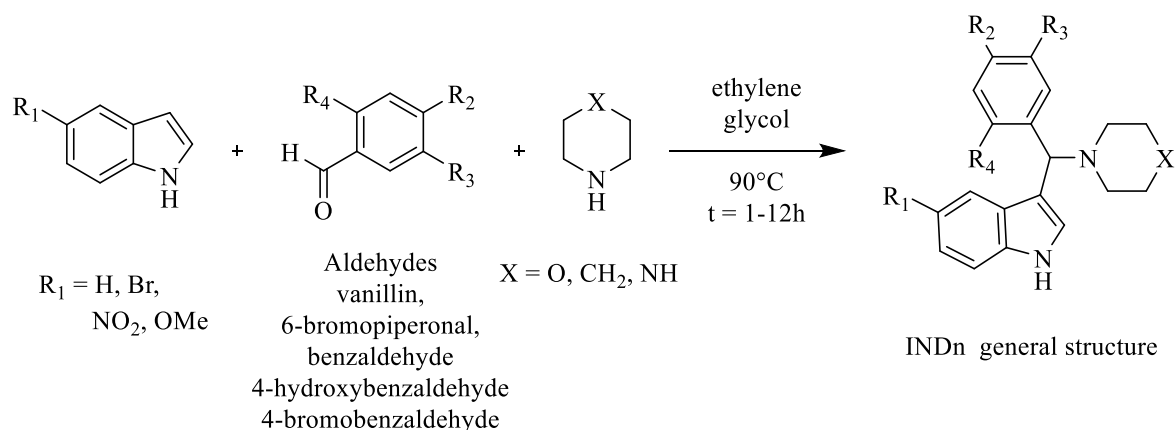
References: 1. García-Osta, A., Cuadrado-Tejedor, M., *et al.* *ACS Chem. Neurosci.* 3, 832–844 (2012). 2. Ricciarelli, R. & Fedele, E. *Br. J. Pharmacol.* 172, 4785–4789 (2015). 3. Bruno O., Ricciarelli R., *et al.* *Neuropharmacology* 85, 290–292 (2014). 4. Gurney, M.E., D'Amato, E.C. & Burgin, A.B. *Neurotherapeutics* 12, 49–56 (2014). 5. Bruno, O., Romussi A., *et al.* *J. Med. Chem.* 52, 6546–6557 (2009). 6. Bruno, O., Fedele E. *et al.* *Br. J. Pharmacol.* 164, 2054–2063 (2011). 7. Brullo, C., Massa M. *et al.* *J. Med. Chem.* 57, 7061-72 (2014). 8. Brullo, C., Massa, M. *et al.* *Bioorg. Med. Chem.* 23, 3426-3435 (2015). 9. Brullo C, Ricciarelli R, *et al.* *Eur J Med Chem.* 124, 82-102 (2016). 10. Ricciarelli, R., Brullo C. *et al.* *Sci. Rep.* 7, 46320 (2017).

A multi-component one-pot synthesis of 3-amino alkylated indoles, new interesting anti-proliferative agents against breast cancer cells

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Indole nucleus is a very useful scaffold to develop biologically active molecules, especially anticancer compounds. (1,2) Several indole-based molecules have been synthesized and their antitumor activity evaluated in various cancer cell lines, including breast cancer ones. (3,4) Breast cancer is the most prevalent cancer and the second leading cause of cancer mortality in women with estrogen receptor α -positive (ER α +) disease. (5) Also, the G protein-coupled estrogen receptor-1 (GPER-1) emerged as a useful target to treat the most aggressive triple negative breast cancer. From the medicinal chemist point of view various scaffolds have been already widely studied. A green chemistry approach was followed to variously decorate the 3-aminoalkylated indole. The antitumor activity of the obtained derivatives was evaluated against three different human breast cancer cell lines (MDA-MB-468, MDA-MB-231, SKBR3). All the compounds showed a dose-dependent anti-proliferative effect, in particular against Triple Negative breast cancer cell line MDA-MB-231. Further investigations will identify the mechanism of action and the biological target of the new derivatives.



References: 1. M. Kidwai, R. Venkataramanan et al., *Curr. Med. Chem.* 2002, 9, 1209-1228. 2. S.A. Patil, R. Patil et al., *Future Med. Chem.* 2012, 4(16), 2085-2115. 3. M.T. El Sayed, N.A. Hamdy et al., *Adv Mod Oncol Res* 2015, 1(1), 20-35. 4. F. Grande, I. Barone et al., *Future Med. Chem.* 2016, 8 (2), 93-106. 5. H.E. Burks, T. Abrams et al., *J. Med. Chem.* 2017, DOI:10.1021/acs.jmedchem.6b01468.

Design and synthesis of a new series of indole-based compounds as antitumor agents

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The indole scaffold represents one of the most important structural motifs for the discovery of new biological active compounds (1).

A series of indole-based derivatives was identified as potential antitumor agents, particularly against HeLa cell line. Compound 3-(((2-([1,1'-biphenyl]-4-yl)ethyl)(methyl)amino)methyl)-N-(4-fluorophenyl)-1-methyl-1H-indole-5-carboxamide (compound **1**) showed an interesting cytotoxic effect with an IC₅₀ of 0.24 μM at 48h (Figure 1).

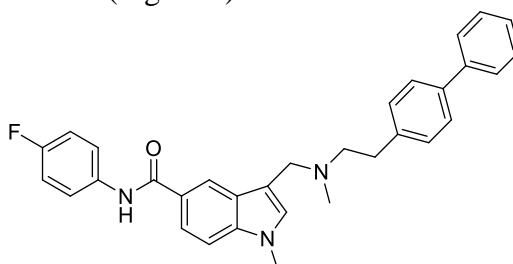


Figure 1: compound **1** (IC₅₀ = 0.24 μM).

Starting from compound **1** and aimed to improve the cytotoxic activity, we have recently designed and synthesized a new series of indole-based derivatives to elucidate the structure-activity relationships at the basis of the biological activity.

The structural modifications involve replacement of the:

- 1) Biphenylethylamine group
- 2) Methyl group on tertiary amine
- 3) Methyl group at the N-1
- 4) Amidic substituent in C-5

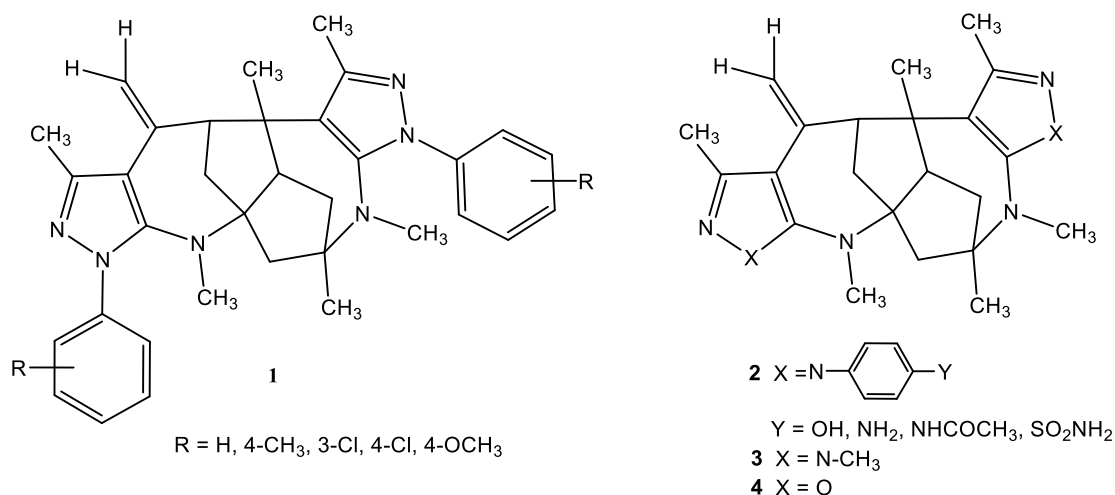
References: Vikas Sharma et al. Biological Importance of the Indole Nucleus in Recent Years: A Comprehensive Review *J. Heterocyclic Chem.*, 47, 491 (2010)

Synthesis and biological activity of new complex polycyclic compounds: autophagy and apoptosis induction

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Previously we reported the synthesis of new polycyclic compounds **1** by reacting methylaminopyrazoles and hexane-2,5-dione in 1,4-dioxane in the presence of p-toluensulfonic acid [1]. Some of them resulted be endowed with antiproliferative activity when tested against the NCI panel of human tumoral cell lines. In order to gain more insight on the SAR of this class of compounds, as well as on their mechanism of action, we synthesized the new analogues **2**, **3** and **4**. Compounds **2** bear hydrophilic substituents to each of two phenyl groups, compound **3** bears methyls linked to pyrazole moieties in the place of phenyls, whereas compound **4** contains the isoxazole ring as heterocycle, in substitution of the pyrazole ring. All the above compounds have an increased potential for H bonds formation and/or higher water solubility as compared to compounds 1. Preliminary studies were concerned with the effect of one of compounds **2** (X= OH) on MDA-MB231 cells, a triple negative breast cancer cell line. This compound reduced cell viability in a dose and time-dependent manner, showing an IC₅₀ at 48 h of treatment of 12.5 μM. Exploring the biological activity of the compound we demonstrated that this compound causes a G2/M cell cycle arrest at 24-48 h of treatment, followed by a remarkable DNA fragmentation at 48-72 h. Morphological analyses of cells incubated with monodansylcadaverine revealed that the effects of the compound observed in the first phase of treatment are related to the production of dot-like structures and activation of LC-3, two known hallmarks of autophagy. Since autophagy occurred in the first 24 h of incubation with the compound, it probably served as a pro-survival mechanism that was followed by the apoptotic program at 48-72h as demonstrated by chromatin condensation, DNA fragmentation and caspase 9 activation.



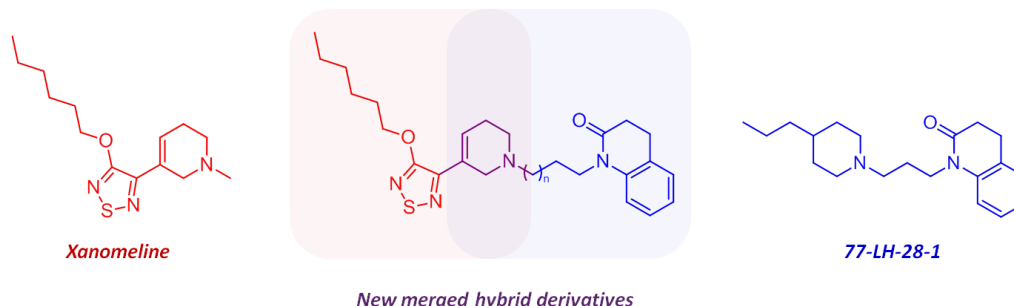
Reference: 1. B. Maggio, D. Raffa, M.V. Raimondi et al., Eur. J. Med. Chem. 72 (2014) 1-9.

Synthesis of a group of novel Xanomeline/77-LH-28-1 hybrid ligands and their FRET investigation at muscarinic acetylcholine receptor subtypes

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In connection with our interest in investigating novel rationally designed bitopic (i.e., orthosteric/allosteric) derivatives targeting muscarinic acetylcholine receptor (mAChR) subtypes (1,2,3), in this study we designed and synthesized a new set of ligands that integrate in the same molecular skeleton the pharmacophoric moieties of Xanomeline and of 77-LH-28-1 (1-[3-(4-butyl-1-piperidinyl)propyl]-3,4-dihydro-2(1*H*)-quinolinone). Xanomeline is a well-known M₁/M₄-preferring orthosteric agonist, which ameliorated cognitive impairments in Alzheimer's disease patients and showed activity in various models of schizophrenia, thus being potentially beneficial for treatment of positive, negative and cognitive symptoms (4). On the other hand, 77-LH-28-1 was characterized as an M₁-selective, positive allosteric modulator, thus representing an interesting pharmacological tool with cognition enhancing properties (5). As illustrated below, we planned the novel biparmacophoric derivatives as merged structures, with the tetrahydropyridine nucleus of Xanomeline as the central core.



In the last years, different receptor sensors, based on the fluorescence resonance energy transfer (FRET), were generated for various G protein-coupled receptors, and represented a valuable tool to investigate real time receptor activation as well as ligand-receptor interactions. Recently, this analysis was performed also on a set of bitopic ligands designed for a selective interaction with M₁ mAChRs (6). Our preliminary results on the group of Xanomeline/77-LH-28-1 hybrid compounds indicate, for the M₁ sensor, a reproducible activation response, which depends on the linker length. Conversely, no FRET-related effect could be detected at the M₂ sensor. Thus, a critical spacer length of the hybrid compounds induces conformational changes with a degree of selectivity for the M₁ muscarinic receptor. The synthesis and the results of pharmacological investigation will be presented and discussed.

References: 1. J. Antony, K. Kellersohn, M. Mohr-Andrä, A. Kebig, S. Prilla, M. Muth, E. Heller, T. Disingrini, C. Dallanoce et al., *FASEB J* **2009**, *23*, 442-450. 2. A. Bock, B. Chirinda, F. Krebs, R. Messerer, J. Bätz, M. Muth, C. Dallanoce et al., *Nat. Chem. Biol.* **2014**, *10*, 18-20. 3. A. Bock, M. Bermudez, F. Krebs, C. Matera, B. Chirinda, D. Sydow, C. Dallanoce et al., *J. Biol. Chem.* **2016**, *291*, 16375-16389. 4. S. Barak, I. Weiner, *Int. J. Neuropsychoph.* **2011**, *14*, 1233-1246. 5. C. J. Langmead, N. E. Austin, C. L. Branch, J. T. Brown, K. A. Buchanan, C. H. Davies, I. T. Forbes et al., *Br. J. Pharmacol.* **2008**, *154*, 1104-1115. 6. R. Messerer, M. Kauk, D. Volpato, M. C. Alonso Canizal, J. Klöckner, U. Zabel, S. Nuber, C. Hoffmann, U. Holzgrabe, *ACS Chem. Biol.* **2017**, *12*, 833-843.

77-LH-28-1 as a model for the rational design of selective dopamine D₄ receptor ligands

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M₁ muscarinic acetylcholine receptor (M₁ mAChR) represents an attractive target for the treatment of cognitive deficits associated with several pathologies, including Alzheimer's disease and schizophrenia. However, the discovery of subtype-selective agonists is hampered by the high degree of homology among the M₁-M₅ mAChR subtypes at the orthosteric binding site. The advent of functional screening assays allowed the identification of ligands, such as 77-LH-28-1, which bound to an allosteric site and selectively activated the M₁ mAChR (1). Initially described as an allosteric agonist by GlaxoSmithKline, at present 77-LH-28-1 is considered a bitopic agonist (2). It displayed antipsychotic and cognition-enhancing efficacy in pre-clinical models of schizophrenia and Alzheimer's disease (1). Unfortunately, its efficacy was confounded by nonselective effects on other receptors (3). Among these receptors, 77-LH-28-1 has been reported to bind the short isoform of the dopamine D₂ receptor (D_{2S}R) (4). Dopamine D₂-like subfamily includes D₂R, D₃R and D₄R subtypes. The wide expression of D₂-like receptors in the central nervous system and the modulation of various neurological processes, including gratification, cognition, learning and memory, make them attractive therapeutic targets (5). To get more information about the pharmacological dopaminergic properties of 77-LH-28-1, this compound was evaluated for its affinity at dopamine D₂-like receptor subtypes by radioligand binding assays. Surprisingly, 77-LH-28-1 showed high affinity and selectivity for D₄R over D₂R and D₃R. To better understand the structural features required for the selective interaction with D₄R, the aliphatic butyl chain of 77-LH-28-1 was modified and the novel compounds **1-6** were prepared. Moreover, the piperidine ring of 77-LH-28-1 was replaced by a piperazine nucleus, to give the novel derivatives **7-13** (Figure 1).

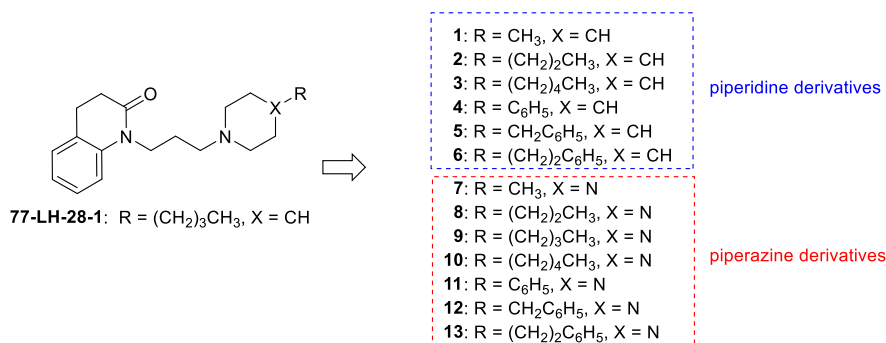


Figure 1

All the compounds were evaluated for their affinity at dopamine D₂R, D₃R and D₄R subtypes, as well as at the five mAChR subtypes. Compounds showing the highest affinities at D₄R were also evaluated for their functional activity considering both G-protein activation and β -arrestin recruitment. The most interesting derivatives can be emphasized as biased D₄R compounds, behaving as potent partial agonists for G-protein activation and potent antagonists in β -arrestin recruitment. The detailed results of the biological assays performed to the new derivatives will be reported.

References: 1. Langmead, C.J.; Austin, N.E.; Branch, C.L.; Brown, J.T.; Buchanan, K.A.; et al. *Br. J. Pharmacol.* **2008**, *154*, 1104-1115. 2. Keov, P.; López, L.; Devine, S.M.; Valant, C.; Lane, J.R.; Scammells, P.J.; et al. *J. Biol. Chem.* **2014**, *289*, 23817-23837. 3. Vanover, K.E.; Veinbergs, I.; Davis, R.E. *Behav Neurosci.* **2008**, *122*, 570-575. 4. Heinrich, J.N.; Butera, J.A.; Carrick, T.; Kramer, A.; Kowal, D.; Lock, T.; et al. *Eur. J. Pharmacol.* **2009**, *605*, 53-56. 5. Zhang, A.; Neumeyer, J. L.; Baldessarini, R. J.; *Chem. Rev.* **2007**, *107*, 274-302.

Design and synthesis of tetrahydrobetacarboline-based derivatives as new TRPM8 modulators

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Transient receptor potential melastatin type 8 (TRPM8) is a transmembrane, nonselective Ca²⁺ permeable cation channel,¹ considered as the major sensor for peripheral innocuous cool, and its modulation contributes to a wide range of physiological and pathophysiological processes.⁽¹⁾ One of the most investigated effects produced by TRPM8 modulation is the analgesia against chronic and neuropathic pain: in fact, it has been reported that peripheral and central activation of TRPM8 induces analgesia, specifically reversing the sensitization of the behavioral reflexes elicited by peripheral nerve injury.⁽²⁾ In the search for TRPM8 inhibitors, we have recently identified two hits bearing a tetrahydrobetacarboline scaffolds (derivatives **1**, **2**). These two small molecules have been characterized both by fluorescence-based and patch-clamp assays. (Figure 1)

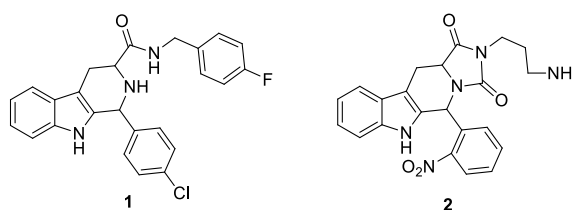


Figure 1. Compounds acting as antagonists of TRPM8

They showed selectivity over TRPM8, lacking of pharmacological activity over TRPA1 and TRPV1 and a potency in the micromolar range. On the basis of these findings, we have designed and synthesized a new library of compounds using a differently decorated tetrahydrobetacarboline motif (figure 2) in the search for a rationale structure-activity relationship and for more potent *lead compound*.

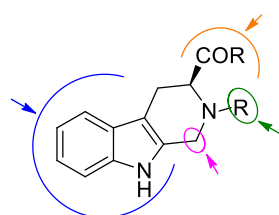


Figure 2. Possible derivatization positions on the tetrahydrobetacarboline motif

References: 1. Bertamino, A. et al. Tryptamine-based derivatives as Transient Receptor Potential Melastatin type-8 (TRPM8) channels modulators. *J. Med. Chem.* **2016**, 59 (5), pp 2179–21. 2. Proudfoot, C. et al. Analgesia mediated by the TRPM8 cold receptor in chronic neuropathic pain. *Curr. Biol.* **2006**, 16, 1591–1605.

Development of small modulators of protein-protein interactions endowed with anticancer activity

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LxxLL-like motif has been reported as one of the most representative protein-recognition motifs in cell cycle regulation (1, 2). Then, the identification of small molecules able to mime the hydrophobic side chains of the interacting residues of this binding motif is an intriguing task potentially endowing compounds with antiproliferative activity. Recently we have reported the cytotoxic activity of a small set of pyrrole derivatives on different tumor cell lines (MCF7, Huh7, M14, Jurkat) as well as on mouse monocyte macrophages (Raw) cell line (3). Molecular modeling studies carried out on the most active compound of this series (4-benzoyl-5-methyl-1-(4-methylbenzylbenzyl)-1H-pyrrole-2-carboxylic acid 3-chlorobenzylamide), indicated its ability to reproduce the same orientation of the hydrophobic side chains of the *i*, *i*+3, *i*+4 as well as *i*, *i*+4, *i*+7 residues in LxxLLxxL-like motifs. Biological studies evidenced the involvement of p53 in its mechanism of action and supported the hypothesis that our lead is a mimetic of *i*, *i*+4, *i*+7 residues of the p53 ¹⁹FxxLWxxL²⁶ motif in its interaction with the binding partner MDM2. In order to extend our SAR investigation, a new set of pyrrole-based analogues has been designed and synthesized. The new analogues have been tested on A375 and HTT-116 tumor cell lines taking into account their solubility in PBS buffer, evaluated by Lipinski's approach (4).

References: 1. Plevin M. J.; Mills M. M.; Ikura M. *Trends Biochem Sci.* **2005**, *30*, 66-69. 2. Litterst C. M.; Pfitzner E. *J. Biol. Chem.* **2002**, *277*, 36052–36060. 3. Persico M.; Ramunno A.; Maglio V.; Franceschelli S.; Esposito C.; Carotenuto A.; Brancaccio D.; De Pasquale V.; Pavone L. M.; Varra M.; Orteca N.; Novellino E.; Fattorusso C. *J. Med. Chem.* **2013**, *56*, 6666–6680. 4. Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Delivery Rev.* **2001**, *46*, 3–26.

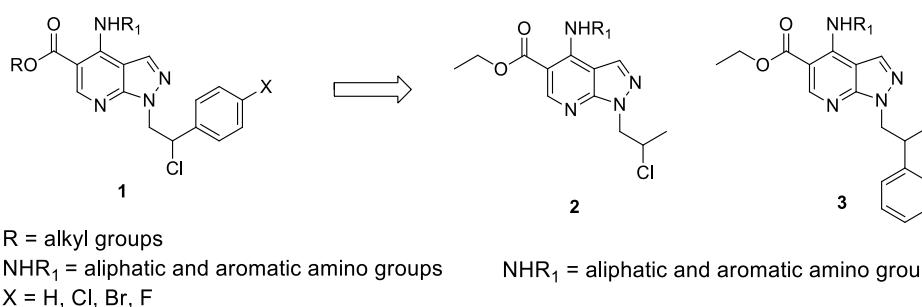
Substituted pyrazolo[3,4-*b*]pyridines as potent A₁ adenosine antagonists

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Adenosine is an endogenous neuromodulator which mediates its effects by interacting with four G-protein-coupled receptor subtypes named A₁, A_{2A}, A_{2B} and A₃. These receptors are distributed in a wide variety of tissues, including the central nervous system (CNS), cardiovascular system and airways, where they play key roles in the regulation of several biological functions. Many studies showed that some pathophysiological states are associated with changes of adenosine levels, making the search for adenosine receptor agonist or antagonist an interesting target in medicinal chemistry (1). In particular, an excessive stimulation of A₁ adenosine receptors (A₁ARs) is related to different pathologies, such as various forms of dementia, including Alzheimer's disease, depression, congestive heart failure, bradyarrhythmias and asystolic arrest. For these reasons, many A₁ARs antagonist have been developed in the last decades (2).

In this context, our group synthesized a wide library of 4-aminopyrazolo[3,4-*b*]pyridine-5-carboxylic acid esters **1** active as A₁AR antagonists both on bovine and human receptors; some of these compounds are characterized by high affinity and selectivity towards A₁AR, with the most active compounds having a bovine A₁AR affinity in the low nanomolar range (3). Starting from these promising results, we decided to synthesize a second generation of compounds **2**, with the aim of obtaining more potent and selective agents for human A₁AR. Since previous studies indicated that human A₁ARs contain a binding pocket smaller than that of bovine receptors, we substituted the N1 2-chloro-2-phenylethyl chain with the less bulky 2-chloropropyl chain. Furthermore, to extend SAR evaluations, we synthesized compounds **3** bearing in N1 the 2-phenylpropyl chain. Assays performed on bovine cortical membranes and human A₁AR CHO transfected cells show that compounds **2** are endowed with an improved activity on human A₁AR compared with the first generation derivatives **1**. Derivatives **3**, as expected, show good affinity for bovine A₁ARs, but are less active on human A₁ARs. Biological data will be reported in the poster section.



General structures of first generation (**1**) and second generation (**2** and **3**) of pyrazolo[3,4-*b*]pyrimidines.

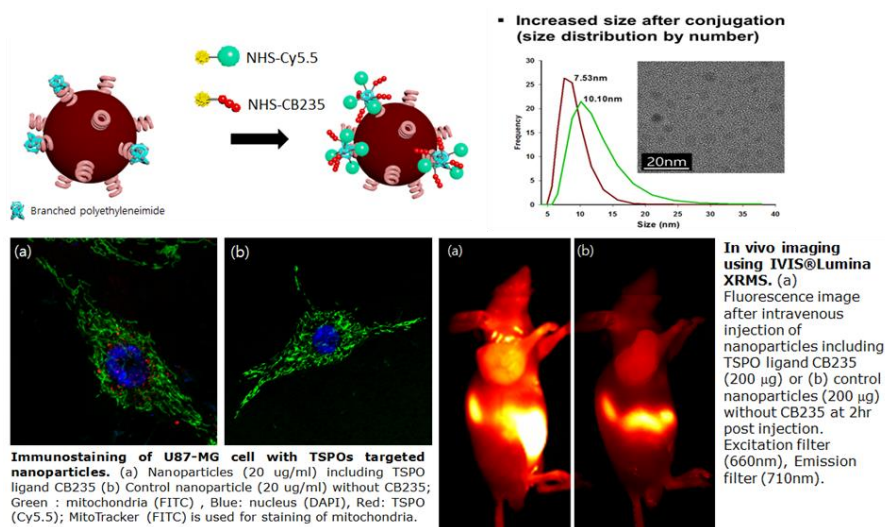
References: 1. Chen, J. F. *et al.* Nat. Rev. Drug Discov. 2013, 12, 265-286. 2. Schenone, S. *et al.* Curr. Top. Med. Chem. 2010, 10, 878-901. 3. Tuccinardi, T. *et al.* Chem. Med. Chem. 2008, 3, 898-913.

***In Vivo* fluorescence imaging of glioblastoma using Translocator Proteins (TSPOs) targeted nanoparticles**

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Translocator protein (TSPO) is a five transmembrane domain protein mainly located in the outer mitochondrial membrane. Interestingly, TSPO is overexpressed in a variety of tumors, namely, ovarian cancer, liver tumors, breast carcinoma, colorectal cancer and certain brain tumors such as the glioblastoma multiforme (GBM) and its expression appears to be related to the degree of tumor malignancy (1). GBM is the most common and lethal type of primary brain tumor. In fact, the median survival of GBM patients is less than 16 months despite optimal treatment of currently available therapies. Complete surgical resection of GBM is critical to improve GBM treatment, thus increasing the survival of affected patients. Based on the enhanced expression of TSPO in GBM, the aim of the study was the development of TSPO targeted iron oxide nanoparticles (10.1 nm) using an imidazopyridine based TSPO ligand, namely CB235 (2), and a near-infrared fluorescent dye, specifically Cy5.5, for successful delineation of GBM during surgery. *In vitro* cell imaging experiment showed selective sensitivity of the developed nano-probe for TSPO-rich cell lines including U87-MG human GBM cells, PC-3 human prostate cancer cells instead of CCD-986sk human fibroblasts used as control and characterized by low TSPO expression. *In vivo* experiments conducted on a human GBM U87-MG xenografts animal model proved the specificity of the probe to target GBM. In particular, TSPO targeted nano-probes were compared to non-targeted control nanoparticles (7.53 nm) and showed superior signal-to-noise ratio for GBM. Taken together, the high affinity for TSPO of compound CB235, the passive targeting of nanoparticles also known as Enhanced Permeability and Retention effect and the suitable optical characteristics of near-infrared fluorescent dye for *in vivo* imaging, highlight the possibility of our imaging technique to improve GBM visualization during surgery.



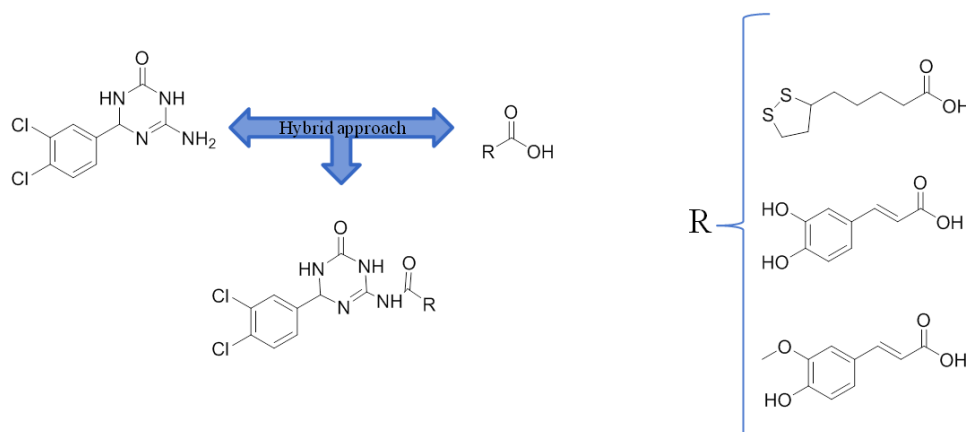
References: 1. Denora N. et al. *Coordination Chemistry Reviews*, **2017**, 341, 1-18. 2. Denora N. et al. *Journal of Controlled Release*, **2013**, 172, 1111-1125.

Novel Hybrid Compounds Dual Targeting GSK-3 β and Oxidative Stress for the Treatment of Alzheimer's disease

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Alzheimer's disease (AD) is a complex multifactorial pathology in which beta amyloid plaques, neurofibrillary tangles and oxidative stress play a fundamental role in the underlying neurodegeneration (1). In this respect, the multi-target-directed ligands (MTDLs) approach could possibly be a more efficient solution to combat the disorder (2). On this basis, the project's purpose was to synthesize novel MTDLs, which can inhibit the GSK-3 β enzyme and at the same time present a strong antioxidant action. Indeed, GSK-3 β is a validated target in the tau cascade and reactive oxygen species (ROS) production is another critical player in AD pathogenesis. To achieve this, we fused two chemical scaffolds, i.e. a triazinone and a structure with antioxidant function, as depicted below. The 6-amino-4-(3,4-dichlorophenyl)-3,4-dihydro-1,3,5-triazin-2(1H)-one fragment has been selected because of its reported ability to inhibit GSK-3 β at a micromolar level concentration (3). Lipoic, ferulic and caffeic acids have been chosen as the anti-oxidant fragments, thanks to their well-known neuroprotective and ROS scavenging properties (4). By exploiting the carboxylic function of the selected acids, a series of new hybrids has been synthesized through coupling reactions with the amino group in position 6 of the triazinone. To preliminary investigate the anti-AD potential of the synthesized hybrids, we will perform biological assays aimed to test their GSK-3 β inhibitory activity and to evaluate their cellular neuroprotective and antioxidant properties.



References: 1. <https://www.nia.nih.gov/alzheimers/publication/alzheimers-disease-fact-sheet>. 2. Bolognesi, ML et al *ChemMedChem*. **2016**, 20;11(12), 1190-2. doi: 10.1002/cmdc.201600161. 3. Prati, F. et al *Angew Chem Int Ed Engl*. **2015**, 26;54(5), 1578-82. doi: 10.1002/anie.201410456. 4. Feng, Y. et al *Oxid Med Cell Longev* **2012**, 17. <http://dx.doi.org/10.1155/2012/472932>

CLIPS Technology Applied to the Design of Cyclic Peptides with Potent Mixed μ/δ Opioid Activity

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Opiates are widely used in the treatment of pain, but their use is strongly limited by serious side effects such as development of tolerance, physical dependence addiction and respiratory depression. Also, they are not efficacious for the treatment of chronic and neuropathic pain. Recently, it has been demonstrated the existence of physical and functional interactions between the opioid receptors and the formation of homo- and hetero-dimers, like the heterodimeric complex of μ/δ receptors and their contemporary activation might lead to a synergic and more potent analgesic effect at relatively minimum dose of drug (1-4).

Biphalin (Tyr-(D)Ala-Gly-Phe-NH-)₂, a potent mixed μ/δ receptors agonist and DPDPE (Tyr-c[(D)Pen-Gly-Phe]-(D)Pen-OH), a reference cyclic peptide selective for δ receptor have been modified in order to obtain novel cyclic compounds with improved metabolic stability, potency and in vivo efficacy. Several cyclization approaches have been done by our research group and recently we used a different linker in place of disulfide bond by CLIPS approach. The D-Cysteine or D-Penicillamine thiol groups were reacted with three di-bromoylene isomers to close the cycle. The substitution of disulfide bond, which is prone to reduction, with more stable bridges may improve the metabolic stability and the potency in order to increase the analgesic activity of the new compounds. After designing and synthesis, we evaluated their affinity at the μ and δ opioid receptors by using *in vitro* models like competition binding assays and GTP stimulation assays. All the cyclic compounds showed good affinity for δ and μ opioid receptors. *In vivo* antinociception assays have been also carried out and evaluated with the tail flick test, hot plate test and formalin test. We observed that the DPDPE analogue with p-xylene regioisomer exerted a potent analgesic effect ranging from 15 to 60 min, after i.c.v. and s.c. administration, whereas the most active biphalin analogue was the compound containing the o-xylene bridge. In conclusion, we have obtained two potent compounds, one biphalin and one DPDPE derivatives able to elicit a robust antinociceptive effect in rats both after central and local peripheral administration.

References: 1. Ananthan, S. Opioid ligands with mixed μ/δ opioid receptor interactions: An emerging approach to novel analgesics. *AAPS J.* 2006, 8, E118-E125. 2. Mollica, A.; Pinnen, F.; Costante, R.; Locatelli, M.; Stefanucci, A.; Pieretti, S.; Davis, P.; Lai, J.; Rankin, D.; Porreca, F.; Hruby, V. J. Biological active analogues of the opioid peptide biphalin: mixed α/β^3 -peptides. *J. Med. Chem.* 2013, 56, 3419-3423. 3. Costante, R.; Pinnen, F.; Stefanucci, A.; Mollica, A. Potent biphalin analogs with μ/δ mixed opioid activity: in vivo and in vitro biological evaluation. *Arch. Pharm. (Weinheim)* 2014, 347, 305-312. 4. Mollica, A.; Pinnen, F.; Feliciani, F.; Stefanucci, A.; Lucente, G.; Davis, P.; Porreca, F.; Ma, S. W.; Lai, J.; Hruby, V. J. New potent biphalin analogues containing p-fluoro-L-phenylalanine at the 4,4' positions and non-hydrazine linkers. *Amino Acids.* 2011, 40, 1503-1511. 5. Mollica, A.; Davis, P.; Ma, S. W.; Porreca, F.; Lai, J.; Hruby, V. J. Synthesis and biological activity of the first cyclic biphalin analogues. *Bioorg Med Chem Lett.* 2006, 16, 367-372.

Efficient antagonists of SMO and GLI1 Hedgehog signaling targets identified by computational screening

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Hedgehog (Hh) signaling is essential for tissue development and stemness. Activating germline or somatic mutations of genes encoding Hh pathway components are found in basal cell carcinoma (BCC) and medulloblastoma (MB), while uncontrolled Hh signaling has been reported to drive tumor progression in several cancers, including lung, breast, stomach, pancreas and hematopoietic malignancies. For this reason, the development of Hh inhibitors is eliciting great interest in drug discovery.(1)

Based on the availability of structural details of SMO and GLI1, which are the most relevant upstream and downstream regulators of the Hh signaling pathway, respectively, we set up a structure-based screening strategy boosted by computational studies. In the case of SMO, the binding site of drugs and drug-candidates is well established and characterized within the heptahelical bundle of the receptor.(2,3) In the case of GLI1, computational and experimental efforts were first spent to clarify the structural requirements of its binding to DNA and to identify a putative ligand binding site.(4) Subsequently, an *in house* library of natural products and their derivatives was screened *in silico* against SMO and GLI1 targets by means of molecular docking, to identify novel Hh inhibitors. A synthetic chalcone derivative emerged as profitable SMO antagonist providing Hh inhibition *in vitro* on cancer (MB and BCC) and cancer stem cells (MB), and *in vivo* (BCC). The molecule proved to inhibit Hh also in the presence of a drug-resistant form of SMO.(5) Glabrescione B (GlaB), an isoflavone naturally found in the seeds of *Derris glabrescens* (Leguminosae),(4,5,6) emerged as efficient GLI1 antagonist that binds GLI1 zinc-finger and interferes with its interaction to DNA. Remarkably, GlaB inhibited the growth of Hh-dependent MB and BCC cells *in vitro* and *in vivo*, as well as the self-renewal ability and clonogenicity of MB cancer stem cells.

In summary, computational tools proved highly versatile and reliable in understanding the structural requirements of Hh target proteins and in identifying highly efficient small molecule modulators of pharmacological relevance.

References: 1. Infante, P.; Alfonsi, R.; Botta, B.; Mori, M.; Di Marcotullio, L. “Targeting GLI factors to inhibit the Hedgehog pathway”. Trends in Pharm Sci, 2015, 36(8):547-58. 2. Wang, C.; Wu, H.; Evron, T.; Vardy, E.; Han, G.W.; Huang, X.P. Hufeisen, S.J.; Mangano, T.J.; Urban, D.J.; Katritch, V. et al. Nat Commun. 2014; 5: 4355. 3. Alfonsi, R.; Botta, B.; Cacchi, S.; Di Marcotullio, L.; Fabrizi, G.; Faedda, R.; Goggiamani, A.; Iazzetti, A.; Mori, M. J Med Chem. 2017; 60(4): 1469-1477. 4. Infante, P.; Mori, M.; Alfonsi, R.; Ghirga, F.; Aiello, F.; Toscano, S.; Ingallina, C.; Siler, M.; Cucchi, D.; Po, A. et al. EMBO J. 2015; 34(2): 200-17. 5. Infante, P.; Alfonsi, R.; Ingallina, C.; Quaglio, D.; Ghirga, F.; D’Acquarica, I.; Bernardi, F.; Di Magno, L.; Canettieri, G.; Screpanti, I et al, Cell Death & Disease, 2016, 7, e2376. 6. Botta, B.; Gulino, A.; Botta, M.; Mori, M.; Di Marcotullio, L.; Infante, P.; Ghirga, F.; Toscano, S.; Ingallina, C.; Alfonsi, R. 2014, PCT Int. Appl., WO 2014207069.

Discovery of tetrahydro-betacarboline based selective TRPM8 antagonists

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Transient receptor potential melastatin type-8 (TRPM8) is a non-selective Ca²⁺ permeable cation channel activated by cold and the cooling compounds menthol and icilin.(1) An increasing body of evidence suggests that TRPM8 may be an important player in various chronic conditions, such as inflammatory/neuropathic pain and prostate cancer, underscoring its potential as pharmacological target in these pathologies. Recently, we have identified two tryptamine-based derivatives acting as selective modulators of TRPM8 channel (Figure 1).(2)

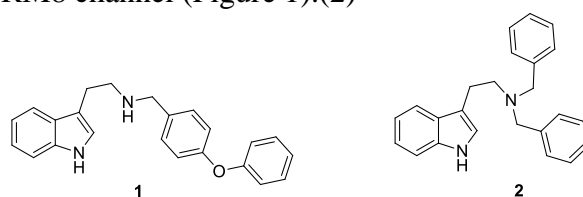


Figure 1: selective activator (1) and inhibitor (2) of TRPM8 channel.

Tetrahydroisoquinoline-derived ureas (3,4 derivatives, Figure 2) have also been identified as selective modulators of TRPM8.(3) To mimic the spatial arrangement observed in the tetrahydroisoquinoline modulators we decided to apply a conformational restriction to the tryptamine nucleus designing and synthesizing a series of tetrahydro-betacarboline compounds (Figure 2, compound 5).

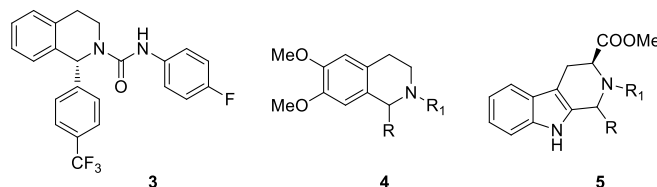


Figure 2: Tetrahydroisoquinoline TRPM8 modulators (3,4) used as starting point for design new tetrahydrobetacarboline

These compounds were tested as TRPM8 modulators by fluorescence and electrophysiology-based (patch-clamp) assays. As a result of preliminary fluorescence-based screening assay, we identified two compounds acting as inhibitors of calcium influx in HEK293 cells, stably expressing TRPM8 channels, with IC₅₀ values of 10.7±0.6 μM and 30.3±0.7 μM respectively.

References: 1. Peier AM, Moqrich A, Hergarden AC, Reeve AJ, Andersson DA, Story GM, Earley TJ, Dragoni I, McIntyre P, Bevan S, Patapoutian A (2002) A TRP channel that senses cold stimuli and menthol. *Cell* 108:705–715. 2. Bertamino, A. et al. Tryptamine-based derivatives as Transient Receptor Potential Melastatin type-8 (TRPM8) channels modulators. *J. Med. Chem.* **2016**, 59 (5), pp 2179–2191. 3. De Petrocellis, L. et al. Tetrahydroisoquinoline-Derived Urea and 2,5-Diketopiperazine Derivatives as Selective Antagonists of the Transient Receptor Potential Melastatin 8 (TRPM8) Channel Receptor and Antiprostate Cancer Agents. *J. Med. Chem.* **2016**, 59, 5661–5683

New pyrrole inhibitors of chronic myeloid leukemia cell growth

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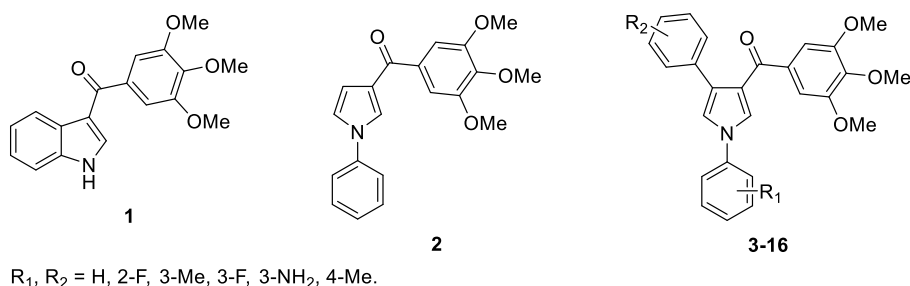
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Microtubules are an attractive target for the development of effective anti-leukemia agents.^[1] Evidence has accumulated correlating inhibition of tubulin polymerization and leukemic cell proliferation.^[2] The activity of colchicine site agents in chronic myeloid leukemia (CML) has not been adequately explored.

Recently, starting from previously reported aroylindoles (ARI, **1**)^[3] we developed a class of 3-aroyle-1-arylpyrroles (ARAPs, **2**) via benzocacking approach by shifting the indole benzene moiety to position 1 of the pyrrole ring.^[4] ARAPs proved to be potent inhibitors of both tubulin assembly and cancer cells growth, by binding the colchicine binding site. Pursuing our studied on tubulin targeting agents, we designed 3-aroyle-1,4-diarylpyrroles (ARDAPs, **3-16**) as potential anticancer agents bearing different substituents at the 1- or 4-phenyl ring (Chart 1).

ARDAPs exhibited potent inhibition of tubulin polymerization, binding of colchicine to tubulin and cancer cell growth. (4-(4-Aminophenyl)-1-phenyl-1*H*-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone inhibited the proliferation of BCR/ABL-expressing KU812 and LAMA84 cells from CML patients in blast crisis and of hematopoietic cells ectopically expressing the imatinib mesylate (IM)-sensitive KBM5-WT or its IM-resistant KBM5-T315I mutation. The same compound minimally affected the proliferation of normal blood cells, indicating that it may be a promising agent to overcome broad tyrosine kinase inhibitor resistance in relapsed/refractory CML patients. New ARDAP significantly decreased CML proliferation by inducing G2/M phase arrest and apoptosis via a mitochondria-dependent pathway and increased the cytotoxic effects of IM in human CML cells.

Chart 1. Chemical structures of ARI (**1**), ARAP (**2**) and ARDAP (**3-16**) derivatives.



References: (1) De Bruin, E. C.; Medema, J. P. *Cancer Treat. Rev.* **2008**, *34*, 737-749. (2) Bates, D.; Feris, E. J.; Danilov, A. V. et al. *Cancer Biol. Ther.* **2016**, *17*, 291-299. (3) La Regina, G.; Sarkar, T.; Bai, R. et al. *J. Med. Chem.* **2009**, *52*, 7512-7527. (4) La Regina, G.; Bai, R.; Coluccia, A. et al. *J. Med. Chem.* **2014**, *57*, 6351-6552.

Rational design of new potent non-nucleoside inhibitors of terminal deoxynucleotidyl transferase active in leukemic cells

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Mammalian terminal deoxyribonucleotidyl transferase (TdT) catalyzes the non-template-directed polymerization of deoxyribonucleoside triphosphates and has a key role in V(D)J recombination during lymphocyte and repertoire development. Elevated TdT activity is showed in leukemic cells of acute lymphocytic leukemia and in the chronic myelogenous leukemia crisis. This finding is connected to a poor prognosis and response to chemotherapy. DNA polymerase lambda (Pol λ), homolog to TdT,¹ can synthesize DNA in a template-independent pathway. Pol λ might be involved in the nonhomologous end joining (NHEJ) recombinational repair pathway of DNA double strand breaks. During a random screening on various polymerases we found some aryl diketo hexenoic acids (DKHAs) (RDS 2119, RDS 2153, RDS 2184) (see figure 1), previously synthesized by us as anti-viral agent, as hits showing interesting activity against mammalian terminal deoxyribonucleotidyl transferases.^{2,3}

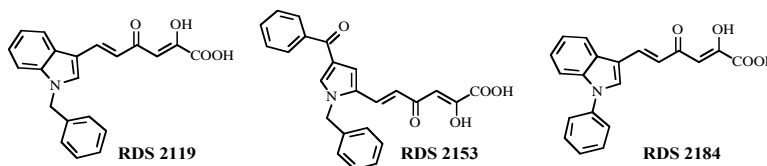


Figure 1. Hit compounds obtained from random screening.

Thus, we started SAR studies on DKHAs and found compounds that specifically target TdT behaving as nucleotide-competitive inhibitors.⁴ These compounds showed a selective toxicity toward MOLT-4 overexpressing TdT, compared to HeLa cells, that well correlate with in vitro selectivity for TdT. The binding site of two of these inhibitors was determined by cocrystallization with TdT, explaining why these compounds are competitive inhibitors of the deoxynucleotide triphosphate (dNTP). These studies opened the possibility to the rational design of TdT inhibitors. Starting from the observed binding pose of inhibitors cocrystallized within the catalytic core, we noted that the phenyl substituent or the benzyl group on pyrrole ring could occupy two different pockets. Thus, we decided to design and synthesize compounds bringing two aryl moieties. The design, synthesis and biological assays performed on newly synthesized compounds will be reported and discussed.

References: 1 Hübscher, U.; Maga, G.; Spadari, G. *Ann. Rev. Biochem.* **2002**, *71*, 133-163. 2 Locatelli, G. A.; Di Santo, R.; Crespan, E.; Costi, R. *Mol. Pharmacol.* **2005**, *68*, 538-550. 3 Di Santo, R.; Maga, G. *Curr. Med. Chem.* **2006**, *13*, 2353-2368. 4 Costi R., Cuzzucoli Crucitti G., Pescatori L., Messori A., Scipione L., Tortorella S., Amoroso A., Crespan E., Campiglia P., Maresca B., Porta A., Granata I., Novellino E., Gouge J., Delarue m., Maga G. and Di Santo R. *J. Med. Chem.*, **2013**, *56*(18), 7431-7441.

Comparative study of Chitosan and PLGA polymeric nanoparticles containing cidofovir

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Cidofovir (CDV) is a small molecule anti-viral drug and has been used as a local intravitreal injection for viral retinitis (1) to avoid systemic complications. Most formulations, containing cidofovir for intravitreal administration, caused retinal toxicity and visual discomfort in some patients. The nanoparticles seem to be a favorable drug carrier due to its low risk on hindering normal vision and to decrease repeated injections needed in chronic ophthalmic pathologies.

In this study nanoparticles constituted by chitosan (CHI) and poly(D,L-lactic-co-glycolic acid) (PLGA) were compared.

The CHI nanoparticles, with diameter ranging from 200 to 300 nm (approx. 400 nm after redispersion in water), were obtained by ionotropic gelation between CDV and the mucoadhesive polymer chitosan (CHI), using a fractional factorial experimental design to investigate the influence of the some selected variables on the formation of chitosan nanoparticles. While the PLGA nanoparticles, with size around 200-250 nm, were prepared by different emulsion solvent diffusion techniques to reach the optimized formulation.

Both formulations have been characterized by particle size, polydispersion index and zeta potential using a photon correlation spectroscopy (PCS) assembly (Zetasizer 3000 HS).

The CHI/CDV nanoparticles showed a zeta potential value of 30 mV, an encapsulation efficiency about 20% w/w and a yield of 15% w/w. The PLGA/CDV nanoparticles had a zeta potential value of -15 mV, an encapsulation efficiency about 21% w/w and a yield of 40% w/w.

Furthermore, stability studies in water have also been carried out both on the freshly prepared sample and on the centrifuged. The two formulations showed good stability at 24h and 7 days, not significantly changing the particle size.

Finally, we compare the two analytical methods (UV and HPLC) used to quantify Cidofovir in the sample. By comparing the encapsulation efficiency data of the different nanoparticles, the two analytical methods are both available for the active ingredient dosage since the obtained values are practically the same.

Therefore, for the same quality of analytical technique, we can choose the most convenient in terms of money and time, therefore the choice falls on UV spectrophotometry.

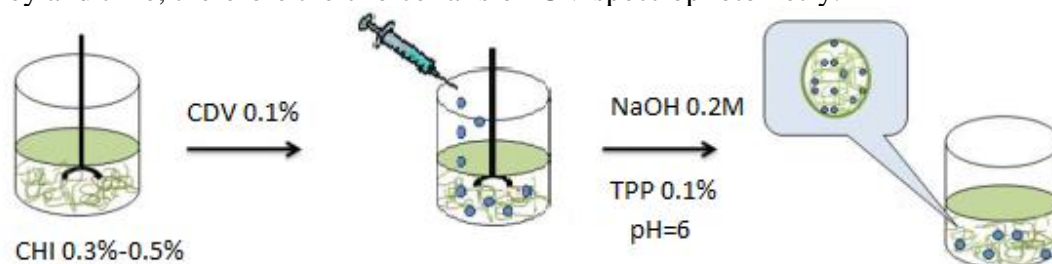


Figure 1: Scheme of CHI nanoparticles preparation containing CDV.

References: 1. F.M. Rahhal, J.F. Arevalo, E. Chavez de la Paz, D. Munguia, S.P. Azen, W.R. Freeman, Treatment of cytomegalovirus retinitis with intravitreal cidofovir in patients with AIDS. A preliminary report, *Ann. Intern. Med.* 125 (1996) 98– 103.

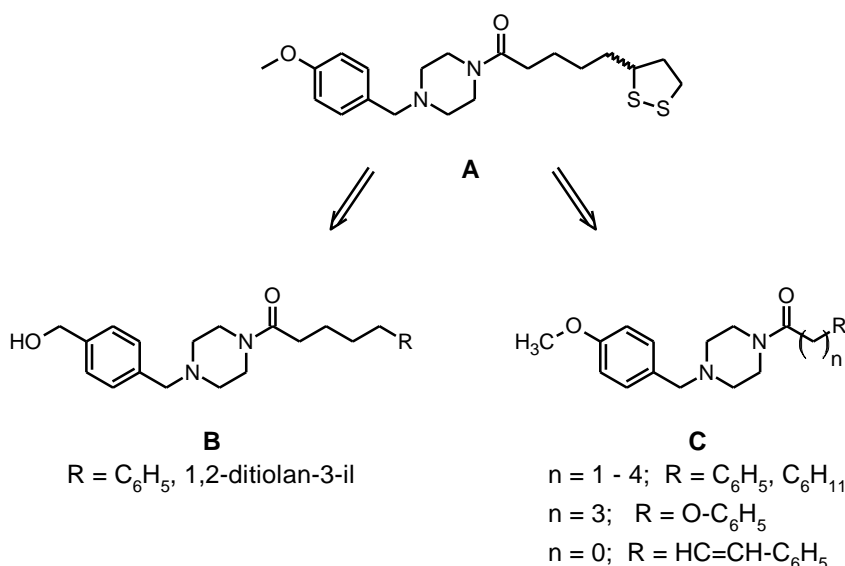
Synthesis of Novel Benzylpiperazine Derivatives as Ligands for the σ_1 Receptor

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Sigma receptors are classified into two subtypes, sigma-1 (σ_1) and sigma-2 (σ_2) receptor. They are distinguished by molecular weight, anatomical localization, and transduction mechanism. Unlike σ_2 receptor, the σ_1 subtype has been cloned in different species and recently the crystal structure of the human protein has been elucidated (1). The σ_1 receptor is widely distributed in both CNS and peripheral human tissues where it works as molecular chaperone. It regulates activity of many neurotransmitter systems and represents a potential therapeutic target in a number of pathologies, including neurodegenerative diseases, neuropathic pain, and cancer (2).

Along the years, several σ_1 ligands have been discovered; in particular, in a study of Prezzavento *et al.* (3), the 4-methoxybenzylpiperazinyl derivative **A** was reported as a good and selective ligand for the σ_1 over the σ_2 receptor ($\sigma_1 K_i = 5.7$ nM; $\sigma_2 K_i = 2460$ nM; $K_i \sigma_2 / K_i \sigma_1 = 432$). In this compound, the σ_1 binding property is coupled to an antioxidant activity given by the 1,2-dithiolan-3-yl moiety. Using compound **A** structure as a template and with the aim to obtain new selective σ_1 ligands, a number of novel derivatives (**B** and **C**) were designed and synthesized. These compounds fulfil the Glennon's σ_1 receptor pharmacophoric model in which the essential features for binding are represented by two distal hydrophobic regions and a central positive ionizable group. In derivatives **B**, the methoxy group in **A** was modified in order to explore the importance for binding of an additional H-bond donor group. On the other hand, in compounds of **C** type, the 4-methoxybenzylpiperazinyl moiety was maintained and modifications were carried on the other distal hydrophobic region, varying its nature and length. Synthetic pathways to title compounds along with their complete binding properties will be given at the meeting.



References: 1. Schmidt H. R. *et al.*, Crystal structure of the human σ_1 receptor. *Nature* 532, 527-530, 2016. 2. Su T.-P. *et al.*, The sigma-1 receptor as a pluripotent modulator in living systems. *Trends Pharm. Sci.* 37, 262-278, 2016. 3. Prezzavento O. *et al.*, Design and synthesis of new bifunctional sigma-1 selective ligands with antioxidant activity. *J. Med. Chem.* 56, 2447-2455, 2013.

Synthesis of a new generation of pyrazolo[3,4-*d*]pyrimidines as Fyn inhibitors

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Fyn is a member of the Src-family of non-receptor tyrosine kinases (TKs) and it phosphorylates a variety of target proteins involved in several signaling pathways (1).

To date, the involvement of Fyn in solid and in hematologic malignancies has become more evident and its abnormal activity has been shown to be related to severe central nervous system pathologies, such as Alzheimer's and Parkinson's diseases (2).

Our group synthesized different libraries of pyrazolo[3,4-*d*]pyrimidines **1** (in the **Figure**) active as c-Src (3), and/or Bcr-Abl (4) inhibitors.

Since Src and Fyn possess similar structures, we decided to investigate if some compounds of our libraries are also active as Fyn inhibitors and, at the same time, we synthesized other analogues of compounds **1**. In particular, compounds **2a,b** (in the **Figure**), bearing a 2-chloro-2-phenylethyl chain in N1, an aromatic group in C3 and a primary amino group in C4, possess high activity toward Fyn, inhibit the phosphorylation of the protein Tau in an Alzheimer's model cell line and show antiproliferative activities against different cancer cell lines (5).

On the basis of these interesting results, we decided to expand the structure-activity relationship studies on this family of inhibitors and we planned the synthesis of compounds **3** (in the **Figure**) bearing in N1 the same chain of compounds **2a,b** and different aromatic groups in C3.

Enzymatic assays on these compounds have demonstrated that these molecules are active towards Fyn. Biological data will be reported in the poster section.

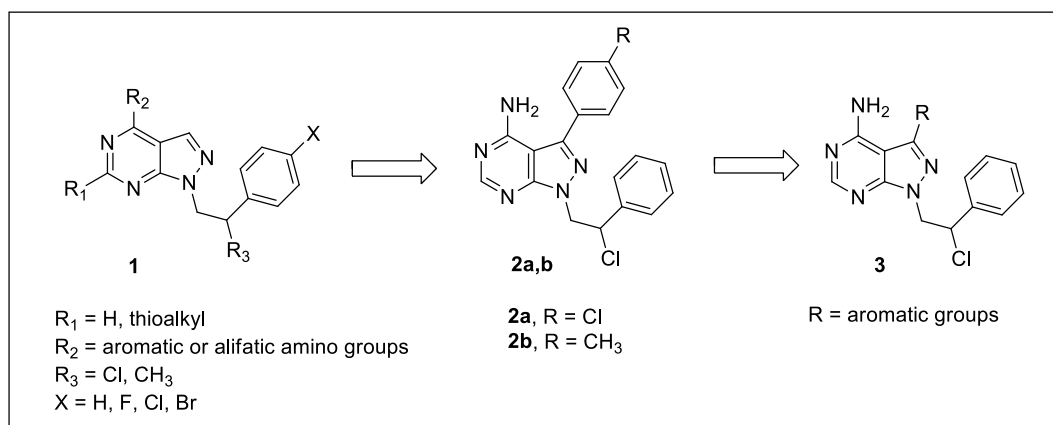


Figure. General structure of our library of pyrazolo[3,4-*d*]pyrimidines **1** and structures of compounds **2a,b** and **3**.

References: 1. Manning, G. *et al. Science*, **2002**, 298, 1912. 2. Schenone, S. *et al. Curr Med Chem*, **2011**, 18, 2921. 3. Tintori, C. *et al. J. Med. Chem.*, **2015**, 58, 347. 4. Radi, M. *et al. J. Med. Chem.*, **2013**, 56, 5382. 5. Tintori, C. *et al. J. Med. Chem.*, **2015**, 58, 4590

Highly potent dual acting A₁ and A₃ adenosine receptor ligands: synthesis, binding, functional assays and analgesic effects in mice

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Adenosine (Ado) is a purine nucleoside endowed with many different physiological and pathological functions. Many studies support the fact that Ado acts as a neurotransmitter and neuromodulator, and as an endogenous agonist on adenosine receptors (ARs). ARs belong to the superfamily of G-protein-coupled receptors (GPCRs) and are represented by four subtypes: A₁, A_{2A}, A_{2B}, and A₃ ARs (1). They are found in almost all kind of tissue: central nervous system (CNS), peripheral neurons, cardiovascular system, respiratory tract and immune system (2). Due to the wide distribution of ARs throughout the body, there is a substantial possibility that Ado ligands will have unwanted effects in non target tissues.

One way to overcome adverse effects is the use of multitarget drugs (3). A multitarget drug may display an improved therapeutic efficacy compared to a highly selective one. In fact, multitarget activities may potentiate the effect of treatment either additively or synergistically. Moreover, a multitarget drug has the advantage of following only one pharmacokinetic and metabolic pattern, thus overcoming the limits of combination therapy.

Substitutions at both purine and sugar moiety of adenosine results on AR ligands endowed with different affinity and selectivity at the four AR subtypes (4). Potent and highly selective A₁AR agonists have been previously obtained by replacement of the 5'-hydroxyl group with a chlorine atom in N⁶-substituted-adenosine derivatives (5). 5'-Chloro-5'-deoxy-N⁶-(±)-(endo-norborn-2-yl)-adenosine (5'⁶C15'⁶d-(±)-ENBA) showed analgesic effects in mice without affecting cardiovascular and motor functions (6).

Combining a 5'-C-ethyltetrazol-2-yl group with the appropriate N⁶-substitution in adenosine derivatives led to an increased affinity versus both hA₁AR and hA₃AR, reaching subnanomolar values, while remaining agonists at hA₁ and antagonists at hA₃AR (7).

In this work a new series of 5'-C-ethyltetrazol-2-yl-N⁶-substituted adenosine derivatives were synthesized and studied both *in vitro* in binding and functional assays and *in vivo* in a mouse model of pain. Through an *in silico* receptor-driven approach, the molecular bases of the hA₁- and hA₃AR recognition and activation of this series of 5'-C-ethyl-tetrazolyl derivatives were explained.

References: 1. Fredholm, B. B.; IJzerman, A. P.; Jacobson, K. A.; Linden, J.; Muller, C. *Pharmacol. Rev.* **2011**, *63*, 1-34. 2. Jacobson, K. A.; Muller, C. E. *Neuropharmacology* **2016**, *104*, 31-49. 3. Anighoro, A.; Bajorath, J.; Rastelli, G. *J. Med. Chem.* **2014**, *57*, 7874-7887. 4. Petrelli, R.; Grifantini, M.; Cappellacci, L. *Curr. Med. Chem.* **2016**, *23*, 3118-3135. 5. Franchetti, P.; Cappellacci, L.; Vita, P.; Petrelli, R.; Lavecchia, A.; Kachler, S.; Klotz, K.-N.; Marabese, I.; Luongo, L.; Maione, S.; Grifantini, M. *J. Med. Chem.* **2009**, *52*, 2393-2406. 6. Luongo, L.; Petrelli, R.; Gatta, L.; Giordano, C.; Guida, F.; Vita, P.; Franchetti, P.; Grifantini, M.; De Novellis, V.; Cappellacci, L.; Maione, S. *Molecules* **2012**, *17*, 13712-13726. 7. Petrelli, R.; Torquati, I.; Kachler, S.; Luongo, L.; Maione, S.; Franchetti, P.; Grifantini, M.; Novellino, E.; Lavecchia, A.; Klotz, K.-N.; Cappellacci, L. *J. Med. Chem.* **2015**, *58*, 2560-2566.

Design, synthesis and biological evaluation of $N^6/5'$ -disubstituted adenosine derivatives as A_1 adenosine receptor agonists

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Adenosine is an endogenous purine nucleoside that modulates a variety of physiological functions as a result of its activation of specific G protein-coupled receptors defined as A_1 , A_{2A} , A_{2B} , and A_3 adenosine receptors (ARs) (1).

The A_1 adenosine receptor (A_1 AR) is the best characterized adenosine receptor subtype. Selective A_1 AR agonists mediate neuro- and cardioprotective effects, reduce lipolysis in adipose tissue, and intraocular pressure in glaucoma (1,2). The A_1 AR is abundantly expressed in spinal cord and other neuronal tissue, and its activation produced pain-relieving effects in a number of preclinical animal models (3). Our previous works discovered that combining the appropriate 5'- and N^6 -substitution in adenosine derivatives, highly selective human (h) A_1 AR agonists (4) or highly potent dual h A_1 AR agonists and h A_3 AR antagonists can be obtained (5). The substitution of OH at the 5'-position of N^6 -substituted adenosine derivatives with a chlorine atom is not only well tolerated by the h A_1 AR but even improves the A_1 AR selectivity and affinity. 5'-Chloro-5'-deoxy- N^6 -(±)-endo-norbornyl-adenosine (5'Cl15'd-(±)-ENBA) turned out to be a potent and the most selective human and mouse (m) A_1 AR agonist vs A_3 AR so far known (4,6) with analgesic effects in a mouse model of neuropathic pain (7). Moreover, it was found to reduce the dyskinesia caused by L-DOPA in a mouse model of Parkinson disease (PD) (8) and the tremor in a harmaline-induced model of essential tremor (ET), suggesting that A_1 AR may be a potential target also for the treatment of ET (9).

In order to explore novel combinations of 5'-modification and N^6 -substitution leading to potent and selective A_1 AR agonists, a series of 5', N^6 -disubstituted adenosine derivatives was synthesized and evaluated for affinity and selectivity at all cloned hAR subtypes.

References: 1. Jacobson, K. A.; Muller, C. E. *Neuropharmacology* **2016**, *104*, 31-49. 2. Donegan, R. K. and Lieberman, R. L. *J. Med. Chem.* **2016**, *59*, 788-809. 3. Sawynok, J. Adenosine receptor targets for pain. *Neuroscience*, **2016**, *338*, 1-18. 4. Franchetti, P.; Cappellacci, L.; Vita, P.; Petrelli, R.; Lavecchia, A.; Kachler, S.; Klotz, K.-N.; Marabese, I.; Luongo, L.; Maione, S.; Grifantini, M. *J. Med. Chem.* **2009**, *52*, 2393-2406. 5. Petrelli, R.; Torquati, I.; Kachler, S.; Luongo, L.; Maione, S.; Franchetti, P.; Grifantini, M.; Novellino, E.; Luongo, L.; Maione, S.; Franchetti, P.; Grifantini, M.; Novellino, E.; Lavecchia, A.; Klotz, K.-N.; Cappellacci, L. *J. Med. Chem.* **2015**, *58*, 2560-2566. 6. Carlin, J. L.; Jain, S.; Gizewski, E.; Wan, T. C.; Tosh, D. K.; Xiao, C.; Auchampach, J. A.; Jacobson, K. A.; Gavrilo, O.; Reitman, M. L. *Neuropharmacology* **2017**, *114*, 101-113. 7. Luongo, L.; Petrelli, R.; Gatta, L.; Giordano, C.; Guida, F.; Vita, P.; Franchetti, P.; Grifantini, M.; De Novellis, V.; Cappellacci, L.; Maione, S. *Molecules* **2012**, *17*, 13712-13726. 8. Mango, D.; Bonito-Oliva, A.; Ledonne, A.; Cappellacci, L.; Petrelli, R.; Nisticò, R.; Berretta, N.; Fisone, G.; Mercuri, N.B. *Exp. Neurol.* **2014**, *261*, 733-743. 9. Kosmowska, B.; Ossowska, K.; Glowacka, U.; Wardas, J. *CNS Neurosci. Ther.* **2017**, DOI: 10.1111/cns.12692

Design, synthesis, and biological evaluation of lactam-constrained PTPRJ-binding peptides

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PTPRJ is a receptor protein tyrosine phosphatase whose expression is drastically reduced in the majority of cancer cell lines. PTPRJ is able to interact and dephosphorylate numerous receptor tyrosine kinases (RTKs) whose aberration in tumor cells is responsible of self-sufficiency cell growth, the first hallmark of cancer.(1) In this context, we recently identified PTPRJ-19, [CHHNLTHAC] (fig. 1A), a disulfide bridged nonapeptide, as a positive modulator of PTPRJ.(2)

As part of a wide research program aimed to the identification of new PTPRJ-targeted antitumoral agents, we considered PTPRJ-19 a valuable starting point to clarify the structural elements that are responsible for its interaction with the biological target.

First, in order to study the chemical nature of the bridge and the structural importance of the ring size, we replaced the disulfide bridge by a side chain-to-side chain lactam bridge, a chemically more stable moiety. So we present the synthesis, the conformational properties and biological activities of new cyclic analogues of PTPRJ-19. Results obtained show that lactam cyclic peptide 7 (fig. 1B) is the most active of the synthesized series.

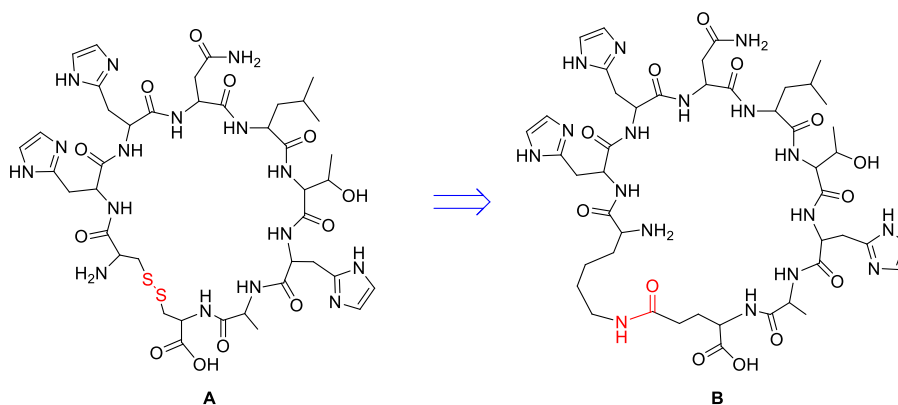


Figure 1. Structure of PTPRJ 19 (A) and peptide 7 (B).

References: 1. Keane M.M. et al. *Cancer Res.* **1996**, 56(18), 4236-4243. 2. Paduano F. et al. *ACS Chem. Biol.* **2012**, 7, 1666–1676. 3. Grieco P. et al. *Bioorg. Med. Chem.* **2002**, 10, 3731–3739.

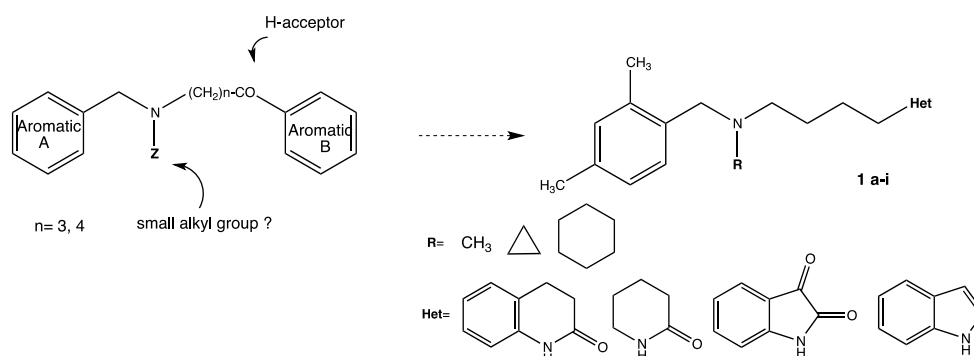
Orienting the design and synthesis towards sigma-2 receptor subtype

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Sigma-2 receptor (σ_2R) subtype is definitely an enigmatic kind of receptor and it has not been cloned yet, remaining an unknown protein. σ_2R s are overexpressed in several tumor cells and can be considered a tool for cancer therapy and diagnosis (i.e. PET and SPECT), indeed, it's well-known that σ_2R -agonists promote apoptosis leading to cell death. In 2010, our group developed a new σ_2R pharmacophore model based on some benzoxazolone derivatives (1). To date, our efforts are focused to discovering new, more selective σ_2 ligands and the purpose is to recognize which features are strictly necessary to drive the selectivity through σ_2R subtype, considering that most of the compounds present in the literature, and gifted with σ_2R affinity, are often structurally different from one another so there's a need to identify the common features to drive the selectivity through σ_2R subtype. Relying on some new derivatives bearing different heterocyclic moiety, we found that one of two aromatic fragments (aromatic-B), usually present in σ_1R ligands and necessary for their σ_1 affinity, can be replaced with a hydrophobic-aliphatic bulky group, as well as the common hydrogen-acceptor function, such as the carbonyl, may be lacking or even reinforced by a further group, still retaining the σ_2R affinity. Moreover, we found that the 2,4-dimethyl-substitution on the Aromatic (-A) ring results ideal for the σ_2 profile, whilst bulky groups, linked to the basic nitrogen atom such as cyclopropyl or cyclohexyl, adversely affect the σR affinities.



From the data obtained, indeed, we found that an aliphatic group as the piperidin-2-one moiety, still retain the σ_2 affinity but drastically reduce the σ_1 affinity ($K_i\sigma_1 > 10000$ nM, $K_i\sigma_2 = 337$ nM, $\sigma_1/\sigma_2 > 30$). Same considerations regarding the presence of a further carbonyl function (indoline-2,3-dione; $K_i\sigma_1 = 8600$ nM, $K_i\sigma_2 = 252$ nM, $\sigma_1/\sigma_2 = 34$) or its lack (indole; $K_i\sigma_1 = 1300$ nM, $K_i\sigma_2 = 440$ nM, $\sigma_1/\sigma_2 = 3$).

In conclusion, our present goal is to expand the library of derivatives having features mentioned above in order to generate a new, more reliable, pharmacophore model for the σ_2R subtype useful for the research in the field for the development of new anticancer drugs.

References: 1. E. Laurini, D. Zampieri, M.G. Mamolo, L. Vio, C. Zanette, C. Florio, P. Posocco, M. Fermeglia, S. Pricl, *Bioorg. Med. Chem. Lett.* 2010, 20, 2954-7.

Is it possible to speed-up the discovery of multi-targeting bioactive compounds?

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Nowadays, our world is affected by relevant social diseases based on multi-factorial variables. Medicinal chemists are fully engaged to find out novel therapeutic tools against them. The “lock-and-key” theory, introduced by the Nobel prize Paul Ehrlich, is the original approach to identify novel bioactive compounds, by the “one-drug one-target” paradigm. Recently, another trend is overcoming this approach to take better into account the multiple nature of the diseases: the “one drug multiple targets” paradigm. It is based on the capability of bioactive compounds to interact selectively with 2 or more macromolecular targets, exerting their effects against certain therapeutic goals in a synergic manner. (1) This innovative concept prompted in 2015 the creation of a COST Action on this topic among European research groups involved in several chemical and biological areas both at academic and industrial level. (2) For Pharma/Biothec companies this approach can fit with the repurposing issue applied to the multi-targeting and poly-pharmacology, since many bioactive compounds, obtained by means of consistent scientific investigations, could be reevaluated and eventually have a new future.

COST Association official link www.cost.eu/COST_Actions/ca/CA15135

MuTaLig COST Action link www.mutalig.eu

Virtual platform chemotheca.unicz.it



In this communication an answer to the question posted in the title will be proposed and discussed, taking into account the purposes of the COST Action MuTaLig (Multi-target paradigm for innovative ligand identification in the drug discovery process) at the beginning of its second grant year. MuTaLig started with 5 co-proposing European research teams and recently expanded to more than 30 countries.

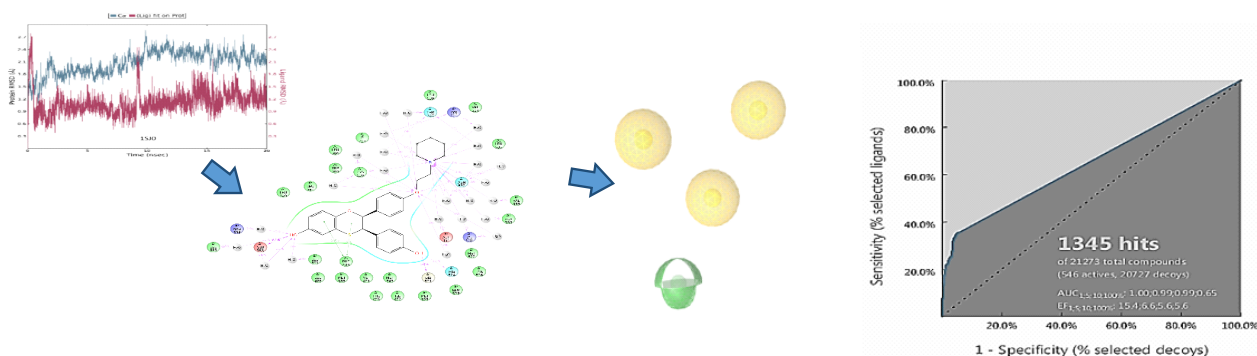
References: 1. Medina-Franco, JL et al *Drug Discovery Today*, **2013**, 18, 495-501. 2. www.calameo.com/read/003272336045b0302678c

The Molecular dYnamics SHared PharmacophorE (MYSHAPE) approach: a new tool to arise docking and pharmacophore modeling performance: virtues and vices

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In a recent paper, we presented a new virtual screening workflow that addresses the arising issues of molecular docking and pharmacophore modeling when using a single set of coordinates and a single active ligand [1]. MD simulations were carried out and ligand-protein interactions were analyzed and collected together with their appearance frequency. A pharmacophore model was then created using only the common feature patterns that all the ligands exhibited during MD simulations. This 'Molecular dYnamics SHared PharmacophorE' was then used for virtual screening on active and inactive molecules library. MYSHAPE was also used as constraints for the creation of the docking grid. The application of the MYSHAPE model showed an interesting increase of the screening capability both in terms of sensitivity of the model and specificity when compared to the PDB models. This work [1] was a first essay for a workflow that should be applied to different proteins. In the present study we tried to apply the MYSHAPE approach to other three different ligand-protein systems (ER α ; RXR α , and MAPKp38) with the aim to optimize the method to each different biological target taking in consideration the early recognition. The obtained results for these new targets confirmed that it is mandatory, to optimize the virtual screening campaign, the selection of dynamic features and constraints for docking. In particular, the addition of the constraints derived from MD simulation leads to an improvement in the model selectivity for RXR α and ER α in standard precision docking mode. For MAPKp38, validation metrics such as ROC, BEDROC, and AUAC are higher in extra precision mode. For the pharmacophore modeling, the addition of the features derived from the common interactions in MD simulations guarantee an improvement in the AUC for RXR α (37%), and ER α (77%), but light improvement for MAPKp38.



MD simulation derived common interactions revealed fundamental for docking selectivity, while they are applied to pharmacophore modeling only when the number of final features in the common and dynamic pharmacophore is higher than the starting static pharmacophore. The strength behind the protocol is the ease of use related to the improvement of results. It also could represent a valid alternative to use very time-consuming techniques such as XP docking with constraints.

Reference: 1. Perricone, U., Wieder, M., Seidel, T., Langer, T., Padova, A., Almerico, A. M., & Tutone, M. (2017). A Molecular Dynamics-Shared Pharmacophore Approach to Boost Early-Enrichment Virtual Screening: A Case Study on Peroxisome Proliferator-Activated Receptor α . *ChemMedChem*, 2017. DOI: 10.1002/cmdc.201600526

Intramolecular oxidative deselenization of acylselenoureas: a facile synthesis of benzoxazole amides and carbonic anhydrase inhibitors

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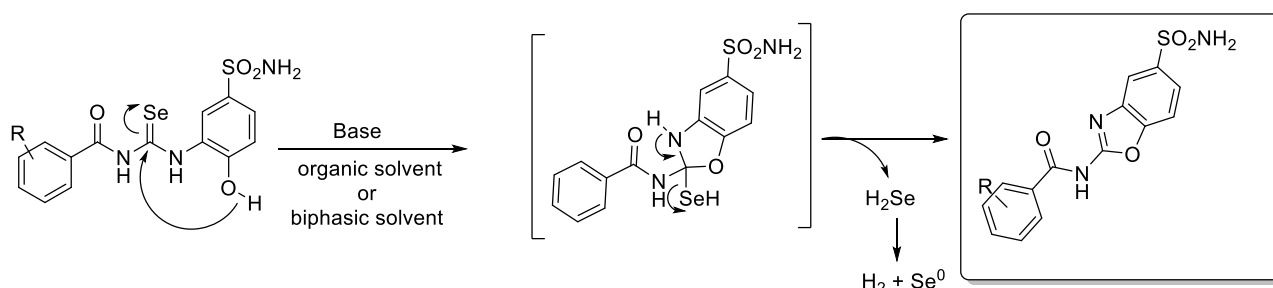
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Natural Products (NPs) have an unmatched chemical diversity, and that makes them an attractive source of new compounds for the development of new and more effective drugs. In this context NPs containing the benzoxazoles moieties are of particular interest as they occur in various structurally complex biologically active NPs and possess interesting antibiotic, anti-inflammatory, antihistaminic properties. (1)

Here we report for the first time a mild and efficient synthetic method to convert acylselenourea derivatives, bearing the O-substituted phenolic moiety, into benzoxazole amides. Mechanistic investigations account for a pH dependent intramolecular cyclization (Scheme 1). (2)

The new synthetic strategy was used to obtain a small series of inhibitors of the metalloenzyme Carbonic Anhydrase (CA; EC 4.2.1.1), by means of introduction of the primary sulphonamide (-SO₂NH₂) moiety at position 5 of the benzoxazole scaffold, and their enzymatic activity was assessed by means of in vitro kinetic assays.

Since CAs (of the human type or expressed in prokaryotic organisms) are validated pharmacological targets, the new synthetic strategy herein reported opens new insights into the development of NPs containing the benzoxazole ring as effective CA modulators.



Scheme 1: Synthetic method to convert acylselenourea compounds in benzoxazole derivatives

References: 1. (a) E. Boyer, M. Arnoult, J. Médebielle, J. Guillemont, D. Unger and D. Jochmans, *J. Med. Chem.*, 2011, 54, 7974–7985; (b) E. H. Sessions, Y. Yin, T. D. Bannister, A. Weiser, E. Griffin, J. Pocas, M. D. Cameron, C. Ruiz, L. Lin, S. C. Schurer, T. Schroter, P. LoGrasso and Y. B. Feng, *Bioorg. Med. Chem. Lett.*, 2008, 18, 6390–6393 2. A. Angeli, T. S. Peat, G. Bartolucci, A. Nocentini, C. T. Supuran and F. Carta, *Org. Biomol. Chem.*, 2016, 14, 11353.

Iminothioethers as a novel class of H₂S-donor: gasotransmitter release and vascular effects

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Hydrogen sulphide (H₂S) is now considered an important gasotransmitter exerting a plethora of effects, in particular in controlling the homeostasis of the cardiovascular system. Endogenous H₂S is mainly produced in various mammalian tissues by specific enzymes, such as cystathionine beta synthase (CBS) and cystathionine gamma lyase (CSE) responsible for metabolizing L-Cysteine (L-Cys). Blunted levels of endogenous H₂S have been found in animal models of many pathological conditions, such as myocardial ischemia, spontaneous hypertension and hypoxic pulmonary hypertension. Therefore, the administration of exogenous H₂S may represent an attractive pharmacological strategy.

The administration of excessively rapid H₂S donors, such as NaHS, is not suitable for clinical purposes. In contrast, organic molecules that are endowed with slow H₂S releasing properties may have a relevant clinical usefulness. (1, 2)

We have recently described a number of arylthioamides characterized by slow and L-cysteine-dependent H₂S-releasing properties. (3) A compound from this class resulted able to strongly abolish the noradrenaline-induced vasoconstriction in isolated rat aortic rings and hyperpolarize the membranes of human vascular smooth muscle cells in a concentration-dependent fashion; in addition, a significant reduction of the systolic blood pressure of anesthetized normotensive rats was observed after its oral administration.

Pursuing our interest in this field, a small library of iminothioethers was synthesised and their H₂S-releasing properties were evaluated in vitro, by amperometric detection, both in the absence and in the presence of organic thiols, such as L-Cys. Furthermore, their vasorelaxing properties were assessed in rat aortic rings. Compounds which exerted the better H₂S releasing properties were selected for further pharmacological evaluation by electrophysiological, spectrofluorimetric and confocal microscopy studies.

References: 1. Martelli A, Testai L, Breschi MC, Blandizzi C, Viridis A, Taddei S, Calderone V. Hydrogen sulphide: novel opportunity for drug discovery. *Med Res Rev* 2012, 32, 1093-1130. 2. Zhao W, Zhang J, Lu Y, Wang R. The vasorelaxant effect of H₂S as a novel endogenous gaseous K(ATP) channel opener. *EMBO J* 2001; 20, 6008-6016. 3. Martelli A, Testai L, Citi V, Marino A, Pugliesi I, Barresi E, Nesi G, Rapposelli S, Taliani S, Da Settimo F, Breschi M C, and Calderone V. "Arylthioamides as H₂S Donors: L-Cysteine-Activated Releasing Properties and Vascular Effects in Vitro and in Vivo" *ACS Medicinal Chemistry Letters*, 2013, 4, 904-908.

Monitoring peptides released after gastro-intestinal digestion by online comprehensive LC × UHPLC-HRMS: A case study on buffalo milk dairy products

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Dairy products contain many bioactive peptides that are encrypted in the sequence of precursor proteins and become bioaccessible and active after release during gastro-intestinal digestion (1). The resulting matrix are often very complex, containing hundreds of compounds. Conventional analytical techniques based on monodimensional liquid chromatography methods coupled to mass spectrometry are not capable to handle this challenging samples and thus high peak capacity values are necessary (2). In this regard we developed an online comprehensive two dimensional liquid chromatography platform by two coupling two reversed phase columns operating at different pH values (3). In the first dimension a microbore RP column was employed whereas in the second dimension two different short sub-2 μm stationary phases were compared: a fully porous monodisperse C18 column and a core-shell C18 column (4). The peptides were monitored by UV detection and identified by tandem mass spectrometry (MS/MS). The developed method provided double peak capacity values with respect to monodimensional methods and high orthogonality, together with a major number of identified peptides and a quick visualization of matrix differences by 2D map comparison. The method is highly suitable for peptidomics studies (5).

References: 1. H. Korhonen, A. Pihlanto, Bioactive peptides: production and functionality, *Int. Dairy J.* 16 (2006) 945–960. 2. B. Hernández-Ledesma, L. Amigo, M. Ramos, I. Recio, Application of highperformance liquid chromatography–tandem mass spectrometry to the identification of biologically active peptides produced by milk fermentation and simulated gastrointestinal digestion, *J. Chromatogr.* 17 (2004) 107–114. 3. P. Donato, F. Cacciola, E. Sommella, C. Fanali, L. Dugo, M. Dachà, P. Campiglia, E. Novellino, P. Dugo, L. Mondello, Online comprehensive RPLC × RPLC with mass spectrometry detection for the analysis of proteome samples, *Anal. Chem.* 83 (2011) 2485–2491. 4. E. Sommella, G. Pepe, G. Ventre, F. Pagano, M. Manfra, G. Pierri, O. Ismail, A. Ciogli, P. Campiglia, Evaluation of two sub-2 μm stationary phases, core–shell and totally porous monodisperse, in the second dimension of on-line comprehensive two dimensional liquid chromatography, a case study: Separation of milk peptides after expiration date, *J. Chromatogr. A*, 1375 (2015) 54–61. 5. J.N. Fairchild, M.J. Walworth, K. Horváth, G. Guiochon, Correlation between peak capacity and protein sequence coverage in proteomics analysis by liquid chromatography–mass spectrometry/mass spectrometry, *J. Chromatogr. A* 1217 (2010) 4779–4783.

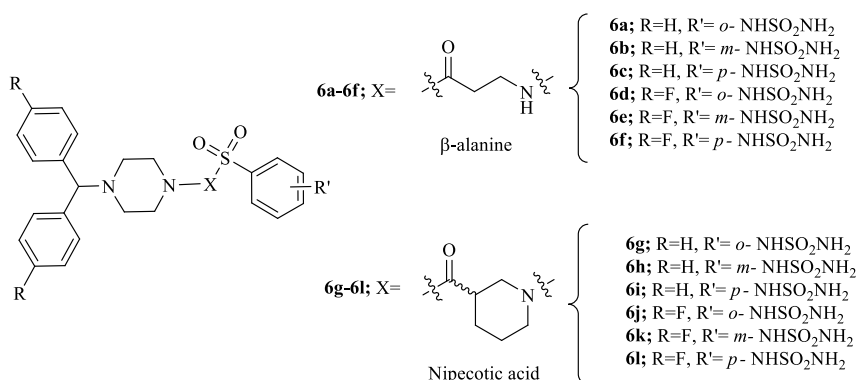
Novel sulfamide containing compounds as selective Carbonic Anhydrase I inhibitors

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The development of isoform selective inhibitors of the carbonic anhydrase (CA; EC 4.2.1.1) enzymes, represents the key approach for the successful development of druggable small molecules useful for the treatment of human diseases, such as glaucoma, oedema, central-nervous-system (CNS) affecting pathologies, obesity as well as hypoxic cancers (1, 2)

Here, and in agreement with the tail approach, (1) we report a series of new sulfamide derivatives (-NH-SO₂NH₂) as isosteres of the conventional and most investigated class of inhibitors of these enzymes: the primary sulfonamides (-SO₂NH₂). All the compounds reported were investigated in vitro for their ability to inhibit in vitro the physiological most relevant human (h) CAs such as I, II, IV and IX. hCA I resulted the most inhibited isoform, whereas all the remaining isoforms showed different inhibition profiles.



References: 1. Carta F, Supuran CT, Scozzafava A. Sulfonamides and their isosters as carbonic anhydrase inhibitors. *Future Med Chem.* 2014, 6, 1149-1165. 2. Supuran CT., Advances in structure-based drug discovery of carbonic anhydrase inhibitors. *Expert Opin Drug Discov.* 2017, 12, 61-88.

Design and synthesis of novel Nonsteroidal Anti-Inflammatory Drugs and Carbonic Anhydrase Inhibitors Hybrids (NSAIDs–CAIs) for the treatment of rheumatoid arthritis

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We report the synthesis of a series of hybrid compounds incorporating 6- and 7-substituted coumarins (carbonic anhydrase, CA inhibitors) and clinically used NSAIDs (indomethacin, sulindac, ketoprofen, ibuprofen, diclofenac, ketorolac, etc., cyclooxygenase inhibitors) as agents for the management of rheumatoid arthritis (RA) (**Fig.1**). Most compounds were effective in inhibiting the RA overexpressed hCA IX and XII, with KI values in the low nanomolar-subnanomolar ranges. The antihyperalgesic activity of such compounds was assessed by means of the paw-pressure and incapitance tests using an in vivo RA model. Among all tested compounds, the 7-coumarin hybrid with ibuprofen showed potent and persistent antihyperalgesic effect up to 60 min after administration.¹

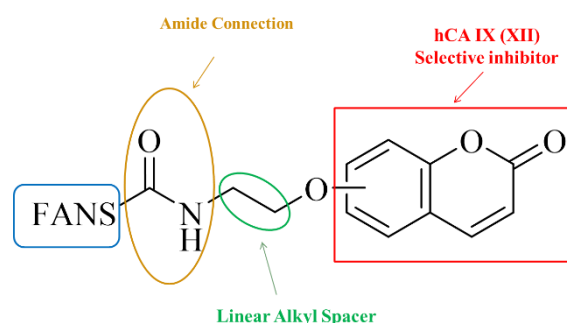


Fig.1: Rational design of the hybrids herein reported.

References 1. Bua S, Di Cesare Mannelli L, Vullo D, Ghelardini C, Bartolucci G, Scozzafava A, Supuran C.T., Carta F. *J Med Chem.* **2017**, 60, 1159-1170.

Peptide- and NMR-based screening assay for inhibitor of protein-protein interactions

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Protein–protein interactions (PPIs) are key elements of several important biological processes and have emerged as valuable targets in medicinal chemistry. Interactions between proteins are involved in the control of nearly all cellular functions. The network of binary protein-protein interactions (PPIs), the so-called interactome, is extremely expanded, and over 14,000 PPIs have been characterized in humans to date (1). The highly important role of PPIs in living organisms contributes to various pathological states, which has been demonstrated for numerous PPIs associated with the development of human diseases, especially cancer (2). As valuable medicinal chemistry molecular targets, PPIs have gained tremendous attention and substantial efforts have been undertaken to identify effective PPI inhibitors (3). Proteins typically interact via large surfaces, although it is possible to indicate ‘hot spots’ that are crucial for these processes in many cases. Interestingly, PPIs are frequently dominated by a continuous binding epitope (hot segment) and it is the presence of a dominant hot segment at a protein-protein interface that often renders this PPI druggable (4).

Isolated peptides encompassing hot segment (hot-peptides) often maintain the capability to bind the counterpart protein with different degrees of stability. Here we describe a convenient method for screening of putative PPI inhibitors based on the use of short peptides and ligand-based NMR techniques. The method will be applied to the p53-HDM2 interaction as a case study.

References: 1. Rolland T. et al., A proteome-scale map of the human interactome network. *Cell* 2014, 159, 1212. 2. Ivanov A.A. et al, Targeting protein–protein interactions as an anticancer strategy. *Trends Pharmacol. Sci.* 2013, 34, 393. 3. Milroy L. G. et al, Modulators of protein-protein interactions. *Chem. Rev.* 2014, 114, 4695. 4. London N. et al, Druggable protein–protein interactions – from hot spots to hot segments. *Curr. Opin. Chem. Biol.* 2013, 17, 952.

Lead development of thiazolylsulfonamides with Carbonic Anhydrase Inhibitory action

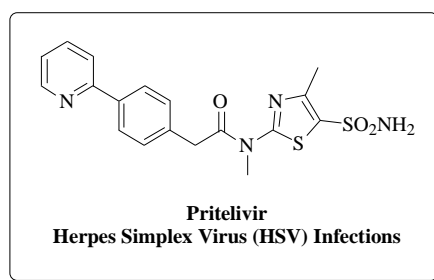
Carta F,^a Birkmann A,^b Pfaff T, Buschmann H,^b Schwab W,^b Zimmermann H,^b Maresca A,^a Supuran CT.^a

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A series of congeners structurally related to pritelivir, *N*-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-*N*-methyl-2-[4-(2-pyridinyl)phenyl]acetamide, a helicase-primase inhibitor for the treatment of herpes simplex virus infections, was prepared.

The synthesized primary and secondary sulfonamides were investigated as inhibitors of six physiologically and pharmacologically relevant human (h) carbonic anhydrase (hCA, EC 4.2.1.1) isoforms, the cytosolic enzymes hCA I and II, the mitochondrial ones hCA VA and VB, and the transmembrane, tumor associated hCA IX and XII.

Low nanomolar inhibition K_i values were detected for all of them, with a very interesting and well-defined structure–activity relationship. As many CAs are involved in serious pathologies, among which are cancer, obesity, epilepsy, glaucoma, etc., sulfonamide inhibitors as those reported here may be of interest as drug candidates. Furthermore, pritelivir itself is an effective inhibitor of some CAs, also inhibiting whole blood enzymes from several mammalian species, which may be a favorable pharmacokinetic feature of the drug which can be transported throughout the body bound to blood CA I and II. (1)



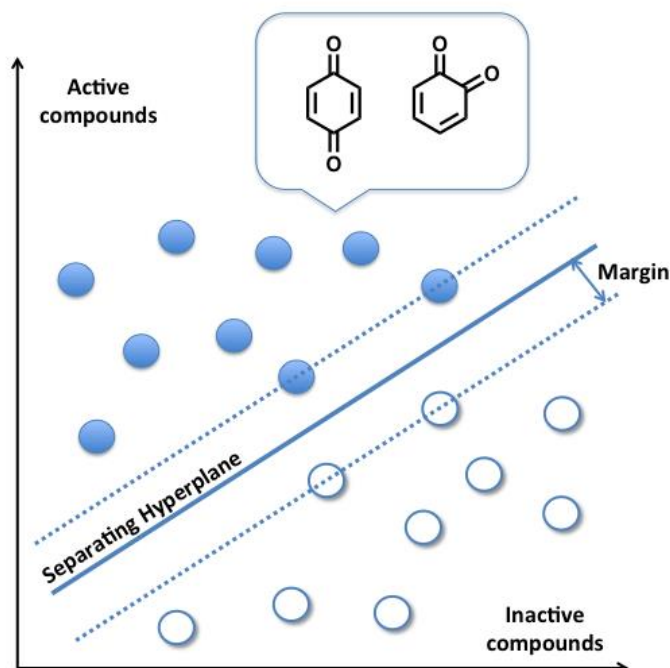
References: 1. Carta F, Birkmann A, Pfaff T, Buschmann H, Schwab W, Zimmermann H, Maresca A, Supuran CT. *J. Med. Chem.* **2017**, *60*, 3154-3164.

Predicting CDC25 inhibitors with machine learning approaches

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Cell division cycle 25 proteins (CDC25s) are dual-specificity phosphatases acting as key regulators of the cell cycle. CDC25s overexpression has been reported in a significant number of human cancers and has been associated with a poor clinical prognosis. (1) Therefore, CDC25s represent promising targets for the development of anti-cancer drugs. Most of the CDC25 inhibitors reported so far are phosphate surrogates, electrophilic entities and quinonoid compounds that are likely to act through irreversible oxidation of the catalytic cysteine residue. (2,3,4,5) Thus, discerning new chemotypes remains highly desirable. Here we report our strategy to predict CDC25B inhibitors with Support Vector Machine (SVM), one of the most widely used supervised machine learning methods because of the high predictive performance in compound classification and virtual screening. (6,7) A set of CDC25B inhibitors, representing the positive instances, was extracted from ChEMBL by applying stringent selection criteria, in order to obtain only high confidence data. As negative instances, compounds were randomly selected from ZINC. The influence of varying the number of quinonoid compounds in the training set on the model performance was also investigated. The obtained model can be applied to predict new scaffolds and inspire new CDC25 inhibitors design.



References: 1. Boutros R. *et al. Nature Rev. Cancer.* **2007**, *7*, 495-507. 2. Lavecchia A. *et al. Mini Rev. Med. Chem.* **2012**, *12*, 62-73. 3. Lavecchia A. *et al. Expert Opin. Ther. Pat.* **2010**, *20*, 405-425. 4. Lavecchia A. *et al. Curr. Med. Chem.* **2009**, *16*, 1831-1849. 5. Lavecchia A. *et al. Anticancer Agents Med. Chem.* **2008**, *8*, 843-856. 6. Lavecchia A. *Drug Discov. Today* **2015**, *20*, 318-331. 7. Heikamp, K. *et al. Expert Opin. Drug Discovery* **2014**, *9*, 93– 104

Peptidomics investigation of *Spirulina platensis* after simulated gastro-intestinal digestion by Ultra High Pressure Liquid Chromatography-High resolution Mass spectrometry (UHPLC-HRMS)

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Microalgae are a rich source of bioactive compounds such as proteins, peptides, carotenoids, polyphenols, polyunsaturated fatty acids and more. Among these *Spirulina* possesses healthy properties. Its major proteins, phycobiliprotein, has several therapeutic activities, namely, hepatoprotective, anti-inflammatory, immunomodulating, antioxidant and anticancer effects (1). With the aim to investigate the release of bioactive peptides, an *in vitro* simulated gastro-intestinal digestion has been carried out on the protein extract of *Spirulina platensis*. The protein fraction was obtained by thermal shock cycles and subjected to digestion protocol. Crude digest was purified and concentrated by Solid Phase Extraction (SPE) by employing Reversed Phase polymeric sorbents. Subsequently, the digest was subjected to UHPLC-HRMS analysis. Peptides were separated on a superficially porous C18 column (100 × 2.1 mm, 1.7 μm) and identified by both Orbitrap and Ion trap-Time of Flight mass spectrometry with the support of Bioinformatics tools. The research led to the identification in the digest of 102 peptides derived from Phycocyanin (alpha and beta-subunits) and Allophycocyanin (alpha and beta- subunits). Peptide extracts were tested ex-vivo on rat blood vessels, showing promising antihypertensive activity. Moreover, the most abundant peptides were synthesized by F-MOC chemistry and tested for further biological evaluation. These data evidence the high nutraceutical value of *Spirulina* peptides.

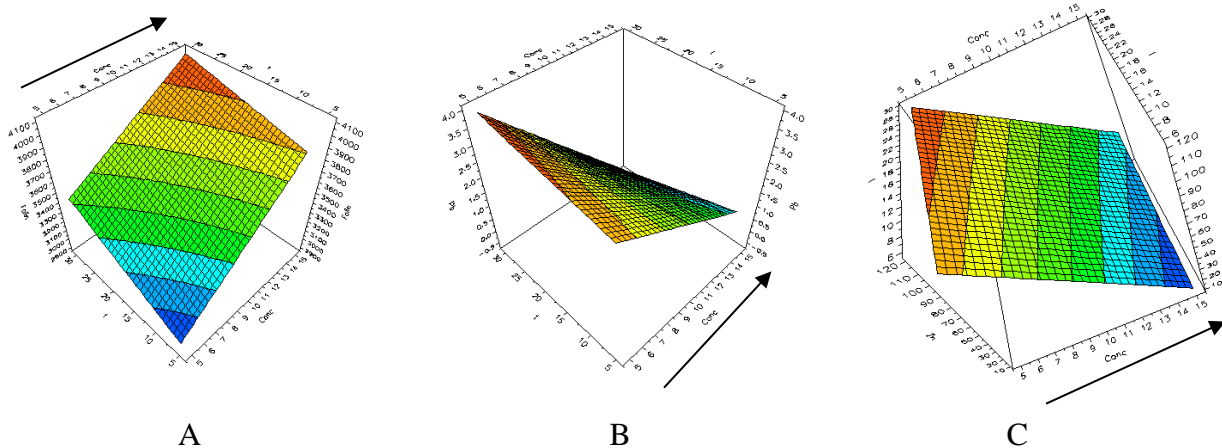
References: 1. Sigamani S., Ramamurthy D., Natarajan H., A Review on Potential Biotechnological applications of Microalgae, J Appl Pharm Sci, 6 (8), 179–184, 2016. 2.

Adsorption of metal ions from a nutraceutically relevant (Poly)phenol aqueous solution by Calcium Carbonate nanoparticles

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The presence of relatively high concentrations of metals, although still within the limits imposed by law, can reduce the nutraceutical value of (poly)phenolic complexes of plant derivation. Reducing metal concentrations could facilitate preclinical evaluation and would allow better clinical outcomes. This communication will illustrate the possibility of reducing the concentration of metals in a highly concentrated (poly)phenolic aqueous solution obtained by extraction from the juice of Apulian olives. Attempts have been made using methods compatible with the intended use of (poly)phenol complexes as nutraceuticals. Our goal was to reduce the metal ion concentrations without affecting the (poly)phenolic content. The results obtained by treating the aqueous solution with calcium carbonate nanoparticles will be reported. The optimization of the experimental parameters was obtained through the Design of Experiments (DoE) approach (1). The chemiometric model indicated that the best results in terms of (poly)phenoyl residues (Folin; A) and metal abatement (e. g., zinc and lead, ICP-MS, B and C) are obtained with relatively high amounts of nanoparticles. The results can be rationalized by admitting that the metal abatement process frees amounts of (poly)phenols otherwise complexed with metal cations.



Reference: 1. Cavalluzzi, M. M.; Bruno, C.; Lentini, G.; Lovece, A.; Catalano, A.; Carocci, A.; Franchini, C. One-Step Synthesis of Homochiral *O*-Aryl and *O*-Heteroaryl Mandelic Acids and Their Use as Efficient ¹H NMR Chiral Solvating Agents. *Tetrahedron: Asymmetry* **2009**, *20*, 1984–1991.

Molecular optimization of *O*-glycoside inhibitors of blood coagulation factors

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Dabigatran etexilate, a selective thrombin (fIIa) inhibitor, and factor Xa (fXa)-selective inhibitors, namely apixaban and rivaroxaban, are new oral active anticoagulants (NOACs), which overcome a number of drawbacks associated to traditional oral anticoagulants (e.g., warfarin) in the therapy of thrombotic disorders (1). Recently, we reported compound **1**, an isonipecotamide-based inhibitor of the serine proteases of the blood coagulation cascade (2,3,4), and its β -D-glucose-containing analogue **2**. The latter compound proved to be a picomolar inhibitor of fXa, with good anticoagulant and profibrinolytic activities. Interestingly, glucosilation resulted in a significant increase of fXa/fIIa inhibition (2,4) (**2**, fXa K_i = 0.090 nM; fIIa K_i = 100 nM). As shown previously, the chlorothiophene moiety is essential for binding of both compounds, whereas comparing the inhibition constant value of **2** with that of the parent compound **1** clearly showed that the removal of the glucose moiety reduces the affinity for fXa by less than ten-fold and for fIIa by more than two orders of magnitude. Moreover, removing the piperidine moiety does decrease affinity to fXa by several orders of magnitude.

Experimental deconstruction of **2** into smaller fragments revealed a binding cooperativity of the piperidine and propylene-linked β -D-glucose fragments, stronger in fIIa (15.5 kJ·mol⁻¹) than in fXa (2.8 kJ·mol⁻¹). For a better understanding of the observed binding cooperativity, the crystal structure of the human α -thrombin in complex with the *O*-glucoside derivative **2** (pdb: 4N3L) has been determined at 1.94 Å resolution, which revealed critical hydrogen bond interactions between the glucose moiety and two basic residues of the Na⁺-binding site (R221a and K224), involved in allosteric activation of thrombin.

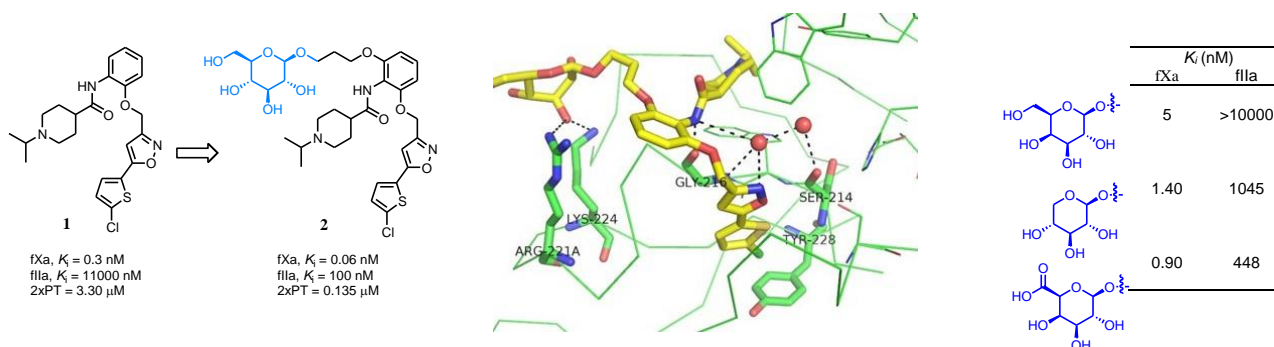


Figure 1. Binding mode of **2** to human α -thrombin as revealed by X-ray crystallography. The ligand structure and the interacting protein residues are shown as stick representation with O in red, N in blue, S in dark yellow, and Cl in dark green; C atoms are in yellow and green for ligand and protein residues, respectively. Structures and bioactivity data of compounds **1** and **2** and their glycoside analogues.

Replacing the glucose moieties with other sugars (i.e. galactose, xylose, and glucuronic acid) revealed the importance of maintaining the β -glucose moiety to stabilize the ligand/enzymes complex. Surface plasmon resonance (SPR) studies and docking calculations provided helpful information for optimizing the design of novel fXa/fIIa inhibitors. SPR has been also used to preliminarily assess parameters related to bioavailability.

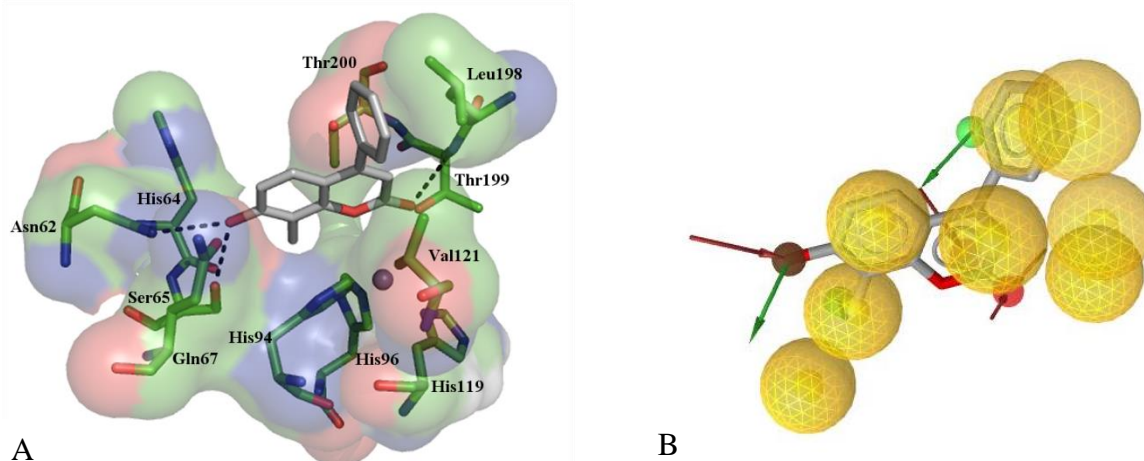
References: (1) Reiffel, J. A. *Am. J. Med.* **2014**, *127*, e16-17. (2) Lopopolo, G., de Candia, M., Panza, L., Romano, M.R., Lograno, M.D., Campagna, F., Altomare, C. *ChemMedChem* **2012**, *7*, 1669-1677. (3) de Candia, M., Fiorella, F., Lopopolo, G., Altomare, C. et al. *J. Med. Chem.* **2013**, *56*, 8696-8711. (4) Belviso, B.D., Caliandro, R., de Candia, M., Zaetta, G., Lopopolo, G., Incampo, F., Colucci, M., Altomare, C.D. *J. Med. Chem.* **2014**, *57*, 8563-8575.

Design of coumarin-based Carbonic Anhydrase IX inhibitors from a fragment pharmacophore model approach

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Carbonic anhydrases (CAs) are metalloenzymes catalysing the hydration of carbon dioxide into bicarbonate and proton. There are 15 different human α -carbonic anhydrase isoforms (hCA), which differ from catalytic activity, sub-cellular localization and organ/tissue distribution. The hCAs have basic physiological roles such as breathing, acid-base balance, calcification, secretion of electrolytes and biosynthetic reactions. It is well-known that several isoforms (hCA IX, hCA XII and hCA XIV) are involved in oncogenesis and tumor progression, thus representing molecular targets for the development of anticancer agents (1). Recently, we have identified a new series of coumarin derivatives acting as selective inhibitors of hCA IX over ubiquitous hCA II isoform. A promising compound is the 7-hydroxy-8-methyl-4-phenyl-3,4-dihydro-2H-1-benzopyran-2-one (**1**, $K_i = 39.5$ nM), for which the plausible binding mode into the catalytic site of hCA IX has been obtained by docking studies performed using AutoDock program (figure A). These results prompted us to exploit this class of selective inhibitors and design new analogues.



Firstly, the main interactions between hCA IX and coumarin **1** have been used as basic information to construct the receptor-based pharmacophore model by LigandScout software. Then, some features have been added as result of an in-depth study concerning the regions surrounding the active site of the apo protein. Therefore, a comprehensive pharmacophore map was obtained (figure B) and it was split in two different fragment pharmacophore models.

Thus, a fragment virtual screening has been performed, based on the versatile and easy synthetic procedure employed to obtain **1**. So further coumarin derivatives were constructed making a selection on the basis of the docking pose and pharmacophore fit value. The selected compounds were synthesized and screened as CA inhibitors.

References: 1. Supuran CT. Advances in structure-based drug discovery of carbonic anhydrase inhibitors. *Expert Opin Drug Discov.* 2017, 12(1):61-88.

***In situ* gelling Ac2-26 loaded submicrometric particles as wound healing drug delivery systems**

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Wound healing is a dynamic ordered process involving a variety of cellular and matrix components that, in some cases, fails in various pathological conditions. ANXA1 has been involved in a broad range of molecular and cellular processes, and its N-terminal derived peptide Ac2-26 is able to activate all three human formyl peptide receptors, promoting calcium fluxes and cell migration, stimulating healing process (1,2). A number of wound dressing devices loaded with active pharmaceutical ingredients have been developed using different polymeric materials. In situ forming gels may combine most of the required properties for an ideal topical formulation (good exudate absorbance, good adherence and removal) with powder easy administration (3). In the present study, we investigated the feasibility of using nanospray drying technology to produce Ac2-26 loaded submicrometric particles able to gel in situ when in contact with wound exudates. Particles have been manufactured using high mannuronic alginate (A), amidated low methoxyl pectin (P) and low molecular weight chitosan (C) for local controlled drug release formulation with enhanced wound healing activity. All formulations loaded with different amount of AC2-26 peptide presented a mean diameter around 750 nm and were able to stabilize the peptide for more than 3 months even at room temperature, where the pure peptide in solid form rapidly degrade after one week. Moreover, the powder was able to move rapidly into a gel when in contact with wound fluids (3-5 minutes) depending on alginate concentration. Proper adhesiveness to of the gel at wound site was found for the most concentrated alginate formulation. Besides, values of all formulations were in a range for easily removal of the formulation after use. Moisture transmission of the in situ formed hydrogel was between 95 and 90 g/m²/h, an optimum range to avoid wound dehydration or occlusion phenomena (3). Release behaviour of Ac2-26 was directly correlated to peptide and polymeric concentration, resulting in positive burst effect in the first hours of administration followed by a prolonged release till 7 days for the most effective formulations.

References: 1. Perretti, M., & D'Acquisto, F. (2009). Annexin A1 and glucocorticoids as effectors of the resolution of inflammation. *Nature Reviews Immunology*, 9, 62–70. 2. Del Gaudio, P., De Cicco, F., Aquino R.P., Picerno, P., Russo, P., Dal Piaz, F., Bizzarro V., Belvedere, R., Parente, L., Petrella, P. (2015). Evaluation of in situ injectable hydrogels as controlled release device for ANXA1 derived peptide in wound healing, *Carbo. Poly.* 115, 629–635. 3. De Cicco, F; Porta, A; Sansone, F; Aquino R.P.; Del Gaudio, P. (2014). Nanospray technology for an in situ gelling nanoparticulate powder as a wound dressing. *Int. J. Pharm.* 473, 30-37.

Antifungal extracts from Chestnut (*Castanea sativa*) by-products: characterization and *in vitro* activity against phytopathogenic fungi

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The need to replace synthetic fungicides used against phytopathogenic fungi, whose security has been questioned, has promoted the research on new sources of active compounds. Phytopathogenic fungi are very detrimental for fruit and vegetable productive systems, causing both yield losses and food decay also determining serious risks for consumers, due to the production of dangerous secondary metabolites [1]. Widespread use of synthetic fungicides involves the development of resistant strains, and raises environmental and human health concerns. Natural plant extracts and derivatives, harvesting and shelling two waste products are produced, the bur and the shell, the latter it is studied as antioxidant characterized by a good toxicological and ecotoxicological profile, and with antimicrobial properties may represent an attractive alternative [2]. As a result of *Castanea sativa* source and currently used as fuel. The disposal of these waste materials represents a serious environmental problem, consequently their recovery and recycling may be of a great economic interest. Our investigation has been directed to burs representing a significant by-product of the edible chestnut productive chain and a potential inexpensive source of active phenolics, with antioxidant properties useful in pharmaceutical, cosmetic or food packaging applications [3]. In the present research, the efficacy of methanolic, hydroalcoholic and aqueous (decoction) extracts from burs against *Alternaria alternata*, *Fusarium solani*, and *Botrytis cinerea* was investigated [2]. Mycelial growth and spore germination rates of the fungi were significantly reduced *in vitro* under exposure to all *C. sativa* bur extracts in a dose-dependent manner. The water-soluble fraction of the methanolic extract showed the highest inhibitory effect. Its main components were isolated and their chemical structures characterized by NMR and MS. Phenolic acids, several flavonol glycosides (kaempferol and quercetin derivatives), phenol glucoside gallates (cretanin, chesnatin, chestanin) and C-glycosyl ellagitannins (castacrenin A and B) were detected. The marker compounds were identified as quercetin 3-O- β -D-glucopyranoside and chestanin, and their quantitative analysis was performed by HPLC-DAD. Results suggested that the major antifungal efficacy of this fraction is due to both higher total phenol (as determined by Folin Ciocalteu test) and markers content. Its radical scavenging activity (against DPPH and ABTS radicals) was higher than hydroalcoholic and aqueous extracts. Our results showed that chestnut wastes have promising prospects for the utilisation to reduce the using of antifungal chemicals and to achieve a more sustainable use of pesticides.

References: [1] Chen et al. J. Sci. Food Agric., 94, 2441–2447, 2014. [2] Pane et al. Crop Protection, 84, 81-87, 2016. [3] Pinto et al. Food Funct., 8, 201–208, 2017

The role of Transcutol® on skin penetration ability of diclofenac acid nanosuspensions

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The poor ability of many drugs to permeate the skin layers is the main limiting factor for the exploitation of the transdermal route for drug delivery. As a consequence, several approaches have been proposed to overcome the skin barrier, such as the inclusion of penetration enhancers in the topically applied drug formulations. Another novel approach to increase skin permeability of poorly water soluble drugs is the production of nanocrystals (pure drug crystals with an average diameter below 1 µm stabilized with a small amount of stabilizer) (1).

In this work novel diclofenac acid nanocrystal formulations were developed using the wet media milling technique, Poloxamer 188 as stabilizer and the penetration enhancer Transcutol® (diethylene glycol monoethyl ether) as excipient (2).

Formulations were characterized by different techniques such as scanning electron microscopy, differential scanning calorimetry, X-ray powder diffractometry, Fourier-transform infrared spectroscopy and photon correlation spectroscopy. The influence of diethylene glycol monoethyl ether on (trans)dermal delivery of diclofenac topically applied as nanosuspensions was evaluated by *in vitro* studies using Franz diffusion cells and pig skin. Diclofenac nanosuspensions without the penetration enhancer, diclofenac coarse suspensions and a commercial gel containing diclofenac sodium were used as controls.

Results demonstrated that the presence of diethylene glycol monoethyl ether influences the Poloxamer 188 ability to stabilize the nanocrystals during the milling process. Indeed, nanosuspensions with the penetration enhancer exhibited a mean diameter greater than those of the nanosuspension without it. Moreover, *in vitro* permeation studies showed that the nanosuspension without diethylene glycol monoethyl ether enhanced diclofenac acid skin delivery compared to coarse suspension and the commercial gel, thus indicating that the nanosizing process and the different ability of diclofenac sodium salt and diclofenac acid to permeate into the skin play a key role in the dermal penetration process. Finally, increased concentrations of the penetration enhancer decreased the diclofenac acid skin accumulation in the stratum corneum.

Overall, the present results exclude a synergistic effect of the nanosizing approach and the addition of diethylene glycol monoethyl ether on the skin penetration of diclofenac applied as a nanosuspension.

References: 1. Lai, F., Schlich, M., Pireddu, R., Corrias, F., Fadda, A.M., Sinico, C., 2015. Production of nanosuspensions as a tool to improve drug bioavailability: focus on topical delivery. *Curr. Pharm. Des.* 21, 6089–103. 2. Pireddu, R., Caddeo, C., Valenti, D., Marongiu, F., Scano, A., Ennas, G., Lai, F., Fadda, A.M., Sinico, C., 2016. Diclofenac acid nanocrystals as an effective strategy to reduce *in vivo* skin inflammation by improving dermal drug bioavailability. *Colloids Surfaces B Biointerfaces* 143, 64–70.

Topically applied baicalin gellan-transfersomes: *in vitro* and *in vivo* evaluation

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In the present work, nanotechnologies of gellan-nanohydrogel and phospholipid vesicles were combined to incorporate baicalin in new gellan-transfersomes obtained by an easy and scalable method. Specifically, the polyphenol was incorporated in transfersomes prepared with soy phosphatidylcholine (Lipoid S75) and tween 80(1,2). Then, considering advantages of the association of phospholipid vesicles and hydrogels, as improvement achieved in skin delivery and formulation stability, transfersomes were combined with a gellan-cholesterol derivative, which is expected to stably interact with the vesicle bilayer due to its amphiphathic nature stemming from the hydrophilic polymeric chains and the lipophilic cholesterol(3). Moreover, this combination may improve both vesicle viscosity and skin delivery capabilities. Nanohydrogels of gellan-cholesterol derivative were produced by ultrasound or autoclave treatment of the polymer suspension, and then used as hydrating medium for the preparation of two different baicalin loaded gellan-transfersomes. Empty and baicalin loaded transfersomes were small in size (~80 nm) and monodispersed (PI ~0.19). The use of the gellan-nanohydrogels as hydrating medium led to the formation of larger vesicles, especially baicalin loaded sonicated gellan-transfersomes, with a mean diameter ~123 nm. The zeta potential was similar for all the nanovesicles, ~-50 mV, due to the contribution of negatively charged S75. Cryo-TEM showed the actual formation of lamellar vesicles in all the three samples. In particular, transfersomes were spherical and unilamellar, sonicated gellan-transfersomes were unilamellar with a peculiar oval and elongated rod-like shape and autoclaved gellan-transfersomes were unilamellar, with irregular round shape. The entrapment efficiency was ~37% for transfersomes and ~45% for gellan-transfersomes, thus, suggesting that baicalin is loaded within the vesicles, but also embedded in the three-dimensional network of the gellan-cholesterol chains, as previously reported for other tree-dimensional vesicle dispersions (4). Gellan was anchored to the bilayer domains through cholesterol, and the polymer chains were distributed onto the outer surface of the bilayer, thus, forming a core-shell structure, as suggested by rheological studies and SAXS analyses. The optimal carrier ability of core-shell gellan-transfersomes was established by the enhanced skin deposition of baicalin, especially in the deeper tissues. Core-shell gellan-transfersomes, especially the system based on autoclaved gellan-nanohydrogel, provided the greatest baicalin *in vitro* deposition in intact skin, thanks to the peculiar assembling structure where the external gellan chains, surrounding the vesicles, favored their adhesion to the skin surface and promoted vesicle diffusion. Moreover, their ability to improve baicalin efficacy in anti-inflammatory and skin repair tests was confirmed *in vivo* in mice, providing the complete skin restoration and inhibiting all the studied inflammatory markers (oedema, MPO and TNF α).

References: (1) S. Mir-Palomo, A. Nacher, O. Díez-Sales, M.A. Ofelia Vila Busó, C. Caddeo, M.L. Manca, M. Manconi, A.M. Fadda, A.R. Saurí, Inhibition of skin inflammation by baicalin ultradeformable vesicles, *Int. J. Pharm.* 511 (2016) 23–29. (2) G. Cevc, U. Vierl, Nanotechnology and the transdermal route: A state of the art review and critical appraisal., *J. Control. Release.* 141 (2010) 277–99. (3) G.A.T. Kaminski, M.R. Sierakowski, R. Pontarolo, L.A. dos Santos, R.A. de Freitas., Layer-by-layer polysaccharide-coated liposomes for sustained delivery of epidermal growth factor, *Carbohydr. Polym.* 140 (2016) 129–135. (4) N. Kaiseret, A. Kimpfler, U. Massing, A. Burger, H. Fiebig, M. Brandl, R. Schubert 5-Fluorouracil in vesicular phospholipid gels for anticancer treatment: entrapment and release properties, *Int. J. Pharm.* 256 (2003) 123–131.

Discovery of store-operated Calcium entry modulators as an effective treatment for calcium-related rare genetic diseases

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Store Operated Calcium Entry (SOCE) is the major route of replenishment of intracellular Ca²⁺ in response to depletion of Ca²⁺ stores in the endoplasmic reticulum (ER). The key molecular components of SOCE machinery are STIM proteins, which function as endoplasmic reticulum calcium sensor, and Orai channels.⁽¹⁾

Recently, several human diseases have been associated with mutations in these two proteins: loss-of-function mutations result in SCID-like immunodeficiencies, while gain-of-function mutations cause Stormorken syndrome, York platelet syndrome and tubular aggregate myopathy (TAM).⁽²⁾ These pathologies are rare diseases with an estimated prevalence of 1 every 500 births and are currently without therapy.

Due to the recent discovery of STIM and Orai proteins, structural information is poor and only a low resolution crystal structure of Orai from *Drosophila melanogaster* has been described.⁽³⁾ Therefore, the search for SOCE modulators perfectly suited to a click chemistry approach. Starting from the structure of known pyrazole derivatives (BTP, Pyr),⁽⁴⁾ a library of candidates was designed and synthesized. Screening was performed by calcium microfluorography in wild type and mutated human embryonic kidney (HEK-293T) cells and led to the identification of both SOCE activators and inhibitors (Figure 1). Selected compounds were further evaluated by electrophysiological experiments and by *ex vivo* studies on muscle biopsies from patients affected by TAM.⁽⁵⁾

Chemical synthesis, metabolic stability profile and biological evaluation of this class of compounds will be discussed.

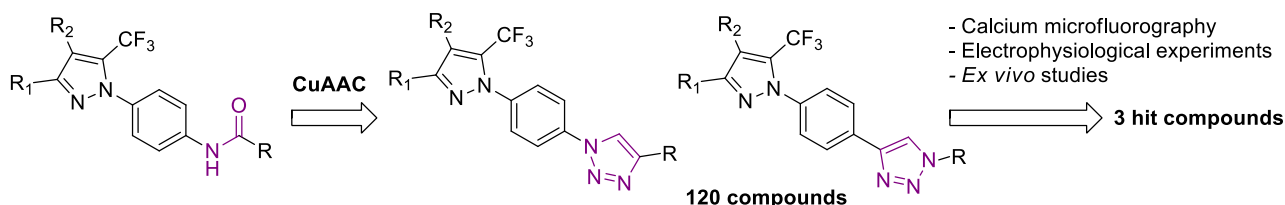


Figure 1

References: 1. A. Verkhatsky, V. Parpura, *Neurosci. Bull.* **2014**, *30*, 125. 2. R.S.Lacruz, S. Feske, *Ann. N.Y. Acad. Sci.* **2015**, *1356*, 45. 3. X. Hou, L. Pedi, M.M. Diver, S.B. Long, *Science* **2012**, *338*, 1308. 4a. S. Kyyonaka, K. Kato, M. Nichida, K. Mio, T. Numaga, Y. Sawaguchi, T. Yoshida, M. Wakamori, E. Mori, T. Numata, M. Ishii, H. Takemoto, A. Ojida, K. Watanabe, A. Uemura, H. Kurose, T. Morii, T. Kobayashi, J. Sato, C. Sato, I. Hamachi, Y. Mori, *Proc. Natl. Acad. Sci.* **2009**, *106*, 5400; 4b. H. Schleifer, B. Doleschal, M. Lichtenegger, R. Oppenrieder, I. Derler, I. Frischauf, T.N. Glasnov, C.O. Kappe, C. Romanin, K. Groschner, *Br. J. Pharmacol.* **2012**, *167*, 1712. 5a. B. Riva, A. Griglio, M. Serafini, S. Aprile, G. Grosa, M. Garibaldi, E. Bertini, G. Tasca, D. Alansary, C. Distasi, B. Niemeyer, T. Pirali, A.A. Genazzani, *Cell Chem. Biol.* Submitted. 5b. "Modulators of SOCE, compositions and use thereof"; T. Pirali, B. Riva, A.A. Genazzani; ITUA20164199.

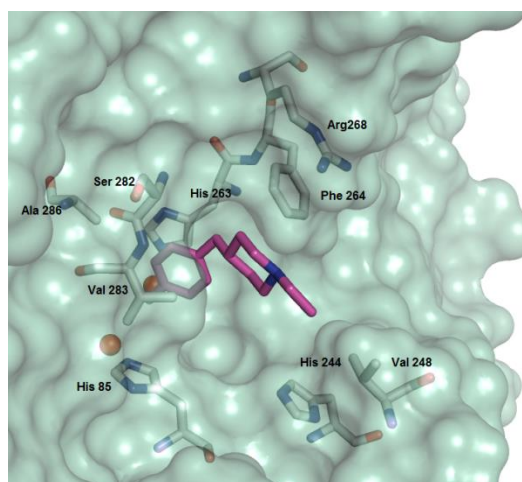
Computational and experimental structural studies leading to new potent Tyrosinase inhibitors bearing 4-Fluorobenzyl moiety

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Tyrosinase (TY) is a copper-containing glycoprotein widely distributed in nature and belonging to the type 3 of copper protein family. TY catalyses and plays a key role in melanin biosynthetic pathway. Although the melanin production shields the human skin from UV radiation, inhibiting photocarcinogenesis and affecting the synthesis of vitamin D₃, an excessive accumulation, or an irregular distribution, can lead to serious cutaneous pigmentation disorders (1). Thus, in the last few years many efforts have been made to identify new and potent enzymatic inhibitors useful in clinical therapeutic applications as well as in cosmetic industry. Recently, we reported small synthetic molecules as a new class of TY inhibitors and some of them displayed higher efficacy than the well-known reference compound kojic acid.

Specifically, the most active inhibitor 1-(5,6-dimethoxy-1*H*-indol-3-yl)-2-(4-(4-fluorobenzyl)piperidin-1-yl)propan-1-one showed promising IC₅₀ value of 7.56 μM and affected diphenolase activity as mixed-inhibitor (2). The structure activity relationship considerations suggested that 4'-fluorobenzyl moiety could exert a crucial role in controlling inhibitory effects. Therefore, we have explored the docking poses of a new series of compounds able to set the 4-fluorobenzyl fragment in the hole of catalytic site.



Then selected compounds were synthesised and assayed against TY, thus identifying new potent inhibitors (IC₅₀ ≤ 2.03 μM) when compared with kojic acid (IC₅₀ = 17.76 μM). Notably, the co-crystal structure with TY confirmed that the 4-fluorobenzyl moiety is situated between the two copper ions, with the aromatic ring stabilized through stacking interactions within hydrophobic wall of catalytic pocket.

References: 1. Zheng, Z.; Zhang, Y.; Zhang, S.; Chen, J. One-pot green synthesis of 1,3,5-triarylpentane-1,5-dione and triarylmethane derivatives as a new class of tyrosinase inhibitors. *Bioorg Med Chem*, 2016 26 795–798. 2. Ferro S., De Luca L., Germanò MP., Buemi MR., Ielo L., Certo G., Kanteev M., Fishman A., Rapisarda A. and Gitto R. Chemical exploration of 4-(4-fluorobenzyl)piperidine fragment for the development of new tyrosinase inhibitors, *Eur J Med Chem*, 2017 125 992-1001

Synthesis of nabumetone analogues for topical use: photodegradation studies and design of light-stable formulations

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Photostability studies applied on topical formulations containing anti-inflammatory drugs have confirmed the sensitivity to light of many of these drugs (1,2). For this reason, their formulation in cream or gel is often avoided in favor of other forms, such as tablets or suspensions.

In this work, the behavior of nabumetone (NA), (4- (6-methoxy-2-naphthyl) butan-2-one) in aqueous solution was tested, revealing the 6-methoxy-naphthalene-aldehyde as the main photoproduct (3). Photodegradation of NA was then investigated in both liquid and gel formulations, according to the ICH rules (4). The experiments were monitored by spectrophotometry and the data processed by Multivariate Curve Resolution (MCR), able to estimate spectra and concentration profiles of the components involved in the kinetic process.

Photostabilization of the drug is proposed by two different approaches:

1. Design and development of specific NA analogs with greater stability and fewer side effects.
2. Incorporation in cyclodextrin matrices aiming to improve the light-stability of NA and analogues in topical formulations.

The new synthesized compounds were designed on the base of the receptor binding-site features, by computer-aided approach. In particular, the compounds with a lactone moiety mimicking the linear butan-2-one portion of NA were prepared. The synthesis of the designed compounds was achieved by newly synthetic strategies as well as optimization of previously reported procedures, with the aim of obtaining compounds with high yield, purity and stability.

All the compounds were incorporated in cyclodextrin matrices and the complexes exposed to forced degradation to test their ability in improving the light-stability. Several type of cyclodextrins were evaluated to increase the encapsulation percentage of the drugs.

References: 1. Ioele G, De Luca M, Tavano L, Ragno G. The difficulties for a photolabile drug in topical formulations: the case of diclofenac. *Int. J. Pharm.* 465(1-2), 284-290 (2014). 2. Ioele G, Tavano L, De Luca M, Ragno G, Picci N, Muzzalupo R. Photostability and ex-vivo permeation studies on diclofenac in topical niosomal formulations. *Int. J. Pharm.* 494(1), 490-497 (2015). 3. Valero M, Costa S.M.B. Photodegradation of Nabumetone in aqueous solutions. *J. Photochem. Photobiol. Chem.* 157, 93-101 (2003). 4. International Conference on Harmonization. ICH Q1A(R2), Stability testing of new drug substances and products, 2003, IFPMA, Geneva.

Design and synthesis of novel macrocyclic Melanocortin peptides: discovery of potent and selective ligands at hMC3 and hMC5 receptors

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The melanocortin system includes five receptor isoforms known as MC1R-MC5R, which are involved in a large variety of physiological functions and are distributed in several different tissues (1). The endogenous ligands, the melanotropins, which bind to these receptors are linear peptides, α -, β -, γ -MSH, and ACTH, and are endowed of low selectivity and therefore the physiological function of each receptor subtype can't be easily delineated. Thus, there is an urgent need for the synthesis of ligands highly selective which would be useful pharmacological tools for further receptor investigation (2,3).

To date, only few synthetic ligands active at hMC1 and hMC5 receptors are available but most do not have appreciable selectivity. Thus, with the aim to discover new potent and selective ligands we designed novel macrocyclic compounds in which a constrained amino acid residue was inserted between His⁶ and Trp⁹ by a lactam bridge using a Glu or Asp residue. We designed and synthesized 2 series of macrocyclic compounds containing Glu or Asp, respectively. The resulting macrocyclic peptidomimetics, characterized to have a 19 or 20-membered ring, conserved the melanocortin core sequence His-Phe/Nal(2')-Arg-Trp (Figure 1).

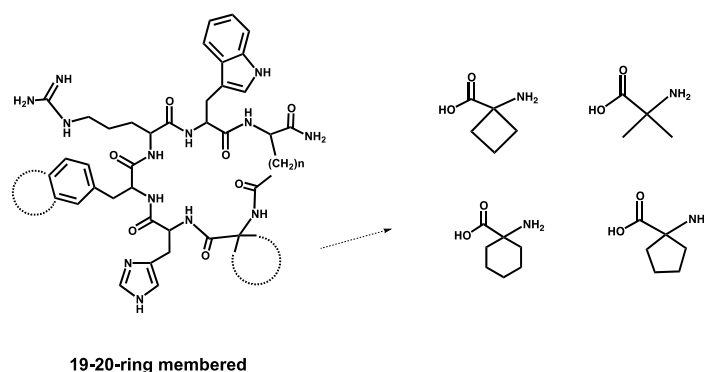


Figure 1. Macrocyclic compounds mimics of melanocortin peptides.

The main intent of the current study was to examine this kind of macrocyclization as an additional approach toward development of MT-II/SHU9119 analogues with enhanced receptor selectivity (4). All synthesized compounds were evaluated for their binding affinities at the human melanocortin receptors 1-5 in competitive binding assays using the radiolabeled ligand [¹²⁵I]-NDP- α -MSH, and for their agonist potency in cAMP assays employing the HEK293 cells expressing those receptors. Here, we report the biological activity and the preliminary conformation properties of synthesized compounds.

References: 1. Cone, R.D. The Melanocortin Receptors. Tortura. Humana Press, NJ. 2000, 15, 551. 2. Mayorov, A. V.; Cai, M.; Chandler, K. B.; Petrov, R. R.; Van Scoy, A. R.; Yu, Z.; Tanaka, D. K.; Trivedi, D.; Hruby, V. J. *J. Med. Chem.* 2006, 49, 1946. 3. Mayorov, A.V.; Han, S.-Y.; Cai, M.; Hammer, M. R.; Trivedi, D.; Hruby, V. J. *Chem. Biol. Drug. Des.* 2006, 67, 329. 4. Grieco, P.; Cai, M.; Liu, L.; Mayorov, A.; Chandler, K.; Trivedi, D.; Lin, G.; Campiglia, P.; Novellino, E.; Hruby, V. J. *Journal of Medicinal Chemistry* 2008, 51, 2701.

Design, synthesis and spectroscopic evaluation of novel fluorescent styryl pyridinium Carbonic Anhydrase inhibitors

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Fluorescence emission by organic molecules is a phenomenon strictly dependent on the surrounding microenvironment. (1) The formation of discrete host/guest complexes of fluorescent dyes with macrocyclic structures has been widely documented (1) and was generally found to elicit a consistent change in the micro-environmental parameters, which subsequently perturbs the fluorescence phenomenon. Fluorescent dyes host/guest complexes possess potential biological and environmental applications in the areas of sensing and signaling.(1) Hence, we designed a set of 4-[4-(dimethylamino)styryl]pyridium based fluorescent dyes (2) bearing classical zinc binding groups (ZBG) such as the sulfonamides, sulfamates and sulfamides to address their spectrum of action to the inhibition of the Zn enzymes carbonic anhydrases (CAs, EC 4.2.1.1). (3,4) The reported derivatives were evaluated for their inhibition profiles against four physiologically relevant human (h) CAs, isoforms hCA I, II, IV and XII. The synthesized dyes demonstrated to possess diverse inhibitory potency depending on the nature of the exhibited ZBG and on the length of the spacer between the fluorescent core and the ZBG itself. The formation of supramolecular host/guest biological complexes was reported by means of UV-vis absorption and fluorescence emission measurements, which were carried out for all the reported derivatives alone and in presence of the ubiquitous isoforms hCA I and hCA II. The X-ray crystal structures of four of the aforementioned host-guest CA-inhibitors complexes were obtained and provided for a valid explanation for the spectroscopic changes the dyes revealed after incubation with the two enzymatic isoforms.

References: 1. Dsouza, R. N.; Pischel, U.; NauJ, W. M. *Chem. Rev.* **2011**, *111*, 7941–7980. 2. Rudat, B.; Birtalan, E.; Thomè, I.; Kolmel, D. K.; Horhoiu, V. L.; Wissert, M. D.; Lemmer, U.; Eisler, H. J.; Balaban, T. S.; Brase, S. *J. Phys. Chem.* **2010**, *114*, 13473-13480. 3. Alterio, V.; Di Fiore, A.; D'Ambrosio, K.; Supuran, C. T.; De Simone, G. *Chem. Rev.* **2012**, *112*, 4421-4468. 4. Supuran, C. T. *Nat. Rev. Drug Discov.* **2008**, *7*, 168-181.

First profiling of flavonoids in Tarocco “Lempso” (*Citrus Sinensis* L. Osbeck) clone variety and its antioxidant potential by DPPH-UHPLC-PDA-IT-TOF

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Clonal selection and hybridization are valid strategies to obtain fruits with enhanced sensorial and nutraceutical properties (1,2). Within *Citrus sinensis* varieties, Tarocco clone “Lempso” is a typical product of Calabria region (Italy) characterized from a red pulp. This is the first report concerning its accurate profiling.

To characterize in detail the flavonoid composition of Lempso clone and to compare its antioxidant potential with other Citrus varieties by a fast screening method, extracts were subjected to solid phase extraction and the quali/quantitative profile was elucidated through ultra high performance liquid chromatography (UHPLC) coupled to photodiode array (PDA) and ion trap-time of flight (IT-TOF) mass spectrometry detection, and compared to both Cleopatra mandarin (*Citrus reticulata*) and blood orange (*Citrus sinensis* (L.) Osbeck) Sanguinello varieties. The antioxidant activity was assessed by pre-column DPPH reaction coupled to UHPLC-PDA (3).

Lempso is characterized by flavonoids and anthocyanins. Flavanones content (Hesperidin: 57.19 ± 0.49 , Vicenin-2: 4.59 ± 0.03 , Narirutin: 5.78 ± 0.13 mg/100 mL) was considerably higher than Cleopatra and Sanguinello varieties. The developed DPPH-UHPLC-PDA method provides information regarding the single contributions to antioxidant activity, highlighting how Ferulic acid, Quercetin and Cyanidin derivatives possess considerable radical scavenging activity (> 50%) (4,5). The total antioxidant activity was also evaluated and compared with positive controls, showing higher scavenging activity than Cleopatra and Sanguinello (IC₅₀: 333.76 ± 10.81 µg/mL vs 452.62 ± 10.81 and 568.39 ± 26.98 µg/mL, respectively).

These data evidence the nutraceutical potential of Lempso variety, which could be an ingredient for functional beverages.

References: 1. Bretó MP, Ruiz C, Pina JA, Asíns MJ. 2001. The diversification of Citrus clementina Hort. ex Tan., a vegetatively propagated crop species. Mol Phylogenet Evol. 21: 285–293. 2. Rapisarda P, Fabroni S, Peterek S, Russo G, Mock HP. 2009. Juice of New citrus hybrids (Citrus clementina Hort. ex Tan. × C. sinensis L. Osbeck) as a source of natural antioxidants. Food Chem. 117: 212–218. 3. Sommella E, Pepe G, Pagano F, Conte G, Carimi F, Tenore GC, Novellino E, Manfra M, Russo M, Campiglia P. 2016. Rapid Screening of Antioxidant Anthocyanins in Autochthonous Nero d'Avola Grape Clones by Pre-column DPPH Reaction Coupled to UHPLC-UV/Vis-IT-TOF: a Strategy to Combine Chemical data and Genetic Diversity. Food Anal Method. 10: 2780-2790. 4. Kanski J, Aksenova M, Stoyanova A, Butterfield DA. 2002. Ferulic acid antioxidant protection against hydroxyl and peroxy radical oxidation in synaptosomal and neuronal cell culture systems in vitro: structure–activity studies. J Nutr Biochem. 13: 273–281. 5. Stintzing FC, Stintzing AS, Carle R, Frei B, Wrolstad RE. 2002. Color and antioxidant properties of cyanidin-based anthocyanin pigments. J Agric Food Chem. 50: 6172–6181.

Benzofuran derivatives: a new class of ‘direct’ AMPK activators

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AMPK (adenosine monophosphate-activated protein kinase) is a serine/threonine heterotrimeric kinase comprising a catalytic subunit (α) and two regulatory subunits (β and γ). It is significantly involved in the regulation of energy demanding/consuming metabolic pathways, playing a key role in maintaining suitable ATP cell levels under conditions depleting energy levels such as exercise, starvation, hypoxia and rapid cell growth. Thanks to the central role played by AMPK in cellular and whole body energy homeostasis, this protein represents an attractive target for the treatment of a number of metabolic diseases, including type 2 diabetes and obesity, as well as of immune-mediated inflammatory diseases and cancer, thus highlighting the persistent need for effective and potent activators (1). Different classes of AMPK activators have been developed, the main relevant one being represented by the so called ‘direct’ activators (2).

We developed a novel class of ‘direct’ AMPK activators, which target the AMP binding site located at the AMPK- γ regulatory subunit of the protein (Fig. 1a) (3). The novel derivatives, characterized by a 3-amino-5(6)-arylbenzofuran-2-carboxamide structure, possess key pharmacophoric elements that allow a profitable interaction with the target enzyme. Actually, both the 2-carboxamide portion and the oxygen atom of the core let the compounds hook the AMPK- γ regulatory subunit through H-bond interactions. Moreover, the wide and aromatic benzofuran core confers lipophilicity, thus assuring a suitable interaction with the lipophilic area of the site and conferring, at the same time, a profitable bioavailability. The novel compounds increased significantly the phosphorylation of AMPK at a concentration of 10 μ M, and proved to be more potent than the well-known AMPK activator Berberine (BBR) (Fig. 1b). In addition, as it is known that stimulation of phosphorylated AMPK is potentially related to the increase of Sirt1 activity, the effects of the novel compounds on Sirt1 activation was investigated as well. Results of this test confirmed the efficacy of the benzofuran derivatives, making them even more attractive drug candidates due to their activity on Sirt1.

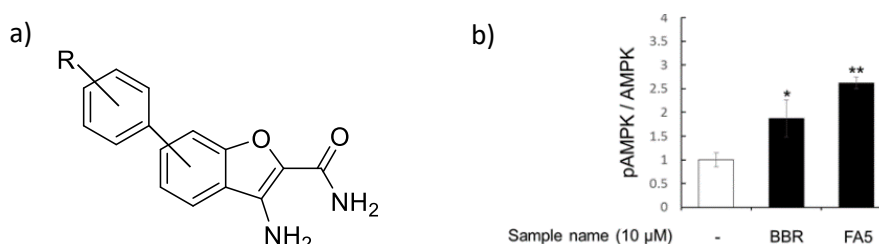


Figure 1

References: [1] J. Kim, G. Yang, Y. Kim, J. Kim, and J. Ha, “AMPK activators: mechanisms of action and physiological activities,” *Exp. Mol. Med.*, vol. 48, no. 4, p. e224, Apr. 2016. [2] S. Rana, E. C. Blowers, and A. Natarajan, “Small molecule adenosine 5'-monophosphate activated protein kinase (AMPK) modulators and human diseases,” *J. Med. Chem.*, vol. 58, no. 1, pp. 2–29, Jan. 2015. [3] F. Angelucci, L. Quattrini, V. Coviello, L. Antonioli, M. Fornai, C. Blandizzi, W.K. Oh, C. La Motta. Italian Patent Application, 102017000039329.

Structure-activity relationship study of a FHIT-mimetic peptide

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The fragile histidine triad (FHIT) protein is a member of the large and ubiquitous histidine triad (HIT) family of proteins. On the basis of the genetic evidence, it has been postulated that the FHIT protein may function as a tumor suppressor, implying a role for the FHIT protein in carcinogenesis.(1) Recently Gaudio et al. reported that FHIT is in a molecular complex with annexin A4 (ANXA4), following to their binding, FHIT delocalizes ANXA4 from plasma membrane to cytosol in paclitaxel-resistant lung cancer cells, thus restoring their chemosensitivity to the drug.(2) They also identified the smallest region of the FHIT protein sequence still interacting with ANXA4. This short sequence, QHLIKPS, ranging from position 7 to 13 of FHIT protein, was not only able to bind ANXA4 but also to keep it in the cytosol during paclitaxel treatment, thus avoiding ANXA4 translocation to the inner side of cell membrane.(2) Starting from these results, we initiated a systematic SAR study on the peptide mentioned above, through an Ala-scan approach, binding assay and structural studies by CD and NMR.

References: 1.Gaudio E. et al. *PLoS one*. **2013**, 8:e78610. 2.Gaudio E. et al. *Oncotarget*. **2016**, 7(21):29927-36.

Structure-activity relationship studies of lactoferrin-derived peptides active towards influenza virus

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Bovine lactoferrin (bLf) is a multifunctional glycoprotein that plays an important role in innate immunity against infections, including influenza.(1, 2) Therefore, bLf was considered a novel drug target for the inhibition of influenza virus infection. Previously, we have identified three C-lobe bLf-derived tetrapeptides (SKHS, SLDC, VLRP) as the minimum fragments expressing the broad anti-influenza activity of bLf. These tetrapeptides inhibit the Influenza virus hemagglutination and cell infection in a concentration range of femto- to picomolar.

In this study, we performed structure-activity relationship (SAR) studies to generate peptides with improved biological activity. All new derivatives were tested for the assessment of their ability to inhibit viral hemagglutination and cell infection.

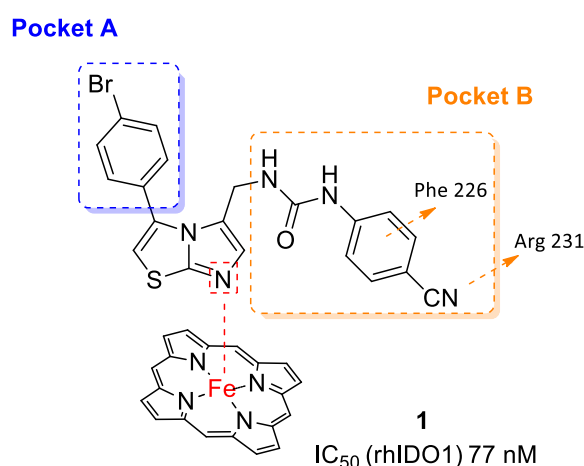
References: 1. P.F. Levay, M. Viljoen. *Haematologica*. **1995**, 80, 252–267. 2. B.W.A. Van der Strate, L. Beljaars, G. Molema, M.C. Harmsen, D.K.F. Meijer. *Antivir. Res.* **2001**, 52, 225–239.

Synthesis, biological evaluation and molecular docking of Ugi and Passerini products as novel indoleamine 2,3-dioxygenase 1 inhibitors

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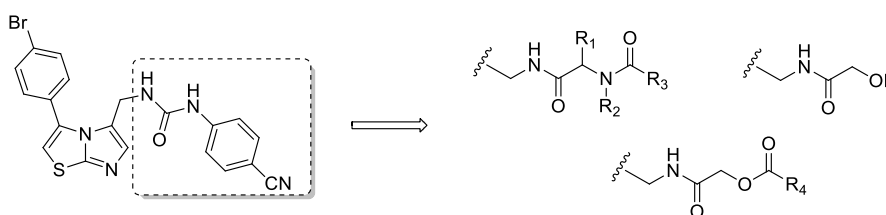
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Indoleamine 2,3-dioxygenase 1 (IDO1) is a heme-containing enzyme involved in tryptophan catabolism through the kynurenine pathway and plays a central role in pathological immune escape process⁽¹⁾. IDO1, overexpressed in a variety of diseases, including cancer and neurodegenerative disorders⁽²⁾, is emerging as an attractive target for immunological cancer treatment. Recently, imidazole⁽³⁾ and imidazothiazole⁽⁴⁾ derivatives have been discovered as promising IDO1 inhibitors. Among them, **1** is the most potent compound identified so far (Scheme 1), with an IC₅₀ value of 77 nM in the enzymatic assay (rhIDO1).



Scheme 1

With the aim of further improving the biological profile and probing interactions with the aminoacids in the catalytic site, we have exploited the Ugi and Passerini multicomponent reactions⁽⁶⁾ to access a library of imidazothiazole derivatives with a diversified side-chain (Scheme 2).



Scheme 2

Preparation, biological evaluation and molecular docking of the synthesized compounds will be discussed.

References: 1. J. M. Gostner, K. Becker, F. Uberall, D. Fuchs, *Expert Opin. Ther. Targets* **2015**, *19*, 605. 2. U. F. Röhrig, S. R. Majjigapu, P. Vogel, V. Zoete, O. Michelin, *J. Med. Chem.* **2015**, *58*, 9421. 3. S. Fallarini, A. Massarotti, A. Gesù, S. Giovarruscio, G. Coda Zabetta, R. Bergo, B. Giannelli, A. Brunco, G. Lombardi, G. Sorba, T. Pirali, *Med. Chem. Commun.* **2016**, *7*, 409. 4. S. Tojo, T. Kohno, T. Tanaka, S. Kamioka, Y. Ota, T. Ishii, K. Kamimoto, S. Asano, Y. Isobe, *ACS Med. Chem. Lett.* **2014**, *5*, 1119. 5. G. C. Tron, T. Pirali, R. A. Billington, P. L. Canonico, G. Sorba, A. A. Genazzani, *Med. Res. Rev.* **2008**, *28*, 278. 6. A. Dömling, W. Wang, K. Wang, *Chem. Rev.* **2012**, *112*, 3083.

Coupling online comprehensive hydrophilic interaction chromatography × reversed-phase ultra-high-pressure liquid chromatography with high resolution mass spectrometry: a powerful platform for complex polyphenolic sample analysis

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Given their complexity, multiclass polyphenolic samples require increased selectivity and resolution to thoroughly characterize their components. For this purpose, in this work we developed an improved online comprehensive two-dimensional liquid chromatography platform coupled to tandem mass spectrometry. A narrowbore hydrophilic interaction chromatography column (150 × 2.0 mm, 3.0 μm, cross-linked diol) was employed in the first dimension, while a reversed-phase column based on monodisperse sub-2 μm fully porous particles (50 × 3.0 mm, 1.9 μm d.p.) with high surface area (410 m²/g) was employed in the second dimension. The combination of a trapping column modulation interface with the high retentive fully porous monodisperse reversed-phase column in the second dimension resulted in higher peak capacity values (1146 versus 867), increased sensitivity, sharper and more symmetrical peaks in comparison with a conventional loop-based method, with the same analysis time (70 min). The system was challenged against a complex polyphenolic extract of a typical Italian apple cultivar, namely Annurca (1), enabling the simultaneous separation of multiple polyphenolic classes in a single analytical run, including oligomeric procyanidins up to degree of polymerization of 10 (2,3). Hyphenation with an ion trap time-of-flight mass spectrometer led to the tentative identification of 121 analytes, showing how this platform could be a powerful analytical tool for the accurate profiling of complex polyphenolic samples.

References: 1. Tenore, G. C., Campiglia, P., Stiuso, P., Ritieni, A., Novellino, E., Nutraceutical potential of polyphenolic fractions from Annurca apple (*M. pumila* Miller cv Annurca). *Food Chem.* 2013, 140, 614–622. 2. Sommella, E., Pepe, G., Pagano, F., Ostacolo, C., Tenore G., C., Russo M., T., Novellino, E., Manfra, M., Campiglia, P., Detailed polyphenolic profiling of Annurca apple (*M. pumila* Miller cv Annurca) by a combination of RP-UHPLC and HILIC, both hyphenated to IT-TOF mass spectrometry. *Food Res. Int.* 2015, 76, 466–477. 3. Mari, A., Tedesco, I., Nappo, A., Russo, G. L., Malorni, A., Carbone, V., Phenolic compound characterisation and antiproliferative activity of “Annurca” apple, a southern Italian cultivar. *Food Chem.* 2010, 123, 157–164.

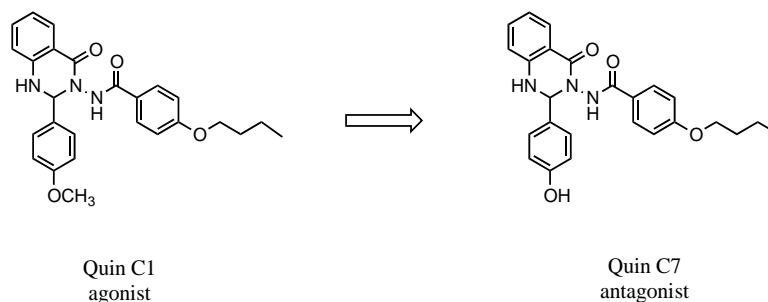
Rational design and function prediction of FPR2 ligands based on docking studies and MD simulations

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Formyl peptide receptor 2 (FPR2) is a G protein-coupled receptor belonging to the *N*-formyl receptor family (FPRs) (1) that plays critical roles in peripheral and brain inflammatory responses and, as such, it has been considered as an attractive therapeutic target for the development of drugs that could halt pathological inflammatory reactions (2). To date several classes of non peptidic FPR2 agonists have been described, whereas only very few antagonists have been reported. With the aim to identify the molecular determinants responsible for functional properties of FPR2 ligands, we constructed a homology model using two antagonist-bound peptide receptor crystal structures as templates (chemokine CXCR4, and angiotensin AT1R receptor) (3). Docking studies on structurally diverse FPR2 agonists and antagonists were performed (4) using Glide in Schrödinger suite. The poses were clustered and molecular dynamics simulations were conducted for the representative poses using AMBER. For each simulation we monitored nonbonded energy, RMSD and ligand-receptor hydrogen bond formation. We observed that the hydrogen bonds between ligand carbonyl group and Arg201 or Arg205 are generally energetically favored. This interaction, observed for all the investigated ligands, seems an essential feature for FPR2 ligand recognition. Next, we focused on the binding mode of quinazolinone derivatives Quin C1 and Quin C7 (Figure I), in which a simple structural modification interconverted the functional properties from agonism to antagonism. We here present docking studies results and the design of new quinazolinone derivatives.

Figure I



References: 1. R.D. Ye, F. Boulay, J.M. Wang, C. Dahlgren, C. Gerard, M. Parmentier, C.N. Serhan, P.M. Murphy. *Pharmacol. Rev.* 2009, **61**, 119-161. 2. S.N. Cooray, T. Gobetti, T. Montero-Melendez, S. McArthur, D Thompson, A.J. Clark et al. *Proc Natl Acad Sci U S A.* 2013, **110**, 18232-7. 3. D. Latek, P Pasznik, T Carlomagno, S. Filipek. *PloS one.* 2013, 56742. 4. E. Lacivita, I.A. Schepetkin, M.L. Stama, L.N. Kirpotina, N.A. Colabufo, R. Perrone et al. *Bioorg Med Chem.* 2015, **23**, 3913-24.

Battle against antimicrobial resistance: FtsZ inhibitors as novel potent Gram-positive antibiotics

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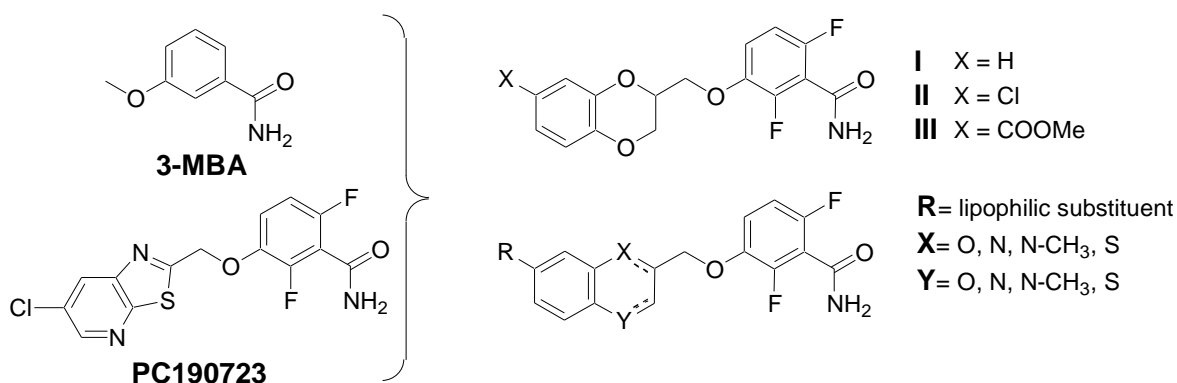
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Antimicrobial resistance is one of the major actual health plagues. Even if it started more than 70 years ago, the problem burst out only in the latest years, prompting to the urgent need of novel efficient antibiotics, showing innovative mechanisms of action.

In this context, the bacterial cell division process turned to be an interesting and promising target (1), firstly because divisome components are crucial for the viability of bacteria. Moreover, the most important division proteins are widely conserved in bacteria and are absent in eukaryotic cells, strengthening the selectivity of the possible novel antimicrobics.

Among the essential cell division proteins, FtsZ (Filamentous temperature sensitive Z), which is a tubulin homologue (2), became an attractive target. FtsZ is the first protein that localizes to the mid-point of the cell and it undergoes polymerization in a GTP-dependent manner, bringing to the formation of the Z-ring. It recruits at least ten other cell division proteins, which enable cell constriction, the formation of mesosome and two daughter cells (3).

In the last 10 years several research group studied and developed FtsZ inhibitors, confirming that protein inhibition results in a bactericidal effect. Interesting results were obtained with synthetic small molecules; specifically with 3-Methoxybenzamide (3-MBA) derivatives: the lead compound of this class of antimicrobics is PC190723 (4-6).



In the attempt to design potent novel antibacterial agents, in the latest years we designed and accomplished several derivatives, firstly replacing the thiazolopyridine of PC190723 with differently substituted 1,4-benzodioxane, bringing in particular to compounds I-III (7,8). These molecules proved to be strong inhibitors of *S. aureus*, *E. faecalis* and *M. tuberculosis* viability. Recently we consolidated the Structure Activity Relationship (SAR) of this class, designing a number of analogues of I and III, through a series of isosteric, positional or substituent modifications (9).

Furthermore, we confirmed the target, performing two different biochemical assays, aimed at studying GTPase and polymerization activities of *S. aureus* FtsZ, when incubated with our compounds.

References: 1. *Nature Reviews Drug Discovery* **2008**, 7, 324-338. 2. *Journal of Molecular Biology* **2004**, 342, 953-970. 3. *Nature Reviews Molecular Cell Biology* **2005**, 6, 862-872. 4. *Science* **2008**, 321, 1673-1675. 5. *B.M.C.L.* **2009**, 19, 524-527. 6. *B.M.C.L.* **2014**, 24, 353-359. 7. *E.J.M.C.* **2015**, 89, 252-265. 8. *E.J.M.C.* **2016**, 120, 227-243. 9. *ChemMedChem* **2017**, accepted.

Novel D- Glucosamine N- Peptidyl derivatives endowed with selective activity towards IKK alpha

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Osteoarthritis (OA) is a rheumatic disease which represents the major cause of disability in the adult population as well as a severe health burden with a significant economic impact. OA is the result of abnormal biomechanics and cell-derived and tissue-derived factors. (1) The NF- κ B family of nuclear transcription factors is involved in the induction of inflammatory disorders, representing a potential therapeutic target in OA. It comprehends ubiquitously expressed proteins responsible for the regulation of a considerable number of genes. These transcription factors are sequestered in the unstimulated cell cytoplasm by inhibitor proteins called I κ Bs, forming inactive complexes. As a result of specific stimuli I κ B is phosphorylated by I κ B kinase (IKK) complex, leading to the dissociation of I κ B from NF- κ B which can migrate into the nucleus, activating the gene transcription. IKK includes three components: IKK α , IKK β and NF- κ B essential modulator (NEMO). IKK α and IKK β are implicated in the regulation of the expression of genes involved in the extracellular matrix remodeling and terminal differentiation of chondrocytes. (2,3) From a random screening of our in house library the compound **RC510** (already known as substrate analog inhibitors of papain and cathepsin-B), (4) a D-glucosamine N-peptidyl derivative, showed selective activity towards IKK α . (5) Following this result we decided to investigate the interactions of this compound with the target by conducting molecular docking studies, in order to speculate about the mechanisms by which it binds to IKK α kinase domain. As docking molecular target we used a three-dimensional model of IKK α , built by homology modelling. Docking experiment showed that **RC510** interacts with ATP binding pocket mainly by the establishment of hydrogen bonds (with backbone atoms of Thr15 and Glu140 and with side chains of Thr15 and Asp94) and of hydrophobic interactions. From these results we decided to design and synthesize a novel series of D-glucosamine N-peptidyl derivatives in order to obtain compounds having an inhibitory activity towards IKK α .

References: 1. L.J. Sandell, *Nat. Rev. Rheumatol.* **2012**, 8, 77–89. 2. E. Zandi, D. M. Rothwarf, M. Delhase, M. Hayakawa, M. Karin, *Cell* **1997**, 91, 243–252. 3. S. Ghosh, M. Karin, N. Haven *Cell* **2002**, 109, S81–96. 4. C. Giordano, C. Gallina, V. Consalvi, R. Scandurra, *E. J. Med. Chem.* **1991**, 26, 753-762. 5. A. Scotto D'Abusco, L. Politi, C. Giordano, R. Scandurra *Arthritis Res. Ther.* **2010**, 12, R18.

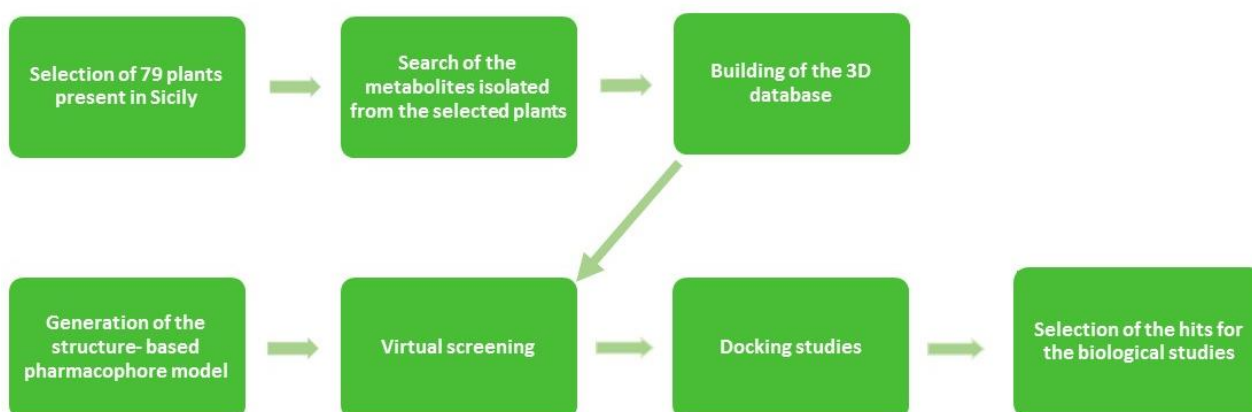
Identification of natural products as anti-melanogenesis agents

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Melanogenesis is a biosynthetic pathway for the formation of melanin pigment in human skin and hair, as well as for the browning of fruit and vegetables. Abnormal production of melanin causes dermatological disorders such as freckles, melasma and cancer. Tyrosinase (EC 1.14.18.1) is the key regulatory enzyme involved in the biosynthesis of melanin pigments. It is a type 3 copper protein widespread in mammals, plants, fungi and bacteria. Specifically this enzyme catalyzes the first two steps of the biosynthetic process: the o-hydroxylation of monophenols and the subsequent oxidation of the resulting o-diphenols into o-quinones. The inhibition of tyrosinase activity represents the most prominent approach to inhibit melanogenesis. A large number of tyrosinase inhibitors have been reported in literature, but their use is limited due to their side effects, low stability and cytotoxicity. This encourages researchers to seek safer tyrosinase inhibitors (1,2).

Herein, structure-based modeling approaches were used to identify new tyrosinase inhibitors from natural sources, considering that the natural products have been and continue to be a rich source for drug discovery. In particular, a pharmacophore model for the tyrosinase enzyme was generated by means of LigandScout software. The obtained model was used to screen the database SiciMet, which has been built in house collecting 791 secondary metabolites from sicilian plants. The hits obtained from the virtual screening runs were subjected to docking studies in order to further investigate both the putative ligand binding-mode within the active site and the biological effects.



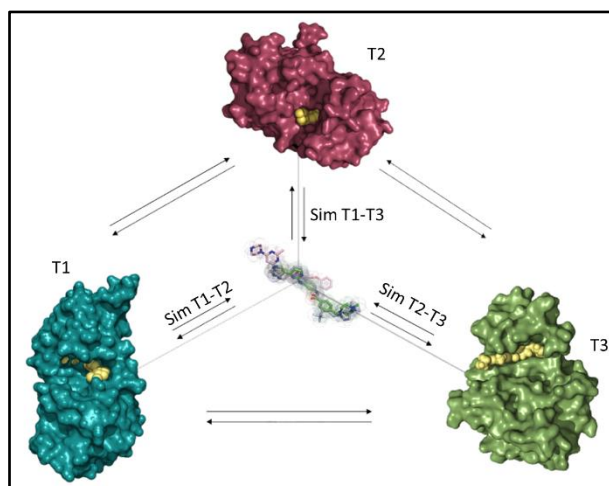
References: 1. Chang TS; *Materials*, 2012, 5, 1661-1685. 2. Bagherzadeh K. et al.; *J Biomol Struct Dy*, 2014, 33(3), 487-501.

Polypharmacology predictions in the Protein Data Bank

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The design of a chemical entity that simultaneously and selectively modulates a selected pool of biological targets represents an attracting goal, especially for the treatment of complex diseases (1). Despite recent successes, two considerations arise: first, *ad hoc* methods to predict the desired polypharmacological profile are needed; second, chemical/structural/biological information contained in publicly available databases is generally not thoroughly exploited to prospectively design polypharmacological compounds (2,3). In this context, the Protein Data Bank (PDB) represents a rich source of information to help predict polypharmacological profiles of ligands. Here, a systematic analysis of the PDB using different integrated computational approaches has been performed. New polypharmacological profiles of ligands deposited into the PDB were established. Moreover, the analysis of the chemical landscape covered by these ligands highlighted interesting relationships between different protein targets and their respective ligands.



References: 1. Reddy, A. S. & Zhang, S. Polypharmacology: drug discovery for the future. *Expert Rev. Clin. Pharmacol.* **6**, 10.1586/ecp.12.74 (2013). 2. Anighoro, A., Bajorath, J. & Rastelli, G. Polypharmacology: Challenges and opportunities in drug discovery. *J. Med. Chem.* **57**, 7874–7887 (2014). 3. Rastelli, G. & Pinzi, L. Computational polypharmacology comes of age. *Front. Pharmacol.* **6**, (2015).

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Galatello Paola*	FAR PO33
Galiotta Luis J. V.	FAR PO24

Gargini Maria	FAR PO52
Garino Claudio	FAR OR12
Garofalo Antonio	FAR PO23
	FAR PO69
Garrido Vanesa	FAR PO10
Gasparrini Francesco	FAR PO77
Gazzarrini Sabrina	FAR OR16
Genazzani Armando	FAR PO67
	FAR OR01
Germanó Maria Paola	FAR PO68
Ghelardini Carla	FAR PO55
Ghirga Francesca	FAR PO38
Giacchello Ilaria	FAR PO44
	FAR OR07
Giacchello Ilaria*	FAR PO34
Giammona Gaetano	FAR OR18
Giancola Concetta	FAR PO56
Giannella Mario	FAR PO31
Gioiello Antimo	FAR OR03
Giordanetti Fabrizio*	FAR KN01
Giordano Libera Federica	FAR OR19
Giorgioni Gianfabio	FAR PO31
Giorgis Marta	FAR OR12
Giovanna Poce	FAR PO20
Giovannoni Maria Paola	FAR OR23
Girardini Miriam	FAR PO17
Gitto Rosaria	FAR PO62
	FAR PO68
Gitto Rosaria*	FAR KN05
Giuntini Stefano	FAR PO56
Goal Parveen	FAR OR12
Gomez-Monterrey Isabel Maria	FAR PO28
	FAR PO32
	FAR PO39
	FAR PO47
	FAR PO74
	FAR PO75
Gonzalez-Rodriguez Sara	FAR PO39
Goracci Laura	FAR PO13
Gramiccia Marina	FAR OR15
Grande Fedora	FAR PO69
Grandi Nicole	FAR PO09
Gratteri Paola	FAR PO71
Greco Chiara	FAR PO34
	FAR PO44
Greish Khaled	FAR OR11
Grieco Paolo	FAR PO03
	FAR PO70
Griglio Alessia	FAR PO76
	FAR OR01
Griglio Alessia*	FAR PO67
Grolla Ambra	FAR OR08
Guerrini Gabriella	FAR OR23
Gul Sheraz	FAR PO05
Hamel Hernest	FAR PO40
Harper Steven	FAR OR05

Hoffmann Carsten	FAR PO30
Holzgrabe Ulrike	FAR PO30
Hruby Victor J.	FAR PO70
Iacovone Antonella	FAR OR23
Ianni Federica	FAR OR03
	FAR OR03
Ibba Roberta	FAR PO02
Ibba Roberta*	FAR PO08
Ielo Laura*	FAR PO68
Ilari Andrea	FAR OR15
Imhof Beat A.	FAR PO25
Imhof Axel	FAR PO01
Infante Paola	FAR PO38
Ingallina Cinzia	FAR PO38
Ioele Giuseppina	FAR OR02
Ioele Giuseppina*	FAR PO69
Irace Carlo	FAR PO33
Ismail Omar H.	FAR PO77
Jakowiecki Jakub	FAR PO78
Jesus Corral Maria Jesus	FAR PO05
Jun Jae Ho	FAR PO35
Kauk Michael	FAR PO30
Kim Sang Eun	FAR PO35
Klotz Karl-Norbert	FAR PO45
	FAR PO46
Kovalenko Lesia	FAR OR05
La Regina Giuseppe	FAR PO06
	FAR PO12
	FAR PO40
Lacivita Enza	FAR PO78
Lai Francesco	FAR PO65
Langer Thierry	FAR PO81
Lauricella Marianna	FAR PO29
Laurini Erik	FAR PO08
Lauro Gianluigi	FAR PO47
Lavecchia Antonio	FAR PO45
	FAR PO46
	FAR PO58
	FAR OR17
Lee Byung Chul	FAR PO35
Lee Byung Chul*	FAR PO35
Lee Jin-Ching	FAR PO06
Lentini Giovanni	FAR PO60
Leoni Alberto	FAR PO36
Leopoldo Marcello	FAR PO78
Licciardi Mariano	FAR OR18
Lolli Marco Lucio*	FAR OR12
Loregian Arianna	FAR PO13
	FAR OR07
Luchinat Claudio	FAR PO56
Luongo Livio	FAR PO45
	FAR PO46
Lupino Elisa	FAR OR12
Ma Rui	FAR PO17
Macchiarulo Antonio	FAR OR03
Macedonio Giorgia	FAR PO37
	FAR PO41

Madia Valentina Noemi	FAR PO80	Merlino Francesco	FAR PO03
	FAR OR15		FAR PO70
Madia Valentina Noemi*	FAR PO09	Merlino Francesco*	FAR PO36
Maga Giovanni	FAR PO41	Mesiti Francesco*	FAR PO41
Magalhaes Joana*	FAR PO10	Messore Antonella	FAR PO25
Maggio Benedetta	FAR PO29	Meta Elda	FAR PO01
Magni Fulvio	FAR PO05	Micheli Fabrizio	FAR OR09
Maione Sabatino	FAR PO45	Micucci Matteo*	FAR PO22
	FAR PO46	Milelli Andrea	FAR PO01
Majellaro Maria	FAR PO61	Milite Ciro	FAR PO04
Malancona Savina	FAR OR05		FAR PO19
Malfanti Alessio	FAR KN06		FAR PO14
Mamolo Maria Grazia	FAR PO48	Milite Ciro*	FAR OR20
Manca Maria Letizia	FAR PO66	Minotti Alberto	FAR PO03
Manconi Maria	FAR PO66	Miro Agnese	FAR PO43
Mancuso Francesca	FAR PO62	Modica Maria N.	FAR OR11
Mandrup Bertozzi Sine	FAR PO24		FAR OR13
Manfra Michele	FAR PO53		Molicotti Paola
	FAR PO59	Mollica Adriano	FAR OR10
	FAR PO72	Mollica Adriano*	FAR PO37
Manfroni Giuseppe	FAR PO13	Mor Marco	FAR KN07
	FAR OR04	Moretti Pasquale	FAR PO60
	FAR OR06	Mori Mattia*	FAR PO38
Manniello Michele Dario	FAR OR05		
Manson Domenico	FAR PO02	Mosquera Jesús	FAR OR10
Maresca Alfonso	FAR PO57	Mozzarelli Andrea	FAR PO10
Margaroli Natasha	FAR PO24	Mugelli Alessandro	FAR PO54
Margiotta Nicola	FAR PO60	Murthy Vallabhaneni S.	FAR PO54
Mariangela Biava	FAR PO20	Musella Simona	FAR PO28
Marinozzi Maura	FAR OR03		FAR PO32
Marongiu Francesca	FAR PO65	Musella Simona*	FAR PO39
Marrazzo Agostino	FAR PO43	Musumeci Francesca	FAR PO34
	FAR OR11	Naccarato Valentina*	FAR PO44
	FAR OR13		FAR PO40
Martelli Alma	FAR PO52	Naesens Lieve	FAR OR16
Marzaro Giovanni*	FAR PO11	Nannetti Giulio	FAR PO13
Marzetti Carla	FAR OR09		FAR OR07
Mascarenas Josè L.	FAR OR10	Natalini Benedetto	FAR OR03
Masci Domiziana *	FAR PO12	Neamati Nouri	FAR PO23
Massari Claudio	FAR PO60	Nesi Giulia	FAR PO52
Massari Serena	FAR OR04	Nocentini Alessio	FAR PO51
Massari Serena*	FAR PO13	Nocentini Alessio*	FAR PO71
Massarotti Alberto	FAR PO76	Notomista Eugenio	FAR PO03
Mastrangelo Eloise	FAR OR04		FAR PO03
Mastrocinque Raffaella	FAR PO53	FAR PO28	
Mastrotto Francesca	FAR KN06	FAR PO32	
Matera Carlo	FAR PO30	FAR PO37	
Matricardi Pietro	FAR PO66	FAR PO39	
Matucci Rosanna	FAR PO31	FAR PO47	
Mazzocanti Giulia	FAR PO77	FAR PO53	
Mazzolari Angelica*	FAR OR24	FAR PO56	
Mely Yves	FAR OR05	FAR PO58	
Mencherini Teresa	FAR PO64	FAR PO70	
Menichincheria Maria*	FAR KN04	FAR PO72	
Mer Georges	FAR PO21	FAR PO74	
Mercolini Laura	FAR OR09	FAR PO75	
		Novellino Ettore	FAR PO77

	FAR OR10
	FAR OR17
Oh W.K.	FAR PO73
Orofino Francesco*	FAR PO15
Orsomando Giuseppe	FAR OR08
Orteca Nausicaa	FAR PO33
Ostacolo Carmine	FAR PO28
	FAR PO32
	FAR PO39
	FAR PO53
	FAR PO59
	FAR PO72
	FAR PO77
Ottonello Giuliana	FAR PO24
Paduano Francesco	FAR PO47
Pagano Francesco	FAR PO53
	FAR PO77
Pagano Francesco*	FAR PO72
Pane Catello	FAR PO64
Paolino Marco*	FAR OR18
Parisini Emilio	FAR PO26
Parodi Brunella	FAR PO42
Pasero Carolina*	FAR PO16
Peat Tom S.	FAR PO51
	FAR PO71
Pedemonte Nicoletta	FAR PO24
Pedretti Alessandro	FAR OR24
Penna Ilaria	FAR PO24
Pepe Giacomo	FAR PO53
	FAR PO59
	FAR PO72
	FAR PO77
Peri Francesco*	FAR OR20
Perrin-Cocon Laure	FAR OR20
Perrone Mara	FAR PO35
Persico Marco	FAR PO33
Pescatore Luca	FAR PO41
Pesce Emanuela	FAR PO24
Petrelli Riccardo	FAR PO45
	FAR PO46
Pfaff Tamara	FAR PO57
Piano Ilaria	FAR PO52
Piccinini Marco	FAR OR12
Piccolo Marialuisa	FAR PO33
Picerno Patrizia	FAR PO64
Pieretti Stefano	FAR PO37
Piergentili Alessandro	FAR PO31
Pieroni Marco	FAR PO10
	FAR OR14
Pieroni Marco*	FAR PO17
Pietrantoni Agostina	FAR PO75
Pinzi Luca	FAR PO82
Pippione Agnese Chiara	FAR OR12
Piragine Eugenia	FAR PO52
Pirali Tracey	FAR PO67
	FAR PO76
Pirali Tracey*	FAR OR01

Piras Sandra	FAR PO02
	FAR PO08
Pireddu Rosa	FAR PO65
Pirrello Giulia	FAR PO62
Pisani Leonardo*	FAR OR21
Pisapia Vincenzo	FAR PO07
	FAR PO21
Pittalà Valeria	FAR PO43
	FAR OR11
	FAR OR13
Pizzo Eliodoro	FAR PO03
Plescia Fabiana	FAR PO29
Polerà Nicoletta	FAR PO23
	FAR PO27
Polerà Nicoletta*	FAR PO18
Porco Melania Francesca	FAR PO69
Prezzavento Orazio	FAR PO43
	FAR OR11
	FAR OR13
Prilc Sabrina	FAR PO08
	FAR PO02
Prosdocimi Tommaso	FAR PO26
Protti Michele	FAR OR09
Pupo Giovanni	FAR PO09
	FAR PO80
	FAR OR15
Pupo Giovanni*	FAR PO41
Purgatorio Rosa	FAR PO61
Quaglia Fabiana	FAR PO03
Quaglia Wilma	FAR PO31
Quaglio Deborah	FAR PO38
Quattrini Luca*	FAR PO73
Quinn Mark T	FAR OR23
Raffa Demetrio	FAR PO29
Ragno Gaetano	FAR PO69
	FAR OR02
Raimondi Maria Valeria	FAR PO29
Ramunno Anna	FAR PO33
Rapisarda Antonio	FAR PO68
Rapposelli Simona	FAR PO52
Rastelli Giulio*	FAR PO82
Rescigno Donatella	FAR PO14
Rescigno Donatella*	FAR PO19
Řezáčová Pavlína	FAR KN05
Riva Beatrice	FAR PO67
	FAR OR01
Rivara Silvia	FAR KN07
Rodriguez-Dorado Rosalia	FAR PO63
Rodríguez-Gimeno Alejandra	FAR PO24
Romeo Giuseppe	FAR PO43
	FAR OR11
Ropraz Patricia	FAR PO25
Russo Debora	FAR PO24
Russo Eleonora*	FAR PO42
Russo Mariateresa	FAR PO72
	FAR PO77
Russo Marina	FAR OR13

Russo Paola	FAR PO63
Russo Paola*	FAR OR19
Sabatini Stefano	FAR PO13
	FAR OR04
	FAR OR06
Saccoliti Francesco	FAR PO09
	FAR PO41
	FAR PO80
Saccoliti Francesco*	FAR OR15
Sainas Stefano	FAR OR12
Sala Marina	FAR PO47
	FAR PO75
Sala Marina*	FAR PO74
Saladini Francesco	FAR OR05
Salerno Loredana*	FAR PO43
	FAR OR11
Salmaso Stefano	FAR KN06
Sanna Monica	FAR PO34
Sanna Monica*	FAR PO44
Sansone Francesca	FAR PO59
	FAR PO64
Santarem Nuno	FAR PO05
Santucci Matteo	FAR OR16
Sardella Roccaldo	FAR OR03
Sarno Federica	FAR PO01
Sbardella Gianluca	FAR PO01
	FAR PO04
	FAR PO07
	FAR PO14
	FAR PO19
	FAR PO21
Scala Maria Carmina	FAR PO47
	FAR PO74
Scala Maria Carmina*	FAR PO75
Scandurra Roberto	FAR PO80
Schenone Silvia	FAR PO34
	FAR PO44
	FAR OR07
Schepetkin Igor A	FAR OR23
Schepmann Dirk	FAR PO48
Schiavone Brigida	FAR PO60
Schlich Michele	FAR PO65
Schwab Wilfried	FAR PO57
Sciabola Simone	FAR OR22
Scialabba Cinzia	FAR OR18
Scipione Luigi	FAR OR15
Scortichini Mirko*	FAR PO45
	FAR PO46
Scotto D'Abusco Anna	FAR PO80
Scozzafava Andrea	FAR PO55
Scudieri Paolo	FAR PO24
Seidel Thomas	FAR PO81
Serafini Marta	FAR PO67
	FAR OR01
Serafini Marta*	FAR PO76
Severi Leda	FAR PO05

Sidibè Adama	FAR PO25
Silvestri Romano	FAR PO06
	FAR PO12
	FAR PO40
Sinico Chiara	FAR PO65
Siracusa Maria A	FAR PO43
Sirianni Rosa	FAR PO27
Slawomir Filipek	FAR PO78
Sommella Eduardo	FAR PO53
	FAR PO59
	FAR PO72
Sommella Eduardo*	FAR PO77
Sorana Federico	FAR PO24
Sorrenti Valeria	FAR OR11
Sortino Salvatore	FAR OR13
Spadoni Gilberto*	FAR KN07
Spano Raffaele	FAR PO24
Spatari Claudia	FAR PO69
Spatari Claudia*	FAR OR02
Spensiero Antonia	FAR PO74
	FAR PO75
Spensiero Antonia*	FAR PO47
Spyrakis Francesca*	FAR OR22
Stama Mada Letizia*	FAR PO78
Stefanucci Azzurra	FAR PO37
Stefanucci Azzurra*	FAR OR10
Straniero Valentina*	FAR PO79
Summa Vincenzo	FAR OR05
Superti Fabiana	FAR PO75
Supuran Claudiu T.	FAR PO57
	FAR PO51
	FAR PO54
	FAR PO55
	FAR PO62
	FAR PO71
Supuran Claudiu T.*	FAR OR14
	FAR KN05
	FAR MD01
Tabarrini Oriana	FAR PO13
	FAR OR04
Taliani Sabrina	FAR PO52
Tamboli Yasinalli	FAR PO54
Tanc Muhammet	FAR PO71
Tarantino Delia	FAR OR04
Tenore Gian Carlo	FAR PO77
Testa Bernard	FAR OR24
Testai Lara	FAR PO52
Tocci Gabriella	FAR OR09
Tomati Valeria	FAR PO24
Tonelli Michele*	FAR OR16
Torrado Juan Torrado	FAR PO05
Tosco Alessandra	FAR PO07
	FAR PO21
Tramontano Enzo	FAR PO09
Trapasso Francesco	FAR PO47
	FAR PO74

Trincavelli Maria Letizia	FAR PO34
Trist Iuni Margaret Laura	FAR PO44
Trist Iuni Margaret Laura*	FAR OR07
Trotta Francesca	FAR PO27
Truglio Giuseppina I.	FAR PO15
Tuccinardi Tiziano	FAR PO34
Tudino Valeria	FAR PO09
	FAR OR15
	FAR PO80
Tudino Valeria*	FAR PO80
Tumiatti Vincenzo	FAR PO22
Tundis Rosa	FAR PO18
Tutone Marco	FAR PO50
Uliassi Elisa	FAR PO36
Ungaro Francesca	FAR PO03
Urbinati Fabrizio	FAR OR03
Valente Sergio*	FAR PZ02
Valenti Donatella	FAR PO65
	FAR PO66
Valoti Ermanno	FAR PO79
Vanella Luca	FAR OR11
Varra Michela	FAR PO33
Vázquez Eugenio	FAR OR10
Vellavita Rosa	FAR PO70
Venditti Giulia*	FAR PO20
Vergaro Viviana	FAR PO60

Vergelli Claudia	FAR OR23
Vijayakumar Vijayaparthisarathi	FAR PO54
Villa Carla	FAR PO42
Vistoli Giulio	FAR OR24
Vittorio Serena*	FAR PO81
Viviano Monica	FAR PO07
	FAR PO19
Viviano Monica*	FAR PO21
Vogt Martin	FAR PO58
Volpato Daniela	FAR PO30
Vullo Daniela	FAR PO55
	FAR OR14
Wang Tung-Cheng	FAR OR20
Wolf Markus	FAR PO05
Wunsch Bernhard	FAR PO48
Yousif Ali Munaim	FAR PO70
Zaccardelli Massimo	FAR PO64
Zaffaroni Lenny	FAR OR20
Zamperini Claudio	FAR PO16
Zampieri Daniele*	FAR PO48
Zanetti Stefania	FAR PO02
Zanusso Ilenia	FAR PO11
Zazzi Maurizio	FAR OR05
Zimmermann Holger	FAR PO57

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- Andrea Pace, Università degli Studi di Palermo
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Delegato di Divisione

- Giuseppe Bifulco, Università degli Studi di Salerno

Programma Scientifico

Divisione di Chimica Organica

Lunedì 11 Settembre 2017

<i>Auditorium Giove</i>	
9:00 – 9:30	Opening Remarks and Awards Ceremony
Plenary Session 1	
Chairperson: Cesare Gennari	
9:30-10:00	ORG MD01 : Adolfo Quilico Medal Lecture - Raffaele Riccio <i>Changing paradigms in natural product chemistry: from structural elucidation to target identification</i>
10:00-10:30	ORG PZ01 : Organic Chemistry for Life Science Award Lecture - Franca Zanardi <i>Playing with Peptidomimetic and Small-Molecule Drug Hybrids to Hit Cancer-Related Biomarkers</i>
10:30-11:00	Coffee Break
<i>Auditorium Giove</i>	
Chairperson: Valeria Conte	
11:00 – 11:30	ORG PZ02 : Organic Chemistry for Process Development and Industrial Products Award Lecture - Giorgio Bertolini <i>From few grams to multi Tons of Active Pharmaceutical Ingredients - Some tips</i>
<i>Sala Argiva</i>	
Parallel Session 1A: Organic and Inorganic Chemistry Divisions' Joint Session on Organometallic Chemistry (GICO)	
Chairperson: Antonella Dalla Cort	
11:30 – 12:00	ORG/INO KN01 : Alessandro Caselli <i>Catalytic Applications of Pyridine-Containing Macrocyclic Complexes</i>
12:00 – 12:30	ORG/INO PZ01 : EurJOC Junior Organometallic Chemist Lecture - Valentina Pirovano <i>Gold(I)-catalyzed [4+2] cycloaddition reactions of vinylindoles and allenes</i>
12:30 – 12:45	ORG/INO OR01 : Elia Matteucci , Andrea Baschieri , Cristiana Cesari , Rita Mazzoni , Claudia Bizzarri , Letizia Sambri <i>Functionalized triazolylidenes as versatile mesoionic carbenes: metal complexes for catalysis and luminescent materials</i>
12:45 – 13:00	ORG/INO OR02 : Andrea Squarcina , Martina Zonzin , Mauro Carraro , Marcella Bonchio <i>Copper complexes with biomimetic antioxidant activity</i>
<i>Auditorium Giove</i>	
Parallel Session 1B: Enerchem	
Chairperson: Alessandro Abbotto	
11:30 – 11:45	ORG OR01 : Giuseppe Sforazzini , Augustina Jozeliunaite , Edvinas Orentas , Daniele Fazzi , Walter Thiel <i>Molecular Engineering of π-Conjugated Systems Towards Light-Responsive Organic Semiconductors</i>
11:45 – 12:00	ORG OR02 : Chiara Liliana Boldrini , Norberto Manfredi , Alessandro Abbotto <i>Organic sensitizers for solar fuels from dye-sensitized water splitting</i>
12:00 – 12:15	ORG OR03 : Gianluigi Albano , Laura Antonella Aronica , Lorenzo Di Bari <i>Solution and solid-state supramolecular aggregates of new chiral oligothiophenes: synthesis and spectroscopic characterization</i>
12:15 – 12:30	ORG OR04 : Francesca Parenti , Mirko Buffagni , Alfonso Zambon , Monica Caselli , Davide Vanossi , Adele Mucci <i>Novel oligothiophenes with reduced HOMO-LUMO band gap for Optoelectronics</i>

12:30 – 12:45	ORG OR05 : Alessandra Operamolla <i>Organic and biological materials for organic electronics: adding functionality</i>
12:45 – 13:00	ORG OR06 : Roberto Grisorio , Bart Roose , Silvia Colella , Andrea Listorti , Gian Paolo Suranna , Antonio Abate <i>Molecular Tailoring of Hole-Transporting Materials for High-Performing Perovskite Solar Cells</i>
13:00 – 13:15	ORG OR07 : Pierluca Galloni , Federica Sabuzi , Barbara Floris , Francesca Valentini , Laura Micheli , Andrea Sartorel , Emanuela Gatto , Giuseppe Palleschi , Valeria Conte <i>KuQuinones as photocatalysts in Light-driven water splitting</i>
13:00 – 14:00	Intervallo Pranzo – Lunch Break
Sala Paestum B	
14:00 – 15:00	Poster Session 1 (ORG PO01 – ORG PO33)
Sala Argiva	
Parallel Session 2A	
Chairperson: Olga Bortolini	
15:00 – 15:30	ORG PZ03 : Methodologies in Organic Chemistry Junior Award Lecture - Giovanni Maestri <i>The chemistry of stable trinuclear all-metal aromatics</i>
15:30 – 16:00	ORG PZ04 : Organic Chemistry for Environment, Energy and Nanoscience Junior Award Lecture - Giulia Fiorani <i>Towards Bio-based Organic Carbonates and Polycarbonates via Coupling of Highly Substituted Oxiranes and CO₂</i>
16:00 – 16:15	ORG OR08 : Gianluca Salerno , Marco Consumi , Agnese Magnani , Cristina Nativi , Barbara Richichi <i>A quick and facile synthesis of stable, water-soluble CdSe/ZnS quantum dots</i>
16:15 – 16:30	ORG OR09 : Francesca Biscaglia , Santina Quarta , Gianmarco Villano , Cristian Turato , Alessandra Biasiolo , Patrizia Pontisso , Moreno Meneghetti , Marina Gobbo <i>PreSI Functionalized Gold Nanostructures for Liver Cancer Cells Targeting and Surface-Enhanced Raman Resonance Scattering Imaging</i>
Auditorium Giove	
Parallel Session 2B	
Chairperson: Giuseppe Musumarra	
15:00 – 15:30	ORG PZ05 : Organic Chemistry in Life Science Junior Award Lecture - Laura Russo <i>When glycochemistry meets biomaterials: from design to application of synthetic glyco-tools</i>
15:30 – 16:00	ORG PZ06 : Organic Chemistry for Process Development and Industrial Products Junior Award Lecture - Andrea Bonetti , <i>Semisynthetic ways for the preparation of Homoharringtonine: an industrial approach</i>
16:00 – 16:15	ORG OR10 : Andrea Rozzi , Saša Korom , Alex Manicardi , Massimiliano Donato Verona , Vincenzo Verdolino , Roberto Corradini <i>Design and Synthesis of polyfunctional PNAs - A Biomolecular Engineering approach</i>
16:15 – 16:30	ORG OR11 : Laura Medve , Sonia Serna , Niels Reichardt , Silvia Achilli , Corinne Vivès , Franck Fieschi , Anna Bernardi <i>A Glycomimetic CHIP for microarray Screening of C-type Lectin Receptors</i>
16:30 – 17:00	Coffee Break

<i>Sala Argiva</i>	
Parallel Session 3A	
Chairperson: Maurizio Benaglia	
17:00 – 17:15	ORG OR12 : Cristina Prandi, Stefano Nejrrotti <i>Gold(I)-catalyzed rearrangement of heterocycles derived 1,3-enynes</i>
17:15 – 17:30	ORG OR13 : Francesca Ghirga, Cinzia Ingallina, Federica Aiello, Federica Balzano, Ilaria D'Acquarica, Bruno Botta, Gloria Uccello-Barretta, Deborah Quaglio <i>Snapshot of Ruthenium–Carbene–Resorc[4]arene Complex in an Olefin Metathesis Reaction</i>
17:30 – 17:45	ORG OR14 : Mauro Sassi, Sara Mattiello, Myles Rooney, Alessandro Sanzone, Paolo Brazzo, Luca Beverina <i>Efficient Suzuki-Miyaura micellar Cross-Coupling in water, at room temperature and under aerobic atmosphere. Organic materials going green</i>
17:45 – 18:00	ORG OR15 : Antonella Leggio, Emilia Lucia Belsito, Alessandra Comandè, Lucia Lo Feudo, Angelo Liguori <i>TiCl₄-Assisted Protocols in Organic Synthesis: the Case of Amides and β-Enaminones</i>
18:00 – 18:15	ORG OR16 : Massimo Mella, M. Vincenzo La Rocca, Egle M. Beccalli, Silvia Gazzola, Gianluigi Broggin <i>Which reaction step controls regio selectivity in CuCl₂-catalyzed cyclization of alkinyl-substituted ureas and carbamates?</i>
18:15 – 18:30	ORG OR17 : Raffaella Mancuso, Bartolo Gabriele <i>Divergent Syntheses of (E)-3-Isobenzofuran-1-(3H)-one and (1H)-Isochromen-1-one Derivatives by Palladium-Catalyzed Carbonylation of 2-Alkynylbenzoic Acids</i>
<i>Auditorium Giove</i>	
Parallel Session 3B	
Chairperson: Angela Zampella	
17:00 – 17:15	ORG OR18 : Roberto Fiammengo, Hui Cai, Federica Degliangeli, Jia Liu, Christian Pett, Jing Hu, Horst Kunz, Ulrika Westerlind, Menji Lu <i>Eliciting specific humoral and cellular immune response by self-adjuvanting gold nanoparticles carrying tumor-associated MUC1 glycopeptides</i>
17:15 – 17:30	ORG OR19 : Alessandro Palmioli, Carlotta Ciaramelli, Michela Spinelli, Gaia De Sanctis, Renata Tisi, Elena Sacco, Cristina Airoidi <i>Natural compounds in cancer prevention: effect of coffee extracts and their main polyphenolic component 5-CQA on oncogenic Ras proteins</i>
17:30 – 17:45	ORG OR20 : Filippo Doria, Matteo Nadai, Matteo Scalabrin, Valentina Pirota, Vincenzo Grande, Greta Bergamaschi, Valeria Amendola, Sara N. Richter, Mauro Freccero <i>Synthesis and Binding Properties of a new Selective Scissoring Tool for Quadruplex Nucleic Acids</i>
17:45 – 18:00	ORG OR21 : Chiara Pennetta, Alessandro Volonterio <i>Amino- and guanidinoglycoside based vectors for cell transfection</i>
18:00 – 18:15	ORG OR22 : Carmen Festa, Simona De Marino, Maria Valeria D'Auria, Angela Zampella, Stefano Fiorucci, Vittorio Limongelli <i>Discovery of a new class of GPBAR1 modulators</i>
18:15 – 18:30	ORG OR23 : Silvana Alfei, Gaby Brice Taptue <i>New promising vectors for gene delivery by a step-wise functionalization of a polyester-based non toxic dendrimer with N, N-dimethylglycine, N-methylglycine, lysine and arginine</i>
18:30 - 20:00	Assembly of the Organic Chemistry Division

Martedì 12 Settembre 2017

<i>Sala Argiva</i>	
Parallel Session 4A	
Chairperson: Emanuela Licandro	
9:00 – 9:15	ORG OR24 : <u>Nadia Barbero</u> , Sonja Visentin, Claudia Barolo, Roberto Buscaino, Guido Viscardi <i>New polymethine dyes for photodynamic therapy</i>
9:15 – 9:30	ORG OR25 : <u>Paola Manini</u> , Carmela Tania Prontera, Valeria Criscuolo, Alessandro Pezzella, Orlando Crescenzi, Michele Pavone, Marco d'Ischia, Maria Grazia Maglione, Paolo Tassini, Carla Minarini <i>From Melanins to OLED Devices: Taking Inspiration from the Black Human Pigments for the Design of Innovative Electroluminescent Materials</i>
9:30 – 9:45	ORG OR26 : <u>Lorenzo Guazzelli</u> , Andrea Mezzetta, Stefano Becherini, Cinzia Chiappe <i>Modification of biopolymers in ionic liquids (ILs) media to access added value materials</i>
9:45 – 10:00	ORG OR27 : <u>Heiko Lange</u> , Reza Ebrahimi Majdar, Claudia Crestini <i>Towards Integrated Continuous-Flow Fractionation and Functionalisation of Technical Lignins</i>
10:00 – 10:15	ORG OR28 : <u>Alice Guarneri</u> , Marco Cesugli, Simone Lotteria, Francesca Vita, Cynthia Ebert, Lucia Gardossi <i>Chemo-enzymatic strategies for the synthesis and functionalization of renewable polymers and composite materials</i>
10:15– 10:30	ORG OR29 : <u>Zoia Luca</u> , Anika Salanti, Marco Orlandi <i>Chemical Modifications for the Valorization of Lignin</i>
<i>Sala Mercurio</i>	
Parallel Session 4B	
Chairperson: Lucio Pellacani	
9:00 – 9:15	ORG OR30 : <u>Luca Banfi</u> , Lisa Moni, Renata Riva, Andrea Basso, Andrea Bozzano, Daniele Cartagenova, Chiara Lambruschini, Elisa Martino, Marta Nola, Gabriella Vitali Forconesi <i>Multicomponent reactions on biocatalytically produced substrates</i>
9:15 – 9:30	ORG OR31 : <u>Andrea Gualandi</u> , Daniele Mazzearella, Aitor Ortega Martínéz, Luca Mengozzi, Fabio Calcinelli, Elia Matteucci, Filippo Monti, Nicola Armaroli, Letizia Sambri, Pier Giorgio Cozzi <i>Photocatalytic Radical Alkylation of Electrophilic Olefins by Benzylic and Alkyl Zinc-Sulfonates</i>
9:30 – 9:45	ORG OR32 : <u>Polyssena Renzi</u> , Johnny Hioe, Ruth M. Gschwind <i>Decrypting Transition States by Light (DTS-hv) in Brønsted Acid Catalysis</i>
9:45 – 10:00	ORG OR33 : <u>Oswaldo Lanzalunga</u> <i>Structural and Medium Effects in the Hydrogen Atom Transfer Processes Promoted by Short-Lived Aminoxyl Radicals</i>
10:00 – 10:15	ORG OR34 : <u>Marco Paolino</u> , Stefania Fusi, Andrea Cappelli, Michael Filatov, Jérémie Léonard, Massimo Olivucci <i>An Ultrafast Molecular Photoswitch Bio-inspired by Green Fluorescent Protein Fluorophore</i>
10:15– 10:30	ORG OR35 : <u>Fabio Bellina</u> , Nicola Guazzelli, <u>Marco Lessi</u> , Chiara Manzini, Giulia Marianetti, Luca A. Perego, Cristofor Pezzetta, Andrea Pucci, Daniele Vergara <i>Highly selective arylation protocols to prepare bioactive and fluorescent imidazole-based compounds</i>

<i>Auditorium Giove</i>	
Parallel Session 4C: Biotechnology	
Chairperson: Francesco Nicotra	
9:00 – 9:15	ORG OR36 : <u>Elena Lenci</u> , Alessio Rossi, Gloria Menchi, Andrea Trabocchi <i>Short Build/Couple/Pair Approaches for the Synthesis of Novel Glyco- and Peptidomimetic Scaffolds</i>
9:15 – 9:30	ORG OR37 : <u>Roberta Teta</u> , Viggo Thor Marteinsson, René Groben, Marie-Lise Bourguet-Kondracki, Valeria Costantino, Alfonso Mangoni <i>A New Antibacterial Cyclic Peptide from Hot Springs</i>
9:30 – 9:45	ORG OR38 : <u>Francesca Leonelli</u> , Angela La Bella, Luisa Maria Migneco, Rinaldo Marini Bettolo <i>Recent advances in the synthesis of stemarane diterpenoids</i>
9:45 – 10:00	ORG OR39 : <u>Veronica Esposito</u> , Antonella Virgilio, Annapina Russo, Teresa Amato, Giulia Russo, Michela Varra, Luciano Mayol, Aldo Galeone <i>Easy chemical modifications to explore the 'Janus face' of TBA: anticoagulant vs antiproliferative properties</i>
10:00 – 10:15	ORG OR40 : <u>Maria Luisa Di Gioia</u> , Monica Nardi, Manuela Oliverio, Antonio Procopio, Rosina Paonessa, Giovanni Sindona <i>The greening of protection/deprotection strategies in peptide synthesis</i>
10:15 – 10:30	ORG OR41 : <u>Cosimo Gianluca Fortuna</u> , Carmela Bonaccorso, Vincenza Barresi, Cristina Satriano, Irina Naletova <i>Design, synthesis of new heterocyclic compounds and their biological activity against MCF-7 cell line</i>
10:30 – 11:00	Coffee Break
Plenary Session 2	
Chairpersons: Luca Banfi, Cinzia Chiappe and Domenico Misiti	
11:00 – 11:30	ORG MD02 : Angelo Mangini Medal Lecture - <u>Maurizio Taddei</u> <i>From ADDA to Antibody Drug Conjugates. Some Examples of Target Oriented Syntheses, a Blessing and a Curse for a Chemist</i>
11:30 – 12:00	ORG MD03 : Giacomo Ciamician Medal Lecture - <u>Davide Ravelli</u> <i>Photocatalytic Hydrogen Atom Transfer (HAT) in Organic Synthesis</i>
12:00 – 12:30	ORG PZ07 : Methodologies in Organic Chemistry Award Lecture - <u>Massimo Bietti</u> , <i>Tuning Reactivity and Selectivity in Hydrogen Atom Transfer from Aliphatic C–H Bonds</i>
12:30 – 13:00	ORG PZ08 : Organic Chemistry for Environment, Energy and Nanoscience Award Lecture - <u>Mauro Comes Franchini</u> <i>Organic coating of Metallic nanoparticles: theranostic applications in nanomedicine</i>
13:00 – 13:10	REAXYS-MYCS : <u>Carlos Rodriguez Del Rio (Elsevier)</u> <i>Oceans of data for informed decisions in chemistry. The shortest path from the question to insight</i>
13:00 – 14:00	Intervallo Pranzo – Lunch Break
Sala Paestum B	
14:00 – 15:00	<i>Poster Session 2 (ORG PO34 – ORG PO72)</i>

Mercoledì 13 Settembre 2017

Sala Paestum B	
14:00 – 15:00	<i>Poster Session 3 (ORG PO73 – ORG PO104)</i>
Auditorium Giove	
Plenary Session 3	
Chairperson: Alberto Brandi	
15:00 – 15:30	ORG MD04 : Piero Pino Medal Lecture - Enrico Dalcanale <i>The evolution of cavitand-based supramolecular polymers: from self-assembly to self-diagnostics</i>
Auditorium Giove	
Parallel Session 5A: Organic Chemistry in Industry	
Chairperson: Paolo Scrimin	
15:30 – 15:45	ORG OR42 : Luciano Lattuada , Lorena Beltrami , Enrico Cappelletti , Aurelia Ferrigato , Giovanni Battista Giovenzana , Loredana Sini <i>Synthesis and application of bifunctional chelating agents based on AAZTA scaffold</i>
15:45 – 16:00	ORG OR43 : Simone Mantegazza , Gabriele Razzetti , Emanuele Attolino , Chiara Vladiskovic <i>QU-IBX and B3-IBX: safe IBX adducts for periodinane oxidation reactions</i>
16:00 – 16:15	ORG OR44 : Aurelio Bonasera , Sebastian Fredrich , Virginia Valderrey , Stefan Hecht <i>Light-Activated Amine Detection via Innovative Diarylethene Probes</i>
16:15 – 16:30	ORG OR45 : Alessandro Agosti , Giorgio Bertolini , Giacomo Bruno , Christian Lautz , Thomas Glarner , Walter Deichtmann <i>Handling Hydrogen Peroxide On Large Scale: Synthesis of 5-bromo-2-nitropyridine</i>
Sala Argiva	
Parallel Session 5B: Green Chemistry - Sustainable Chemistry	
Chairperson: Marco d'Ischia	
15:30 – 15:45	ORG OR46 : Matteo Tiecco , Raimondo Germani <i>Zwitterionic Deep Eutectic Solvents as Effective Alternatives to Organic Solvents and to Ionic Liquids</i>
15:45 – 16:00	ORG OR47 : Serena Gabrielli , Enrico Marcantoni , Roberto Ballini , Susanna Sampaolesi , Elena Chiurchiù , Alessandro Palmieri <i>Innovative Two-Step Synthesis of Polysubstituted 6-NitroIndoles</i>
16:00 – 16:15	ORG OR48 : Marco Chiarini , Giorgio Cerichelli <i>NMR study of mixed micelles: zwitterionic – cationic surfactant systems</i>
16:15 – 16:30	ORG OR49 : Salvatore Marullo , Francesca D'Anna , Rossella Arrigo , Nadka Tzankova Dintcheva , Renato Noto , Carla Rizzo <i>Diimidazolium-based supramolecular ionogels for dye removal from wastewaters</i>
16:30 – 17:00	Coffee Break
Sala Nettuno	
Parallel Session 6A: Inorganic and Organic Chemistry Divisions' Joint Session on Organometallic Chemistry (GICO)	
Chairperson: Fabio Ragaini	
17:00 – 17:30	ORG/INO KN02 : Lorenzo Zani <i>Conjugated Organic Compounds for Solar Energy Conversion to Electricity and Fuels</i>
17:30 – 18:00	ORG/INO PZ02 : EurJIC Junior Organometallic Chemist Lecture - Marco Bellini <i>Hydrogen and chemicals from renewable alcohols by Organometallic Electro-Reforming (OMER)</i>
18:00 – 18:15	ORG/INO OR03 : Walter Baratta , Rosario Figliolia , Salvatore Baldino , Hans Günter Nedden , Antonio Zanotti-Gerosa <i>Mild N-Alkylation of Amines with Alcohols Catalyzed by Acetate Ruthenium Complexes</i>

18:15 – 18:30	ORG/INO OR04 : Rita Mazzoni , Cristiana Cesari, Andrea Cingolani, Valerio Zanotti, Fabrizio Cavani, Francesco Puzzo, Carlo Lucarelli, Massimo Mella, Andrea Tagliabue, Tom Baker <i>The power of ligand combination in redox active ruthenium and iron complexes</i>
18:30 – 18:45	ORG/INO OR05 : Rosario Figliolia , Salvatore Baldino, Walter Baratta, Steven Gibolout, Hans Günter Nedden, Antonio Zanotti-Gerosa <i>Synthesis of New Carbonyl Diphosphane Ruthenium Complexes for Catalytic C-H Bond Activation Reactions</i>
Auditorium Giove	
Parallel Session 6B	
Chairperson: Giulia Licini	
17:00 – 17:15	ORG OR50 : Laura Goracci , Martina Ceccarelli, Björn Wagner, Rubén Alvarez-Sanchez, Gabriele Cruciani <i>Assessment of drug-induced phospholipidosis risk based on distribution coefficient in brain polar lipids</i>
17:15 – 17:30	ORG OR51 : Assunta Giordano , Giovanni Forte, Fabrizio Dal Piaz, Federica del Gaudio, Nunziatina De Tommasi, Patrizia Gazzero, Raffaele Riccio, Giuseppe Bifulco, Simone Di Micco <i>Identification of new ErbB4 inhibitors by inverse virtual screening</i>
17:30 – 17:45	ORG OR52 : Gianluigi Lauro , Stefania Terracciano, Ines Bruno, Raffaele Riccio, Vincenza Cantone, Oliver Werz, Andreas Koeberle, Michele Manfra, Paolo Tortorella, Pietro Campiglia, Giuseppe Bifulco <i>Recent advances in the discovery of novel microsomal prostaglandin E₂ synthase-1 (mPGES-1) inhibitors</i>
17:45 – 18:00	ORG OR53 : Vittoria Graziani , Valentina Belli, Monica Scognamiglio, Brigida D'Abrosca, Angela Chambery, Severina Pacifico, Simona Piccolella, Teresa Troiani, Nicoletta Potenza, Antonio Fiorentino <i>Cytotoxic secondary metabolites from Mediterranean Fabaceae species display antiproliferative activity against colon cancer cell lines</i>
18:00 – 18:15	ORG OR54 : Sara Piantini , Stefano Menichetti, Luisa Bracci, Chiara Falciani, Jlenia Brunetti <i>Synthesis of new peptide-drug conjugates for targeted cancer diagnosis and therapy</i>
18:15 – 18:30	ORG OR55 : Salvatore Vincenzo Giofrè , Roberto Romeo, Consuelo Celesti, Maria Assunta Chiacchio <i>Synthesis and Biological Evaluation of Some Pyrimidin-2,4-diones as Novel Non-Nucleoside Reverse Transcriptase Inhibitors</i>
18:30 – 18:45	ORG OR56 : Elena Petricci , Fabrizio Manetti, Elena Cini, Roberta Santini, Barbara Stecca, Giuseppe Giannini <i>Synthesis and decoration of small molecules targeting the Hedgehog Signaling Pathway</i>
18:45 – 19:00	ORG OR57 : Francesco Sansone , Stefania E. Sestito, Fabio A. Facchini, Iaria Morbioli, Jean-Marc Billod, Sonsoles Martin-Santamaria, Alessandro Casnati, Francesco Peri <i>Amphiphilic Guanidinocalixarenes Inhibit Lipopolysaccharide- and Lectin-stimulated Toll-like Receptor 4 Signaling</i>
Sala Argiva	
Parallel Session 6C	
Chairperson: Vito Capriati	
17:00 – 17:15	ORG OR58 : Silvia Cauteruccio , Davide Dova, Clara Baldoli, Roberta Franzini, Claudio Villani, Emanuela Licandro <i>Synthesis and stereochemical properties of axially chiral benzo[1,2-b:4,3-b']dithiophene derivatives</i>
17:15 – 17:30	ORG OR59 : Margherita De Rosa , Pellegrino La Manna, Carmen Talotta, Carmine Gaeta, Annunziata Soriente, Antonio Rescifina, Giuseppe Floresta, Placido Neri <i>Bioinspired organocatalysis of C-C bond-forming reactions</i>

17:30 – 17:45	ORG OR60 : Marina Sicignano, Rosaria Schettini, Antonella Dentoni Litta, Francesco De Riccardis, Irene Izzo, Giorgio Della Sala <i>Highly diastereoselective synthesis of γ-butenolides and phthalides by Michael addition catalyzed by crown ethers</i>
17:45 – 18:00	ORG OR61 : Carla Sappino , Paolo Bovicelli, Federica Di Pietro, Giuliana Righi, Marzia Oneto, Ludovica Primitivo, Lorenza Suber <i>Design of a new chiral nanosupported catalyst for asymmetric reactions</i>
18:00 – 18:15	ORG OR62 : Vincenzo Algieri, Antonio De Nino , Loredana Maiuolo, Beatrice Russo, Pedro Merino <i>Asymmetric 1,3-dipolar cycloadditions catalyzed by a new imidazolidinone organocatalyst</i>
18:15 – 18:30	ORG OR63 : Susanna Sampaolesi , Federico Vittorio Rossi, Alessandro Palmieri, Pietro Allegrini <i>A new highly efficient strategy to prepare racemic Anatabine</i>
18:30 – 18:45	ORG OR64 : Carlo Bravin, Elena Badetti, Giulia Licini, Cristiano Zonta <i>Molecular Events within Confined Spaces</i>
18:45 – 19:00	ORG OR65 : Carlo F. Morelli , Fabio Romagnuolo, Gabriele A. Franza, Cinzia Calvio, Giovanna Speranza <i>Synthetic application of bacterial γ-glutamyltransferases (GGTs)</i>

Medaglie e Premi della Divisione di Chimica Organica

Medaglia d'Oro “Adolfo Quilico”

Prof. Raffaele Riccio, Università degli Studi di Salerno

Medaglia d'Oro “Piero Pino”

Prof. Enrico Dalcanale, Università degli Studi di Parma

Medaglia d'Oro “Angelo Mangini”

Prof. Maurizio Taddei, Università degli Studi di Siena

Medaglia d'Argento “Giacomo Ciamician”

Dott. Davide Ravelli, Università degli Studi di Pavia

Premi alla Ricerca

Chimica organica per l'ambiente, l'energia e le nanoscienze

Prof. Mauro Comes Franchini, Università degli Studi di Bologna

Dott.ssa Giulia Fiorani (*Junior*), University of Oxford

Chimica organica per le scienze della vita

Prof.ssa Franca Zanardi, Università degli Studi di Parma

Dott.ssa Laura Russo (*Junior*), Università degli Studi di Milano Bicocca

Chimica organica nei suoi aspetti metodologici

Prof. Massimo Bietti, Università degli Studi di Roma “Tor Vergata”

Dott. Giovanni Maestri (*Junior*), Università degli Studi di Parma

Chimica organica per lo sviluppo di processi e prodotti nell'industria

Dott. Giorgio Bertolini, Olon S.p.A.

Dott. Andrea Bonetti (*Junior*), Indena S.p.A.

Changing paradigms in natural product chemistry: from structural elucidation to target identification

Raffaele Riccio

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Natural products have largely shown to be a huge source of bioactive molecules, often with fantastic and unprecedented structures. They have been an immense source of inspiration for the process of DD&D and many of them have reached the drug market after a long, complex and expensive process of drug development. In a series of comprehensive reviews by Newman and Cragg, analyzing the sources of new drugs from 1981-2014 [1], the contribution of natural products is estimated in about 50%, taking into account also what they cite as “*natural product derived drugs*”, any new drug that in some way was developed on the basis of a bioactive structural framework, a putative pharmacophoric group or bioactivity information arising from a natural product. It is indeed highly common that, in addition to the direct use of a natural product in an unmodified form, the structure of a novel natural compound or its relevant structure activity relationship information are utilized as a lead to be optimized for the development of a new drug. The scientific literature is full of such kind of examples and the valuable role of natural product scaffolds in synthesis-driven pharma exploitation has been clearly evidenced in a Danishefsky review [2]. Of course, the complete structural elucidation of a new natural product is a fundamental starting point for any DD&D process. This has been for decades an intriguing and challenging task attracting the interest of organic chemists. The extraordinary development of spectroscopic techniques and informatics tools have drastically modified the approach to a structural elucidation process and have opened new perspectives for target identification and for drug-receptor interaction studies. Our group has been largely involved in the area of natural product chemistry, isolating and investigating bioactive natural products from marine and terrestrial sources. In most recent years prominent attention has been dedicated to: application of QM calculation for structural and stereochemical determination of organic compounds [3-8]; development of an Inverse Virtual Screening (IVS) protocol for target prediction [9-12]; application of chemical proteomics approaches in bioactive natural products target profiling [13-25]. A set of investigation protocols recently applied also to the development of natural products as dietary supplements (Nutraceuticals). Solving the stereochemistry of natural product structures can still be a quite challenging task, requiring time and expertise. The knowledge of the stereochemistry, especially in complex structures with several stereocenters, is essential for undertaking total synthesis, performing conformational and structure activity relationship studies, investigating the biological mechanism of action at the molecular level. On the other end, the identification of the cellular targets of bioactive small-molecules is often a crucial step in pharmaceutical research, where the identification of target proteins and investigation of ligand-receptor interactions are recognized as essential requirements in the process of drug D&D. Protocols based on IVS or chemical proteomics appear to be attractive alternatives to in vitro binding assays, since they can be profitably applied in the early stages of the process of drug D&D. Representative case studies for the described approaches, derived from recent research activity of our group, will be illustrated in this communication.

References: 1. Newman D. J., Cragg G. M. *J. Nat. Prod.*, 2016, 79 (3), 629–661 (and previous in the series). 2. Danishefsky S. *Nat Prod Rep.* 2010; 27:1114–1116. 3. Bifulco G. *et al. Chem. Rev.* 2007, 107, 3744–3779. 4. Di Micco S. *et al. Eur. J. Org. Chem.* 2010, 1411–1434. 5. Di Micco S. *et al.* In: *Handbook of Marine Natural Products* E. Fattorusso, W. H. Gerwick and O. Tagliatella-Scafati (Eds.); Springer, 2012, Part 2, 571–599. 6. Chini M. G. *et al. Eur. J. Org. Chem.* 2015 (6), 1320–132. 7. Sun P. *et al. J. Nat. Prod.*, 2016, 79 (10), 2552–2558. 8. Li J. *et al. Marine Drugs* 2017, 15 (5), 129. 9. Lauro, G. *et al. J. Nat. Prod.* 2011, 74 (6), 1401–1407. 10. Lauro, G. *et al. Bioorg. Med. Chem.* 2012, 20 (11), 3596–3602. 11. Jun Gong, *et al. Org. Lett.* 2014, 16(8), 2224–2227. 12. Scrima M *et al. J. Med. Chem.* 2014, 57 (18), 7798–7803. 13. Margarucci, L. *et al. Angew. Chem. Int. Ed.* 2010, 49, 3960–3963. 14. Margarucci, L. *et al. Mol. Biosyst.* 2011, 7, 480–485. 15. Margarucci, L. *et al. Mol Biosyst* 2012, 8, 1412–1417. 16. Cassiano, C. *et al. ChemBioChem* 2012, 13 (13), 1953–1958. 17. Vilasi, A. *et al. Mar. Drugs* 2013, 14, 1288–1299. 18. Margarucci, L. *et al. Chem. Commun.* 2013, 49, 5844–5846. 19. Cassiano, C. *et al. Natural Product Communications* 2015, 10 (6), 1013–1016. 20. Cassiano, C. *et al. Chem. Commun.* 2014, 50, 406–408. 21. Margarucci, L. *et al. Chem. Commun.* 2015, 51(9), 1591–1593. 22. Cassiano, C. *et al. Chem. Commun.* 2014, 50 (45), 6043–6045. 23. del Gaudio F. *et al. Mol Biosyst* 2016, 12 (10), 3132–3138. 24. Casapullo A. *et al. J. Mass Spect.* 2016, 51 (9), 821–827. 25. Capolupo A. *et al. J. Nat. Prod.* 2017, 80 (4), 909–915.

From ADDA to Antibody Drug Conjugates. Some Examples of Target Oriented Syntheses, a Blessing and a Curse for a Chemist

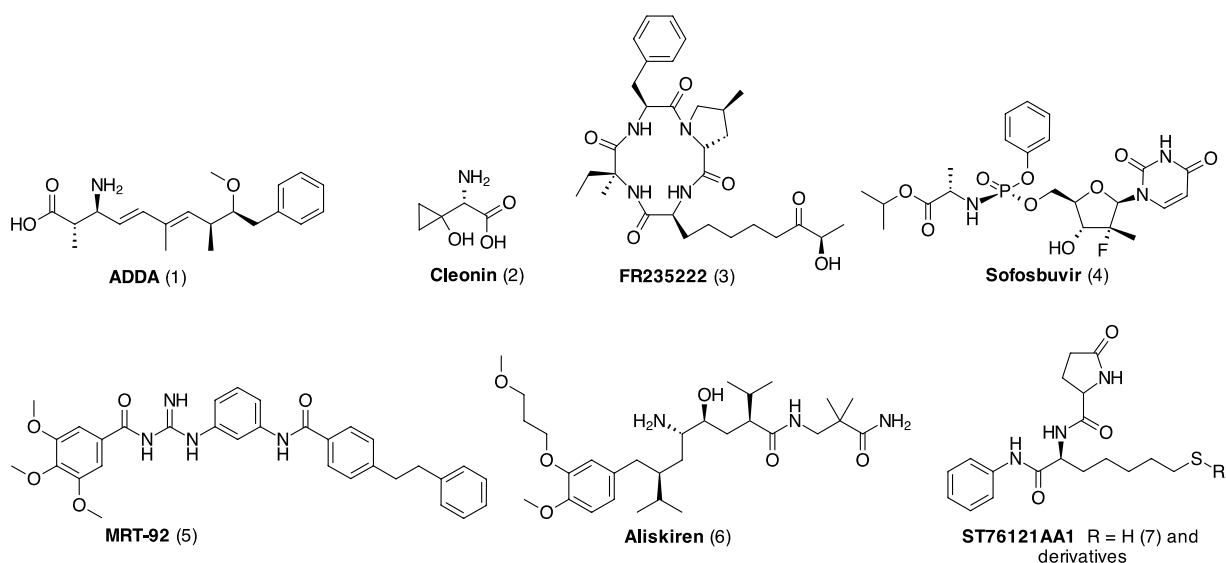
Maurizio Taddei

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After more than seventy years since the Woodward-Doering total synthesis of quinine, the society is still seeking for new molecules as drugs, dyes, soaps, perfumes, semiconductors, polymers and molecular tools for biology, medicine, biotechnology and nanotechnology.

As the yearned molecule has often a precise structure, only a target oriented synthesis can provide it. Science and creativity are the pillars of total synthesis but frustration is just around the corner, full of (simple) transformations that do not work or substrates with capricious reactivity. However, the reward is the creation of a matter that didn't exist before, an achievement that the synthetic chemist shares only with God.

I report here the syntheses of several molecules we prepared in the last twenty years (with a complexity appropriate to an Italian team) through the classic trial-and-error experiment procedure. Although orchestration of the skeleton construction with functional group transformation is important, I focus herein on the issues which were keys to our success as: (i) availability of starting materials and scalability of intermediate production; (ii) use of the chiral pool to solve stereochemistry problems; (iii) commitment to deliver the molecules to somebody for a specific use.



The lecture will cover also the last and mostly unpublished results on the conjugation of small molecules to antibodies with the everlasting problem to assemble simple chemicals in the complex contest of an immunoglobulin going around in the hematic torrent and in diseased tissues.

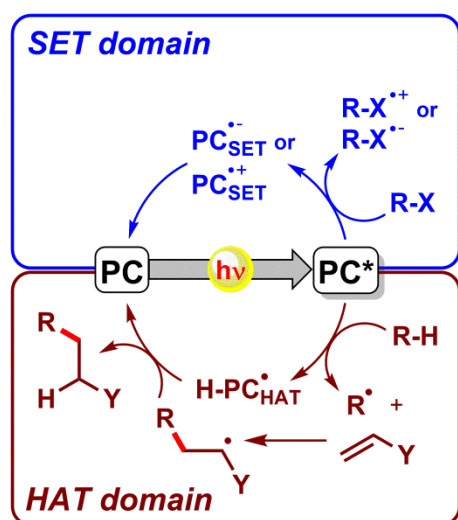
1. F. D'Aniello, et al. *J. Org. Chem.* **1996**, *61*, 4870. 2. A. Esposito et al. *Org. Lett.* **2001**, *3*, 3273. 3. M. Rodriguez et al. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 423-427. 4. G. Barreca et al. WO 2016151542. 5. L. Hoch et al. *FASEB J.* **2015**, *29*, 1817. 6. E. Cini et al. *Org. Proc. Res. Develop.* **2016**, *20*, 270. 7. G. Giannini et al. *J. Med. Chem.* **2014**, *57*, 8358

Photocatalytic Hydrogen Atom Transfer (HAT) in Organic Synthesis

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Photocatalytic reactions applied to organic synthesis have recently gained increasing attention, thanks to the unconventional pathways offered and the mild conditions involved, in accordance with the core principles of Green Chemistry. These reactions are based on the use of a photocatalyst (PC, Scheme 1), a species that is responsible for light absorption and for the subsequent activation of the substrate through a chemical step. (1) Among the activation modes of PC, two main fields can be recognized, viz. Single Electron Transfer (SET) and Hydrogen Atom Transfer (HAT) processes. The former approach is undoubtedly the most investigated one: visible light absorbing Ru- and Ir-polypyridyl complexes and organic dyes are the key actors of a *hot topic* tagged as "photoredox catalysis with visible light". (1) These reactions involve the transfer of one electron between PC* and the substrate R-X, leading to the formation of the corresponding radical ion R-X^{•+} or R-X^{•-} (Scheme 1, upper part). However, the main drawback of this strategy consists in the requirement of redox active reagents, matching the redox potentials of PC. In contrast, HAT processes offer the possibility of activating directly a C-H bond in the substrate (Scheme 1, lower part). The main limitation to the development of this pathway is represented by the limited number of PCs able to promote HAT steps. (2,3)



Scheme 1

In recent years, we developed a number of photocatalytic methods for the photogeneration of C-centered radicals and the ensuing addition onto C=C double bonds, including electron-poor olefins (4) and vinyl aromatics. (5) This strategy is based on the use of UV-light absorbing tetrabutylammonium decatungstate (TBADT, (nBu₄N)₄[W₁₀O₃₂]) as the photocatalyst. (6,7) Upon irradiation, excited PC* cleaves homolytically (often with high chemo- and regioselectivity) C-H bonds in a variety of organic derivatives. (6,7) Thus, the functionalization of C(sp²), sp³-H bonds (R-H in Scheme 1) of aldehydes, amides, ethers and acetals, as well as alkanes, was smoothly achieved. This approach was demonstrated to proceed also under solar light irradiation (6) and could be optimized under flow conditions. (8)

Recent developments in the field of photocatalytic HAT processes involve the design and optimization of visible light absorbing photocatalysts, including porphyrin complexes, the uranyl cation and aromatic ketones.

References: 1. Ravelli, D.; Protti, S.; Fagnoni, M. *Chem. Rev.* **2016**, *106*, 9850-9913. 2. Protti, S.; Fagnoni, M.; Ravelli, D. *ChemCatChem* **2015**, *7*, 1516-1523. 3. Capaldo, L.; Ravelli, D. *Eur. J. Org. Chem.* **2017**, *2017*, 2056-2071. 4. Lazzaroni, S.; Ravelli, D.; Protti, S.; Fagnoni, M.; Albini, A. *C. R. Chimie* **2017**, *20*, 261-271. 5. Capaldo, L.; Fagnoni, M.; Ravelli, D. *Chem. Eur. J.*, DOI: 10.1002/chem.201701346. 6. Ravelli, D.; Protti, S.; Fagnoni, M. *Acc. Chem. Res.* **2016**, *49*, 2232-2242. 7. Tzirakis, M. D.; Lykakis, I. N.; Orfanopoulos, M. *Chem. Soc. Rev.* **2009**, *38*, 2609-2621. 8. Bonassi, F.; Ravelli, D.; Protti, S.; Fagnoni, M. *Adv. Synth. Catal.* **2015**, *357*, 3687-3695.

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The evolution of cavitand-based supramolecular polymers: from self-assembly to self-diagnostics

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In the last few years the merging of polymer science with supramolecular chemistry has created a new, thriving field of research (1), known under the name of supramolecular polymer chemistry (2). The driving force behind this methodological breakthrough is the ability to control noncovalent interactions with the same precision achieved by synthetic organic chemistry. Molecular recognition is the most sophisticated form of weak interaction in terms of precise responsiveness, since it requires a well-defined arrangement of complementary non-covalent interactions to operate at its best. Some of the most relevant issues associated to the development of supramolecular polymers are: (i) achieve macroscopic expression of molecular recognition, (ii) trigger stimuli specific responses in polymeric materials and (iii) move self-assembly from the nano to the meso and macroscale. In the Medaglia Pino lecture, supramolecular polymers based on phosphonate cavitands will be presented, in which the polymerization is driven by host-guest complexation (3,4) (Figure 1). In particular, the following examples will be discussed: (i) polymer blending as macroscopic expression of molecular recognition (5) (Figure 2), (ii) electrochemical responsive host-guest polymers in the solid state (6) and (iii) strain-field self-diagnostic elastomers.

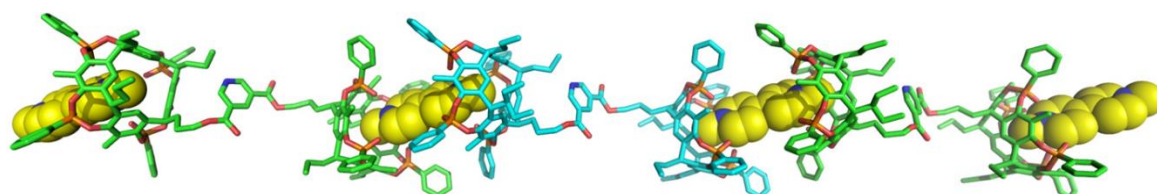


Figure 1. Crystal structure of the alternate copolymer formed by self-assembly between methyl viologen and ditopic phosphonate cavitand.

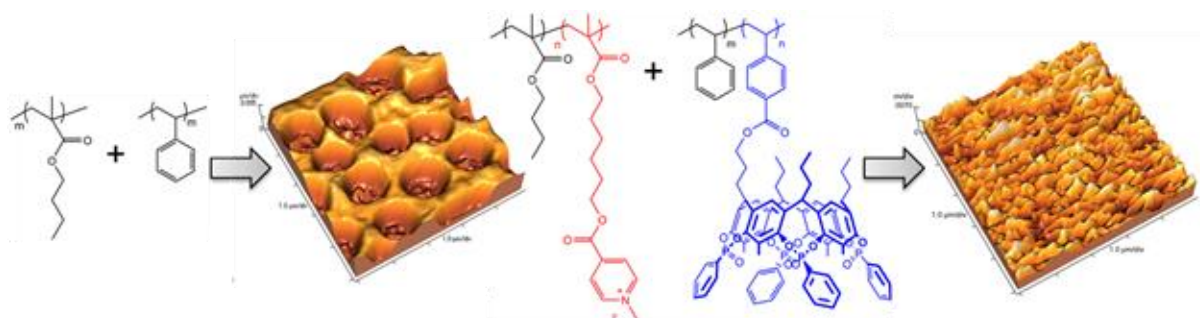


Figure 2. Polymer blending of a polystyrene HOST and a poly(butylmethacrylate) GUEST seen by AFM

References

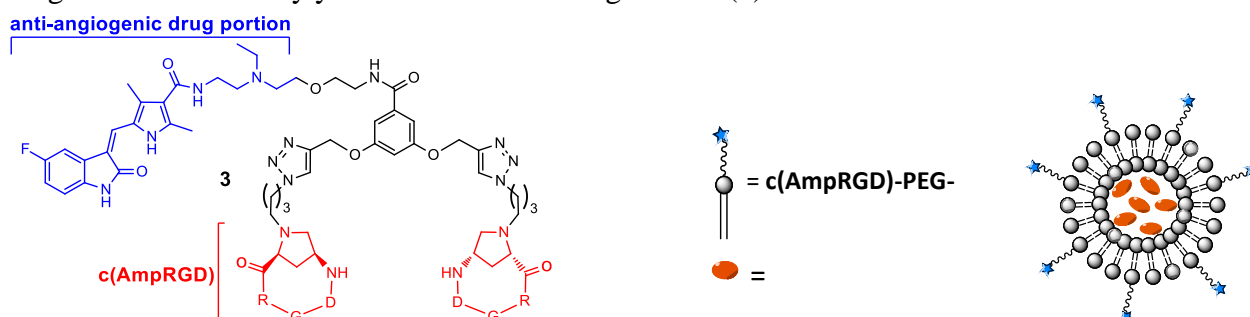
1. A. Ciferri, (ed.) *Supramolecular Polymers*, Second Edition, Francis & Taylor, New York (2005).
2. J.-M. Lehn, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1304.
3. R. M. Yebeutchou, F. Tancini, N. Demitri, S. Geremia, R. Mendichi, E. Dalcanale, *Angew. Chem. Int. Ed.*, **2008**, *47*, 4504.
4. F. Tancini, R.M. Yebeutchou, L. Pirondini, R. De Zorzi, S. Geremia, O.A. Scherman, E. Dalcanale, *Chem. Eur. J.*, **2010**, *16*, 14313.
5. M. Dionisio, L. Ricci, G. Pecchini, D. Masseroni, G. Ruggeri, L. Cristofolini, E. Rampazzo, E. Dalcanale, *Macromolecules*, **2014**, *47*, 632.
6. D. Orsi, A.E. Fruh, M. Giannetto, L. Cristofolini, E. Dalcanale, *Soft Matter*, **2016**, *12*, 5353.

Playing with Peptidomimetic and Small-Molecule Drug Hybrids to Hit Cancer-Related Biomarkers

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Relevant perspectives in modern tumor pharmacotherapy are rapidly widening, addressing several crucial issues such as drug specificity, minimization of off-target toxicities and by-passing drug-resistance mechanisms which were almost neglected by traditional, still-in-use cytotoxic chemotherapeutics. Thus, targeted drugs – either monotherapeutics, combinations, or hybrid constructs – selectively perturbing diverse and intertwined molecular targets are arising as privileged therapeutic options (1). It is well known that tumor endothelial cells show increased levels of expression of several cell-surface molecules that potentiate cell proliferation, invasion and survival during tumor vascular remodeling and angiogenesis. One such molecule is the $\alpha_v\beta_3$ integrin receptor, whose overexpression in both tumor-associated vascular endothelial cells and various tumor types – including glioblastoma and melanoma, breast, prostate, cervical, pancreatic, and ovarian carcinomas – renders it an eligible biomarker of these cancer diseases (2). In recent years, our efforts in the area of specific integrin ligands led to the discovery and development of a new series of γ -aminoproline-based Arg-Gly-Asp cyclic peptidomimetics, c(Amp)RGD, which showed low-nanomolar affinity toward the $\alpha_v\beta_3$ integrin in both cell-free and in-cell assays (3). The incorporation of these ligands within hybrid constructs – be they small molecule covalent conjugates, radioimaging active constructs or nanosized assemblies – led to the identification of multifunctional systems where the tumor-homing ability of the RGD ligands is integrated with ancillary yet crucial tumor-hitting entities (4).



The role of the c(Amp)RGD peptidomimetics in impairing tumor-associated angiogenesis and melanoma tumor growth in vitro and in vivo by using selected examples of hybrid constructs from our laboratories will be discussed; in confirmation that alliance between the science of chemical synthesis and life sciences is possible and even fruitful.

1. Dar, A. C.; Das, T. K.; Shokat, K. M.; Cagan, R. L. *Nature* **2012**, *486*, 80.
2. Desgrosellier, J. S.; Cheresh, D. A. *Nat. Rev. Cancer* **2010**, *10*, 9.
3. (a) Zanardi, F.; Burreddu, P.; Rassu, G.; Auzzas, L.; Battistini, L.; Curti, C.; Sartori, A.; Nicastro, G.; Menchi, G.; Cini, N.; Bottoncetti, A.; Raspanti, S.; Casiraghi, G. *J. Med. Chem.* **2008**, *51*, 1771; (b) Battistini, L.; Burreddu, P.; Carta, P.; Rassu, G.; Auzzas, L.; Curti, C.; Zanardi, F.; Manzoni, L.; Araldi, E. M. V.; Scolastico, C.; Casiraghi, G. *Org. Biomol. Chem.* **2009**, *7*, 4924.
4. (a) Sartori, A.; Portioli, E.; Battistini, L.; Calorini, L.; Pupi, A.; Vacondio, F.; Arosio, D.; Bianchini, F.; Zanardi, F. *J. Med. Chem.* **2017**, *60*, 248; (b) Battistini, L.; Burreddu, P.; Sartori, A.; Arosio, D.; Manzoni, L.; Paduano, L.; D'Errico, G.; Sala, R.; Reia, L.; Bonomini, S.; Rassu, G.; Zanardi, F. *Mol. Pharmaceutics* **2014**, *11*, 2280; (c) Sartori, A.; Bianchini, F.; Migliari, S.; Burreddu, P.; Curti, C.; Vacondio, F.; Arosio, D.; Ruffini, L.; Rassu, G.; Calorini, L.; Pupi, A.; Zanardi, F.; Battistini, L. *MedChemComm* **2015**, *6*, 2175.

From few grams to multi Tons of Active Pharmaceutical Ingredients - Some tips

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In the phase of identification and selection of a new synthetic route for the preparation of Active Pharmaceutical Ingredients (API) all the attention is focused on the chemistry of each single steps evaluating the yield, the conditions (high vs low temperature and/or pressure) the selectivity and so on.

When the synthetic method is then identified and in some cases even optimized, several other aspects must be taken in consideration to move from a synthetic method to a chemical process that can be scale-up from Lab to the plant.

In this phase some critical points could be identified slowing down or in some cases even stop the scale-up of the process forcing the researcher to go back in the Lab to slightly change, or in some cases even completely redesign the synthetic route.

In order to have a real industrial chemical process for the production of fine chemicals or APIs, not only the simple organic chemistry has to be considered but many other aspects and for this reason a Process Development Chemist should have a multidisciplinary expertise including the knowledge, even if at high level, of Process Safety, Inorganic Chemistry, Regulatory, Chemical Engineering and Economy (process/product cost structure).

Using this knowledge he must have the ability to combine all these requests and information to design and select from the beginning the most promising synthetic route.

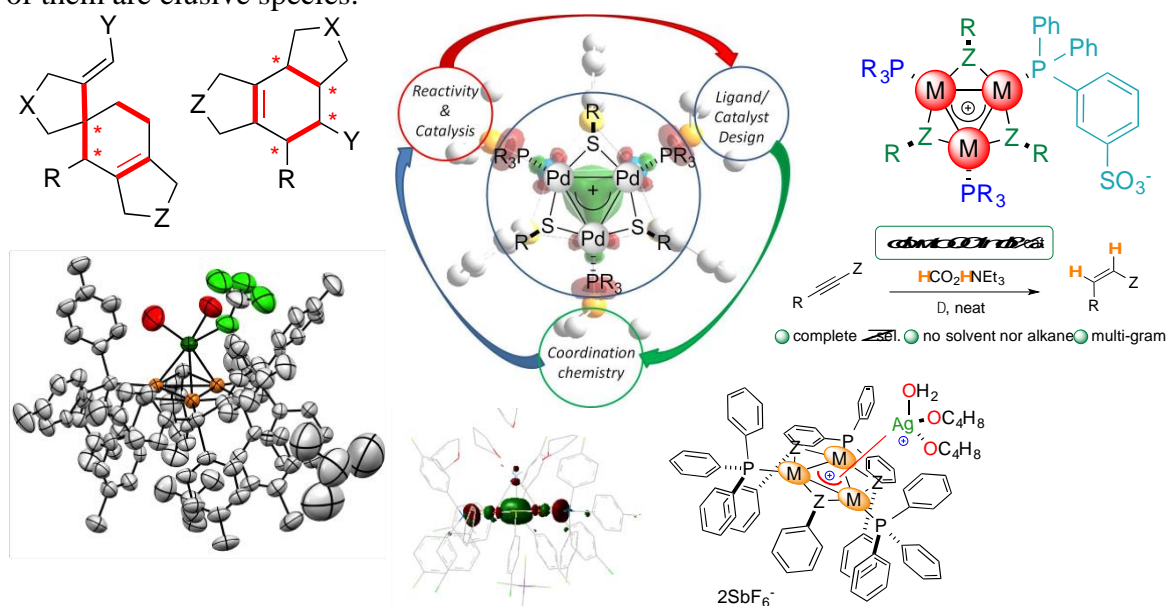
In this lecture some examples will be presented demonstrating that a smooth scale-up of a economic, safe and environmentally friendly chemical process depends in some cases on small details that have however a critical impact on the real success the project.

The chemistry of stable trinuclear all-metal aromatics

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Aromaticity is a concept invented to account for the properties of an important class of organics. For decades, chemists played with a few bricks only to construct aromatics, mostly H, C, N and O. Nonetheless, their scope of applications is nearly boundless. This bonding mode broke the boundaries of organic chemistry with reports on all-metal aromaticity, although applications remains rare as most of them are elusive species.



Observation of this bonding mode on stable Pd_3^+ complexes presenting a perfectly equilateral metal kernel (1) pushed the development of a simple synthetic method to access an ample library of structures. (2) This in turn paved the way for the introduction of these prototypical subnanometric metal surfaces in catalysis, showing unique features in alkyne semireductions. (3,4) Ongoing developments highlight that tuneable all-metal aromatic frameworks can trigger complex cascades for C-C bond formation and, furthermore, that they can act as ligand to bind Lewis acidic atoms.

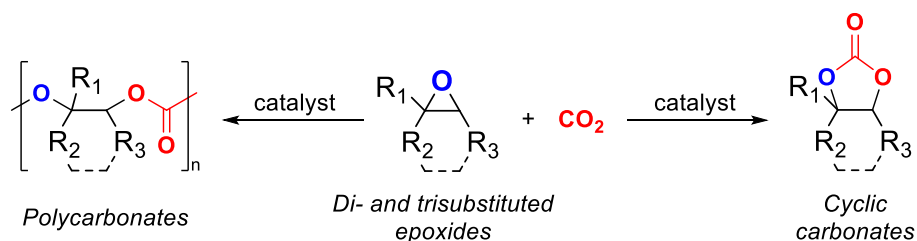
References: 1. S. Blanchard, L. Fensterbank, G. Gontard, E. Lacôte, G. Maestri and M. Malacria, *Angew. Chem. Int. Ed.* 2014, 53, 1897. 2. Y. Wang, P.-A. Deyris, F. Blanchard, Y. Li, F. Bigi, R. Maggi, S. Blanchard, G. Maestri and M. Malacria, *Chem. Eur. J.* 2015, 21, 12271. 3. P.-A. Deyris, T. Caneque, Y. Wang, P. Retailleau, F. Bigi, R. Maggi, G. Maestri and M. Malacria, *Chem. Cat. Chem.* 2015, 7, 3266. 4. A. Monfredini, V. Santacroce, P.-A. Deyris, R. Maggi, F. Bigi, G. Maestri and M. Malacria, *Dalton Trans.* 2016, 45, 15786.

Towards Bio-based Organic Carbonates and Polycarbonates via Coupling of Highly Substituted Oxiranes and CO₂

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Non-reductive CO₂ coupling reactions using highly reactive substrates (such as oxiranes) can be regarded as a topical milestone within the field of CO₂ conversion. These processes require an appropriate catalytic system comprising both a Lewis acid catalyst (M) and a nucleophile (Nu) and can selectively lead to heterocyclic scaffolds or CO₂ based polymers. The majority of this research focuses on petro-derived epoxides and CO₂, although promising recent reports highlight the potential for bio-derived epoxides. (1) In particular, CO₂ coupling with challenging di- and tri-substituted oxiranes can expand both the scope and possible applications of organic carbonates and polycarbonates. Here we report the application of highly active catalytic systems to the coupling of di- and tri-substituted epoxides and CO₂. The catalytic systems investigated are either Al^{III} aminotriphenolate complexes which form an interesting class of modular, homogeneous catalysts, highly active towards cyclic carbonate formation (2) or bimetallic macrocycles and metal salen based systems which are selective towards polycarbonate formation. (3) These catalysts are capable of selectively forming either cyclic or polycarbonate structures. An appropriate substrate scope will be presented, highlighting renewable, naturally occurring compounds and how they compare with more traditional epoxides. (4) The structural properties of the resulting cyclic and polymeric products will also be discussed being of interest for practical applications.



References: 1. a) C. M. Byrne, S. D. Allen, E. B. Lobkovsky, G. W. Coates, *J. Am. Chem. Soc.*, **2004**, *126*, 11404-11405; b) L. Peña Carrodegua, J. González-Fabra, F. Castro-Gómez, C. Bo, A. W. Kleij, *Chem. Eur. J.*, **2015**, *21*, 6115-6122; c) O. Hauenstein, M. Reiter, S. Agarwal, B. Rieger, A. Greiner, *Green Chem.*, **2016**, *18*, 760-770; d) M. Winkler, C. Romain, M. A. R. Meier, C. K. Williams, *Green Chem.*, **2015**, *17*, 300-306; e) D. J. Darensbourg, W.-C. Chung, A. D. Yeung, M. Luna, *Macromolecules*, **2015**, *48*, 1679-1687. 2. a) C. J. Whiteoak, N. Kielland, V. Laserna, E. C. Escudero-Adán, E. Martín, A. W. Kleij, *J. Am. Chem. Soc.*, **2013**, *135*, 1228-1231; b) C. J. Whiteoak, N. Kielland, V. Laserna, F. Castro-Gomez, E. Martín, E. C. Escudero-Adán, C. Bo, A. W. Kleij, *Chem. Eur. J.*, **2014**, *20*, 2264-2275. 3. a) M. R. Kember, C. K. Williams, *J. Am. Chem. Soc.*, **2012**, *134*, 15676-15679; b) D. J. Darensbourg, R. M. Mackiewicz, J. L. Rodgers, C. C. Fang, D. R. Billodeaux, J. H. Reibenspies, *Inorg. Chem.*, **2004**, *43*, 6024-6034. 4. a) V. Laserna, G. Fiorani, C. J. Whiteoak, E. Martín, E. Escudero-Adán, A. W. Kleij, *Angew. Chem. Int. Ed.*, **2014**, *53*, 10416-10419; b) G. Fiorani, M. Stuck, C. Martín, M. Martínez Belmonte, E. Martín, E. C. Escudero-Adán, A. W. Kleij, *ChemSusChem*, **2016**, *9*, 1304-1311.

When glycochemistry meets biomaterials: from design to application of synthetic glyco-tools

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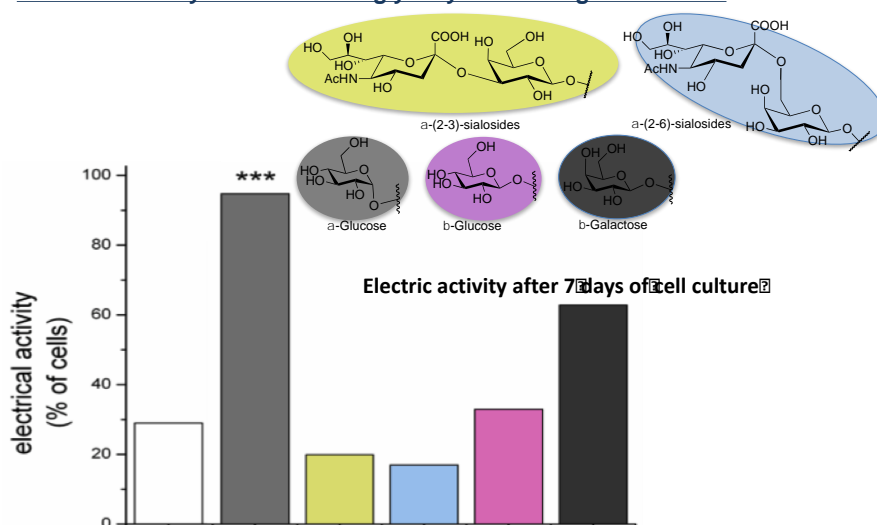
e-mail: laura.russo@unimib.it

Glycans are ubiquitous in all living cells and organisms, where they serve essential functions, ranging from acting as structural components to regulate physiological and pathological processes. Evidence clearly indicates that glycans represent a largely untapped resource for biological discovery as well as unanticipated therapeutic opportunities. Recent studies have challenged the classical view of protein glycosylation as an intracellular event by demonstrating that glycans may experience further structural remodelling by extracellular enzymes. This makes the glycome a highly dynamic molecular entity that mirrors a biological milieu and confer to cell microenvironment an important regulatory role. The design of new synthetic strategies aimed to obtain new biomaterials able to mimic the extracellular environment and its glycosignature has impact in different biomedical fields, from tissue engineering to cell biology studies [1,2]. Here in this talk functionalization strategies of different materials and their biomedical application will be presented.

NEURO-REGENERATION

Neuroblastoma F11R cells

Functional Analysis on different glycosylated Collagen Scaffolds



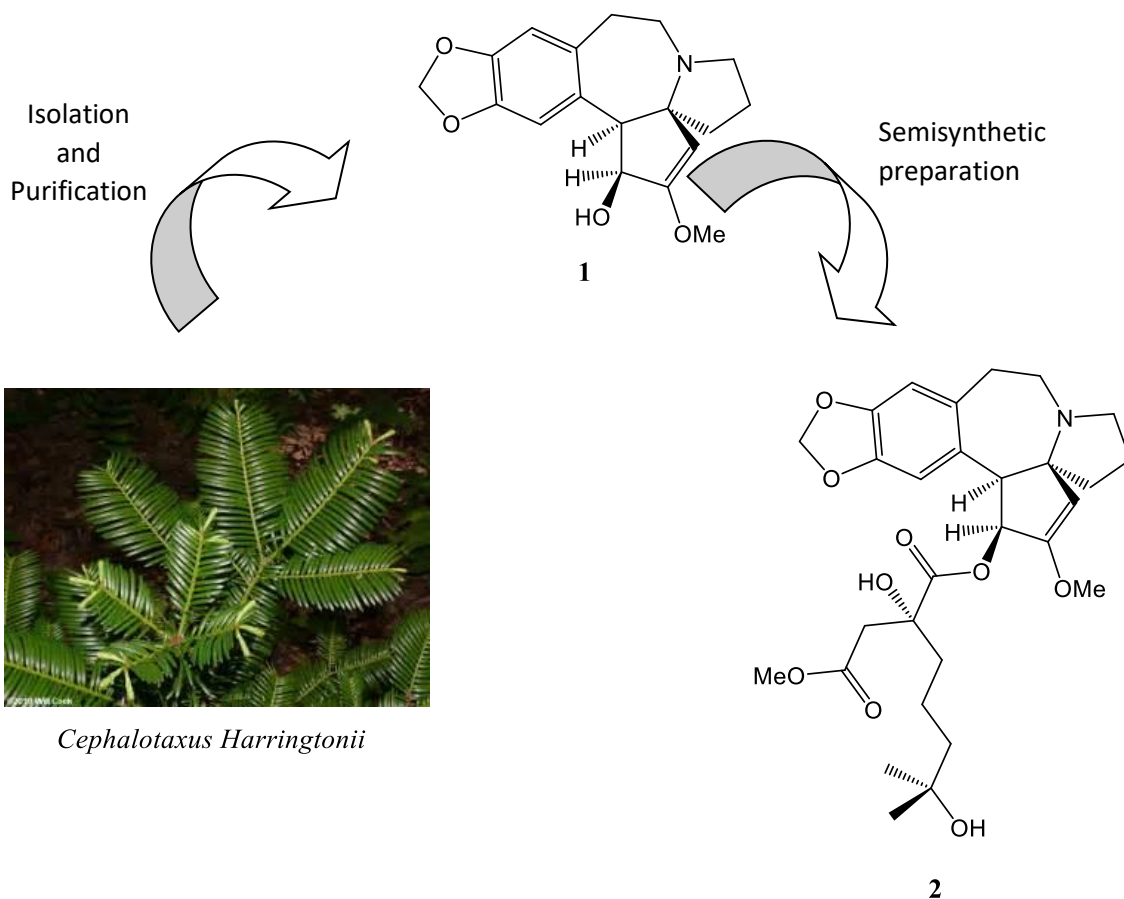
References: 1. Reference n. 1. Russo et al. *ACS Chem. Neurosci.* 2014, 5(4), 261-265. Reference n. 2 Russo et al. *Materials Today*, 2011, 14, 165-169

Semisynthetic ways for the preparation of Homoharringtonine: an industrial approach.

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Homoharringtonine **2**, a natural alkaloid obtained from various *Cephalotaxus* species is used in the treatment of myeloid leukemia. The mechanism of action by which Homoharringtonine exerts its antitumor activity is through inhibition of protein synthesis and promotion of apoptosis. It can be extracted from various botanical species, but its preparation by a synthetic way has always represented a challenge. An efficient industrial route for the isolation of pure omacetaxine **1** and the semisynthesis of Homoharringtonine is discussed.



Tuning Reactivity and Selectivity in Hydrogen Atom Transfer from Aliphatic C–H Bonds

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Hydrogen atom transfer (HAT) represents one of the most fundamental chemical reactions that plays a major role in a variety of important chemical and biological processes. Relevant examples include enzymatic and biomimetic reactions, the mechanism of action of natural and synthetic radical scavenging antioxidants, radical-induced damage to biomolecules and polymers, the degradation of volatile organic compounds in the atmosphere, as well as a large number of synthetically useful C–H functionalization procedures.

The factors that govern HAT reactivity from aliphatic C–H bonds have been discussed in detail (1-3). The main contributor is generally represented by bond strengths, but other factors such as steric, stereoelectronic, strain release and polar effects have also been shown to play an important role.

Within this framework, we have been interested in the study of HAT reactions from aliphatic C–H bonds, with the main objective of obtaining quantitative kinetic information on the role of structural and medium effects on the reactivity and selectivity patterns. This goal has been mostly achieved through time-resolved kinetic studies of the reactions of an alkoxy radical such as cumyloxy (PhC(CH₃)₂O, CumO•) with a large variety of substrates (hydrocarbons, alcohols, ethers, aldehydes, amines, amides) carried out employing the laser flash photolysis technique, with particular attention being devoted to the role of solvent effects and of added Lewis and Brønsted acids (4). These studies have provided a consistent set of second order rate constant values (k_H), through which useful guidelines for the description of the factors that govern these reactions have been obtained. The results of these studies will be discussed

References: 1. Newhouse, T.; Baran, P. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 3362-3374. 2. Mayer, J. M. *Acc. Chem. Res.* **2011**, *44*, 36-46. 3. Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25-35. 4. Salamone, M.; Bietti, M. *Acc. Chem. Res.* **2015**, *48*, 2895-2903.

Organic coating OF Metallic nanoparticles: theranostic applications in nanomedicine

Mauro Comes Franchini

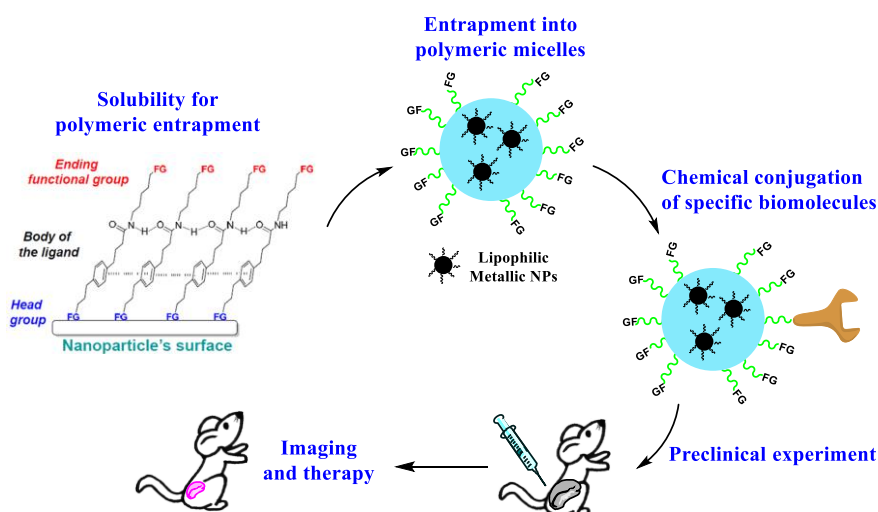
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Metal nanoparticles (MNPs) have various unusual chemical and physical properties compared with those of metal atoms. The role of organic ligands and their coating of MNPs, on the other hand, are increasing the importance in nanoscience. Once grafted with organic molecules the metallic nanoparticles change their solubility and can therefore be further elaborated and/or entrapped into suitable (bio)polymers.

The functionalization of MNPs with specific organic molecules is therefore a key step in nanomedicine.

Nanomedicine is the application of nanoscience to medicine and one possible approach describe the use of multi-functional nanocarriers containing organic molecules (drugs) together with smaller lipophilic metallic nanoparticles suitable for imaging/therapy.

This concept seems to be particularly important in view of the emerging concept of theranostic in which both therapeutic and diagnostic capabilities can be present in nanocarriers.



In this talk:

Several metallic nanoparticles (Gold, Silver, Iron oxide) will be presented with specific organic coating, synthesis and characterization. Different shapes will be also considered.

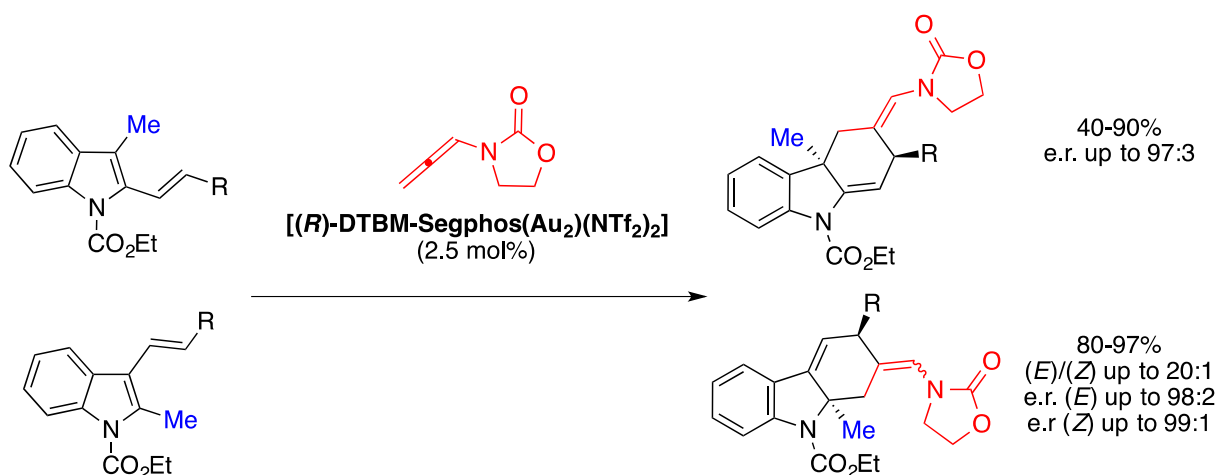
Polymeric entrapment and chemical conjugation with specific biomolecules (peptides, monoclonal antibodies, aptamers) giving targeted-nanocarriers, will be also shown.

Biological results *in vitro* on several cancer cells will be presented as well as some pre-clinical *in vivo* experiments in tumor-bearing mice will show the final application, one step before entering in clinical trials.

Gold(I)-catalyzed [4+2] cycloaddition reactions of vinylindoles and allenes

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Carbazole and tetrahydrocarbazole rings are the key structural motif in a great number of biological active molecules, including natural alkaloids and synthetic products.(1) For this reason, strategic syntheses of these indole derivatives are highly required, in particular when based on asymmetric methodologies. In this research field, 2- and 3-vinylindoles have become versatile 4C building blocks for the synthesis of complex tetrahydrocarbazole derivatives by means of [4+2] cycloadditions.(2) Among dienophiles, it has been shown that gold activated allenes could participate in [4+2] processes(3) and we published the first example of gold catalyzed reaction of 2- and 3-vinylindoles with allenamides(4) and allenyl esters.(5) In this latter work we reported also some preliminary investigations on enantioselective synthesis of tetrahydrocarbazoles, by conducting the reaction in the presence of a chiral gold(I) phosphoramidites. Prompted by these results and taking into account the importance of asymmetric tetrahydrocarbazole synthesis, we next explored the reactivity of 3/2-substituted-2/3-vinylindoles with *N*-allenamides under chiral gold(I) catalysis for the synthesis of a new series of dearomatized indoles bearing a quaternary C4a/C9a stereocenter (Scheme 1).(6) The results obtained in this work will be presented in the context of our investigations on gold(I) catalyzed syntheses of tetrahydrocarbazoles.



References: (1) A. W. Schmidt, K. R. Reddy, H.-J. Knölker, *Chem. Rev.* **2012**, *112*, 3193; A. Głuszyńska, *Eur. J. Med. Chem.* **2015**, *94*, 405; L. S. Tsutsumi, D. Gundisch, D. Sun, *Curr. Top. Med. Chem.* **2016**, *16*, 1290. (2) U. Pindur, *Heterocycles* **1988**, *27*, 1253; R. F. Kester, S. J. Berthel, F. Firooznia, *Top. Heterocycl. Chem.* **2010**, *26*, 327. (3) Y. Li, W. Li, J. Zhang, *Chem. Eur. J.* **2017**, *23*, 467; F. López, J. L. Mascareñas, *Chem. Soc. Rev.* **2014**, *43*, 2904. (4) V. Pirovano, L. Decataldo, E. Rossi, R. Vicente, *Chem. Commun.* **2013**, *49*, 3594. (5) V. Pirovano, E. Arpini, M. Dell'Acqua, R. Vicente, G. Abbiati, E. Rossi, *Adv. Synth. Catal.* **2016**, *358*, 403. (6) V. Pirovano, M. Borri, G. Abbiati, S. Rizzato, E. Rossi, *Adv. Synth. Catal.* **2017**, accepted, DOI: 10.1002/adsc.201700280.

Hydrogen and chemicals from renewable alcohols by Organometallic Electro-Reforming (OMER)

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The production of hydrogen by electrolysis of water is a well-established technology but it does not have a significant commercial impact due to its high energy cost.

A recent strategy for reducing the energy cost of electrolytic hydrogen production involves the replacement of water oxidation at the anode of the electrolytic cell with the oxidation of a soluble substrate, like a bioalcohol, whose oxidation potential is much lower than that of water. This leads to a significant reduction of the potential required to produce hydrogen (1). The original idea presented here, consists in coupling the partial oxidation of renewable alcohols promoted by an organometallic complex $[\text{Rh}(\text{OTf})(\text{trop}_2\text{NH})\{\text{P}(4\text{-}n\text{-butyl-Ph})_3\}]$ ($\text{trop}_2\text{NH}=\text{bis}(5\text{-H dibenzo}[a,d]\text{cyclohepten-5-yl})\text{-amine}$; $\text{OTf} = \text{CF}_3\text{SO}_3^-$ = triflate; (see 1@C in figure 1 for a structure plot) with the cathodic hydrogen evolution reaction (2). We report an electrolytic device that achieves the simultaneous selective production of carboxylate compounds and high-purity hydrogen gas. This electrolyzer, that we call OrganoMetallic ElectroReformer (OMER), in contrast to electrolysis technologies based on nanoparticles, offers potentially enormous advantages as in principle every single metal atom is catalytically active, thus allowing a vastly reduced metal loading. At the same time, this technology is capable of providing simultaneously high levels of pure hydrogen production and chemicals of industrial importance by the exploitation of bioalcohols. The absence of oxygen production in the anode compartment facilitates the production of hydrogen at elevated pressures. Consequently, we hypothesize the exploitation of bioalcohol electroreforming as an essential component of the biorefinery platform using this new class of electrolyzers based on organometallic complexes.

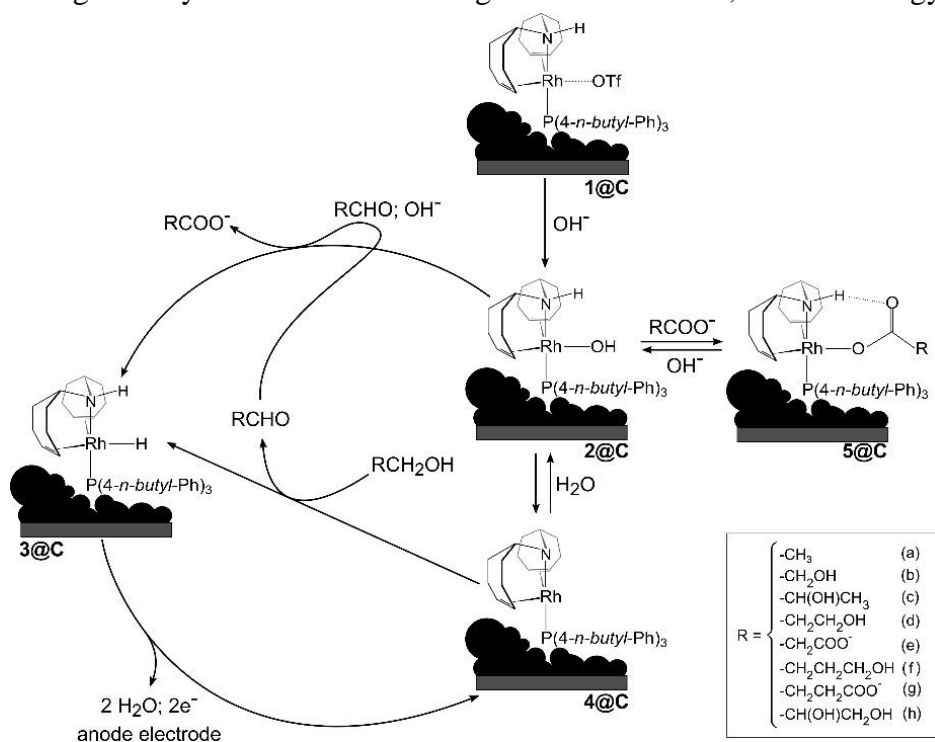


Figure 1: proposed mechanism for the reactions occurring on the anode coated with 1@C.

References: 1. F.Vizza et al., Nat. Comm. 5, 4036 (2014). 2. M. Bellini et al., ChemCatChem 9, 746 (2017).

Keynote e Conferenze su Invito

- [ORG/INO KN01](#): Alessandro Caselli, Università degli Studi di Milano
- [ORG/INO KN02](#): Lorenzo Zani, CNR, Sesto Fiorentino (Fi)

Catalytic Applications of Pyridine-Containing Macrocyclic Complexes

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Polyazamacrocycles are a common class of macrocyclic compounds, utilized across a number of fields, including, but not limited to, catalysis, selective metal recovery and recycling, therapy and diagnosis, and materials and sensors.¹ Worth of note is their ability to form stable complexes with a plethora of both transition, especially late, and lanthanide metal cations.² Deviation of the macrocycle donor atoms from planarity often leads to rather uncommon oxidation states.³ Both the thermodynamic properties and the complexation kinetics are strongly affected by the introduction of a pyridine moiety into the skeleton of polyazamacrocycles by increasing the conformational rigidity and tuning the basicity.⁴ Pyridine-containing ligands engender great interest due to various potential field of applications. They have been successfully employed in biology, Magnetic Resonance Imaging, molecular recognition, supramolecular chemistry and self-assembly, molecular machines and mechanically interlocked architectures.⁵ In this lecture, I will provide a perspective on the catalytic applications of metal complexes of pyridine-containing macrocyclic ligands (Pc-L's) which have been studied in our group (Figure), with a focus interest on the structural features relevant to catalysis.⁶ The increased conformational rigidity imposed by the pyridine ring allowed for the isolation and characterization of metal complexes which showed a rich coordination chemistry.⁷ The very different conformations accessible upon coordination and the easy tuneable synthesis of the macrocyclic ligands have been exploited in stereoselective syntheses.⁸

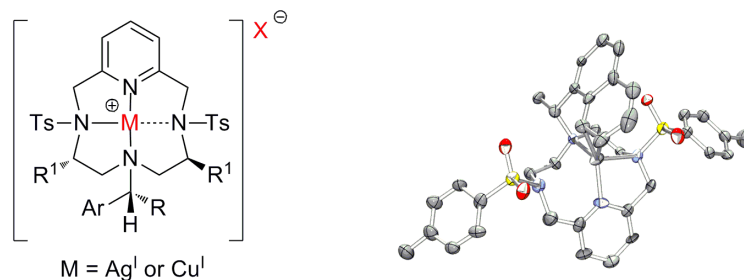


Figure. Metal complexes of Pc-L's and X-ray structure of a Cu(I) complex with a rare η^2 -naphthyl moiety coordinated to the metal center.

Key words: macrocyclic ligands, homogeneous catalysis, copper, silver, C-C and C-O bond forming reactions.

References:

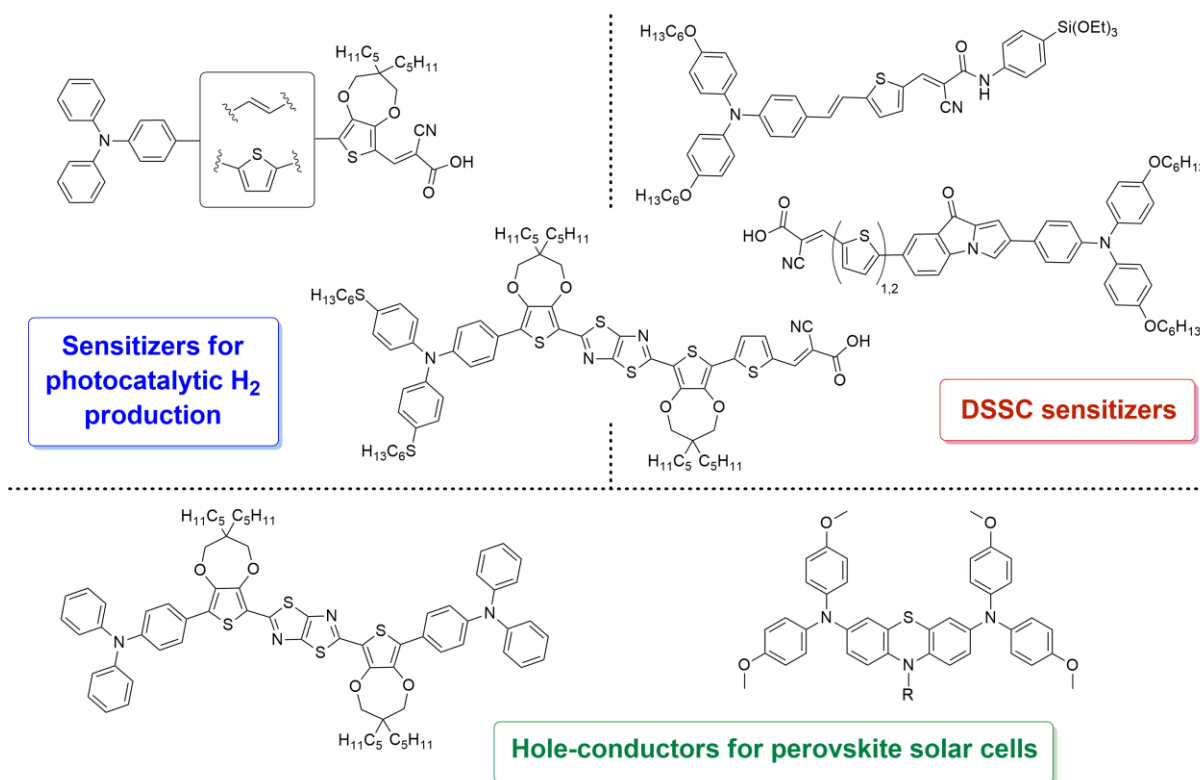
- ¹ L. F. Lindoy, G. V. Meehan, I. M. Vasilescu, H. J. Kim, J.-E. Lee, S. S. Lee, *Coord. Chem. Rev.* **2010**, *254*, 1713.
- ² T. Ren, *Chem. Commun.* **2016**, *52*, 3271.
- ³ A. Casitas, X. Ribas, *Chem. Sci.* **2013**, *4*, 2301.
- ⁴ K. M. Lincoln, M. E. Offutt, T. D. Hayden, R. E. Saunders, K. N. Green, *Inorg. Chem.* **2014**, *53*, 1406.
- ⁵ M. Rezaeivala, H. Keypour, *Coord. Chem. Rev.* **2014**, *280*, 203.
- ⁶ B. Castano, S. Guidone, E. Gallo, F. Ragaini, N. Casati, P. Macchi, M. Sisti, A. Caselli, *Dalton Trans.* **2013**, *42*, 2451.
- ⁷ a) G. Tseberlidis, M. Dell'Acqua, D. Valcarenghi, E. Gallo, E. Rossi, G. Abbiati, A. Caselli, *RSC Adv.* **2016**, *6*, 97404; b) T. Pedrazzini, P. Pirovano, M. Dell'Acqua, F. Ragaini, P. Illiano, P. Macchi, G. Abbiati, A. Caselli, *Eur. J. Inorg. Chem.* **2015**, *2015*, 5089.
- ⁸ a) M. Dell'Acqua, B. Castano, C. Cecchini, T. Pedrazzini, V. Pirovano, E. Rossi, A. Caselli, G. Abbiati, *J. Org. Chem.* **2014**, *79*, 3494; b) M. Trose, M. Dell'Acqua, T. Pedrazzini, V. Pirovano, E. Gallo, E. Rossi, A. Caselli, G. Abbiati, *J. Org. Chem.* **2014**, *79*, 7311; c) B. Castano, E. Gallo, D. J. Cole-Hamilton, V. Dal Santo, R. Psaro, A. Caselli, *Green Chem.* **2014**, *16*, 3202.

Conjugated Organic Compounds for Solar Energy Conversion to Electricity and Fuels

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Over the years, conjugated organic compounds have been extensively employed in devices for solar energy exploitation, both as light-harvesting materials and semiconductors with high charge carrier mobility: relevant examples include sensitizers for dye-sensitized solar cells (DSSC) (1) and hydrogen photocatalytic production (2), small-molecule donor materials in organic solar cells (3) and hole-conductive materials for perovskite solar cells (4). In this communication, we will provide an overview of our group's recent activity in the design, synthesis and application of donor-acceptor conjugated compounds for solar energy conversion (5-9). Compounds containing different heterocyclic rings (Figure 1) were assembled by means of typical organometallic and transition metal-catalyzed transformations, such as halogen-lithium exchange and Pd- or Cu-mediated coupling



reactions, and were characterized using various spectroscopic and electrochemical techniques. The influence of their optical and redox properties on the efficiency of solar energy conversion devices will be discussed, together with the role of charge transfer processes taking place between them and other device components (such as inorganic semiconductors, electrolytes, sacrificial electron donors).

Figure 1. Examples of conjugated organic compounds employed in devices for solar energy exploitation.

References: 1. C.-P. Lee *et al.*, *RSC Adv.* **2015**, *5*, 23810. 2. B. Cecconi *et al.*, *Eur. J. Org. Chem.* **2016**, 5194. 3. A. Mishra, P. Bäuerle, *Angew. Chem. Int. Ed.* **2012**, *51*, 2020. 4. J. Seo *et al.*, *Acc. Chem. Res.* **2016**, *49*, 562. 5. A. Dessì *et al.*, *Chem. Commun.* **2014**, *50*, 13952. 6. D. Franchi *et al.*, *Tetrahedron* **2014**, *70*, 6285. 7. A. Dessì *et al.*, *RSC Adv.* **2015**, *5*, 32657. 8. B. Mátravölgyi *et al.*, *Eur. J. Org. Chem.* **2017**, 1843. 9. E. Castellucci *et al.*, *Phys. Chem. Chem. Phys.* **2017**, DOI: 10.1039/C7CP01956D

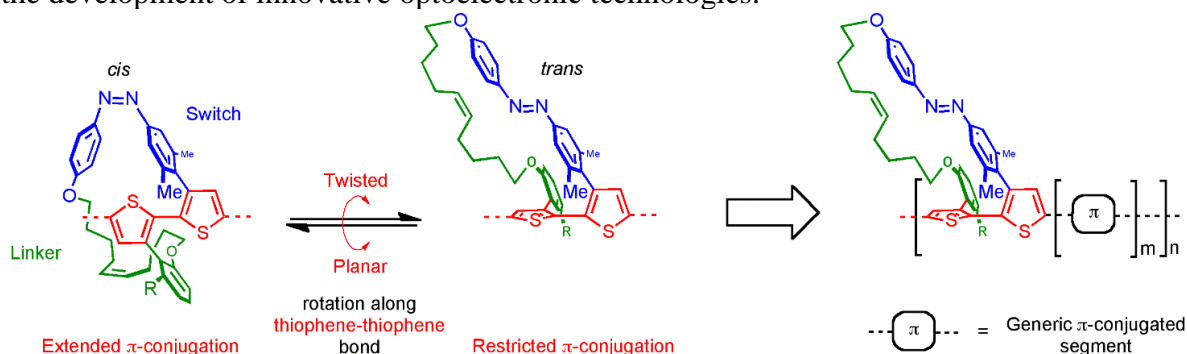
Comunicazioni Orali

Molecular Engineering of π -Conjugated Systems Towards Light-Responsive Organic Semiconductors

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Conjugated oligomers and polymers are under widespread investigation as active components in various optical and electronic technologies. The chemical-physical properties of these compounds strongly depend on the geometric arrangement of their molecular π -orbitals. The ability to modulate the π -bond geometry, e.g. the planarity, is particularly desirable as it can offer the possibility to dynamically tailor their π -conjugation extension, thus tuning their optical and electronic properties. Light-responsive switches, e.g. photochromic dyes, have been successfully used to modulate the effective conjugation length of linear π -systems.^[1,2] However, such molecules experience a drop in their photo-switching efficiency by increasing the π -conjugation length.^[3] Here, we present an alternative *design philosophy* called *photochromic torsional switch* (PTS), that exceeds the current limits of conventional photochromic molecular switches. The PTS design comprises an azobenzene-switch laterally connected to a bithiophene π -conjugated unit by both direct and aliphatic linker-assisted bonding. The planarity of the bithiophene can be *mechanically* tuned *via* the photochromic isomerization of the azobenzene unit. Upon exposure to 350 nm wavelength, the azobenzene moiety switches to a *cis* configuration, causing the planarization of the bithiophene. In the absence of light, or upon exposure to a 254 nm wavelength, the azobenzene moiety assumes its extended *trans* conformation, forcing the bithiophene backbone to be twisted out of planarity. The described PTS molecular design was then extended to thiophene-based oligomers and polymers. In order to probe the structural variations of the thiophenic backbone, as well as the reversible tuning of the optical and electronic properties of these PTS derivatives, we used state-of-the-art spectroscopic and computational quantum-chemical techniques. Noticeably, the switchability of these PTS-based oligothiophenes and polythiophenes is not adversely affected by the extension of their π -conjugation. Thus, PTS-based oligomers were successfully used for the fabrication of working light-responsive organic field effect transistors (OFET). This novel class of photochromic compounds open, thus, new avenues towards the design of *adaptive* and *responsive* π -conjugated molecular materials, and allow for the development of innovative optoelectronic technologies.



References: 1. S. Ko, E. T. Hoke, L. Pandey et al., *J. Am. Chem. Soc.*, **2012**, 134, 5222-5232. 2. R. Rieger, D. Beckmann, A. Mavrinskiy et al., *Chem. Mater.*, **2010**, 22, 5314-5218. 3. F. Stellacci, C. Bertarelli, F. Toscano et al., *Adv. Mater.*, **1999**, 11, 292-295. 4 J. Maciejewski, A. Sobczuk, A. Claveau, A. G. Nicolai, R. Petraglia, L. Cervini, E. Baudat, P. Mieville, D. Fazzi, C. Corminboeuf, G. Sforazzini, *Chem. Sci.* **2017**, 8, 361-365.

Organic sensitizers for solar fuels from dye-sensitized water splitting

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The need for energy is increasing all around the world, so it is very important to find clean sources to produce it. Among the new approaches to solar energy conversion, photoelectrochemical cells (PEC) represent an interesting solution to obtain hydrogen and oxygen from water splitting. Hydrogen is a clean fuel, with zero carbon footprint, and is very versatile since it can be used to produce electricity but also as an automotive fuel that ensures a far bigger range than batteries for electric cars.

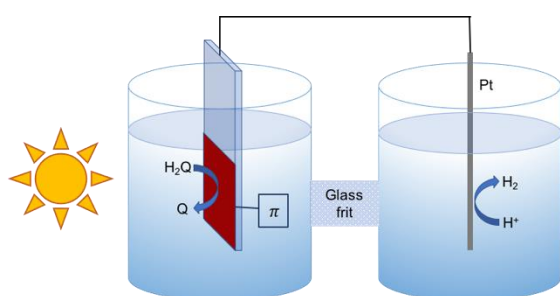


Figure 3. Scheme of a device for dye-sensitized generation of H₂ (π = organic sensitizer).

tested a series of D-(π -A)₂ dyes where D is a substituted phenothiazine, phenoxazine or carbazole donor core, A is the acceptor-anchoring cyano-acrylic group, and π is a thiophene spacer (Fig. 2), previously used in photocatalytic hydrogen production (2, 3). To better investigate the electron transfer process from the sensitizer to the semiconductor, a comparative study in presence of different sacrificial electron donors has been performed (namely triethanolamine, TEOA, and hydroquinone, H₂Q). Compared to the reference dye (phenothiazine-based dye) (4), the new sensitizers revealed improved optical properties and enhanced photocurrent in photoelectrochemical experiments (5).

The sustainable production of fuels from Sun and water via organic dye-sensitizers is an emerging field of research, where the organic design is strategic in order to get improved technological performances. In the frame of our investigation on dye-sensitized solar cells in the last years we have pioneered a multi-branched multi-anchoring D-(π -A)₂ geometry, now widely used in the field (1).

In this work we present the application of specifically engineered di-branched dyes to the dye-sensitized PEC (DS-PEC) for water splitting (Fig. 1). Namely, we

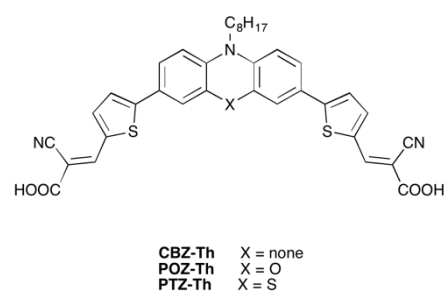


Figure 2. Sensitizers investigated in this work.

References: 1. Manfredi, N.; Cecconi, B.; Abbotto, A. *Eur. J. Org. Chem.* **2014**, 7069 (review). 2. Manfredi N.; Monai M.; Montini T.; Salamone M. M.; Ruffo R.; Fornasiero P.; Abbotto A. *Sustainable Energy Fuels*, **2017**, DOI: 10.1039/C7SE00075H. 3. Manfredi, N.; Cecconi, B.; Calabrese, V.; Minotti, A.; Peri, F.; Ruffo, R.; Monai, M.; Romero-Ocana, I.; Montini, T.; Fornasiero, P.; Abbotto, A. *Chem Commun* **2016**, 52, 6977. 4. Cecconi, B.; Manfredi, N.; Ruffo, R.; Montini, T.; Romero-Ocaña, I.; Fornasiero, P.; Abbotto, A. *ChemSusChem* **2015**, 8, 4216. 5. Cecconi B.; Manfredi N.; Montini T.; Fornasiero P.; Abbotto A. *Eur. J. Org. Chem.* **2016**, 5194 (review).

Solution and solid-state supramolecular aggregates of new chiral oligothiophenes: synthesis and spectroscopic characterization

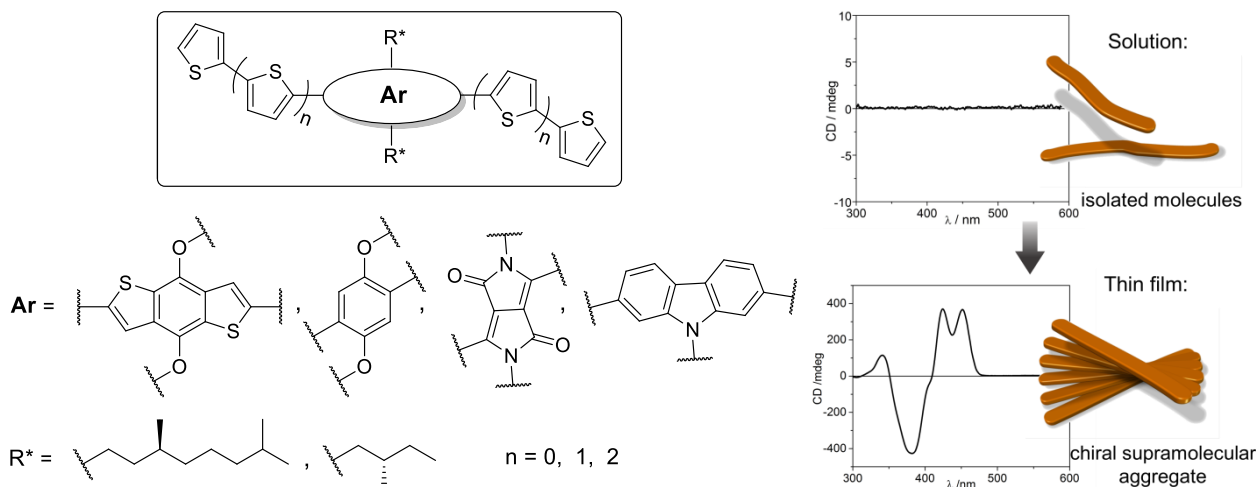
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In recent years, π -conjugated oligomers have emerged as ideal organic semiconductors for various electronic and optoelectronic applications, thanks to the possibility to modulate their electronic and optical properties (charge and exciton transport, light absorption and emission, response to external stimuli), which depend not only on their chemical structure and the conformation assumed, but also on the nano/mesoscale organization in the solid state. (1)

Chirality represents one of the most sophisticated expedients to control supramolecular aggregation of similar systems, in particular their interchain spacing and/or alignment. (2) Furthermore, chiral nanostructures may display various intriguing physicochemical properties, exploited for example in sensors able to discriminate enantiomers (3) and in circularly polarized (CP) light detectors (4, 5) or emitters (6). However, since most studies have concentrated only on inorganic chiral nanomaterials, the creation of chiral organic semiconductors may open new doors for optoelectronics.

We decided to work with new oligothiophenes (π -conjugated systems well known in optoelectronic devices) functionalized with some inexpensive alkyl chiral groups derived from natural sources, seeking self-assembly properties, which would ensure supramolecular chirality and the onset of extraordinary optical and electrical properties.



In particular, we will describe: a) the synthetic route developed for the preparation of these oligomers; b) their spectroscopic characterization (UV-Vis, ECD, fluorescence) to investigate the supramolecular organization both in solution and in thin films (prepared by drop casting and spin coating techniques), in connection with standard and polarized optical microscopy analysis.

References: 1. F. J. M. Hoeben, P. Jonkheijm, E. W. Meijer, A. P. H. J. Schenning, *Chem. Rev.* **2005**, *105*, 1491-1546. 2. L. A. P. Kane-Maguire, G. G. Wallace, *Chem. Soc. Rev.* **2010**, *39*, 2545-2576. 3. L. Torsi, G. M. Farinola, F. Marinelli, M. C. Tanese, O. H. Omar, L. Valli, F. Babudri, F. Palmisano, P. G. Zambonin, F. Naso, *Nat. Mater.* **2008**, *7*, 412-417. 4. Y. Yang, R. C. da Costa, M. J. Fuchter, A. J. Campbell, *Nat. Photon.* **2013**, *7*, 634-638. 5. X. Shang, I. Song, H. Ohtsu, Y. H. Lee, T. Zhao, T. Kojima, J. H. Jung, M. Kawano, J. H. Oh, *Adv. Mater.* **2017**, 1605828. 6. Y. Yang, R. C. da Costa, D. M. Smilgies, A. J. Campbell, M. J. Fuchter, *Adv. Mater.* **2013**, *25*, 2624-2628.

Novel oligothiophenes with reduced HOMO-LUMO band gap for Optoelectronics

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Thiophene-based copolymers are conjugated materials with a wide range of interesting chemical physical properties.(1) They are widely studied as active layer in organic solar cells, light emitting diodes and field effect transistors, and other optoelectronic devices.(1, 2) The electronic energy levels of these copolymers can be fine-tuned through synthesis (e.g. choosing the backbone units, alternating electron-donor and electron-acceptor units, changing the substituents on the backbone) to optimize the HOMO-LUMO band gap in order to confer better performances to the final device. When compared to polymers, oligomers offer potential advantages, such as a defined molecular structure and molecular weight, easy purification, mass-scale production, and good batch-to-batch reproducibility. Recently, several small molecules (including oligothiophenes) with performance in optoelectronic devices comparable to that of their polymeric analogues were reported.(3, 4, 5)

Here we present the synthesis of A- π -D- π -A thiophene-based oligomers (Figure 1); in the design of these materials we incorporated both electron-donor and electron-acceptor groups by having a central donor dithienosilole, two terminal methylcyanovinyl acceptor groups and two bithienyl units, functionalised with alkyl or alkylsulfanyl chains, as π -bridges.

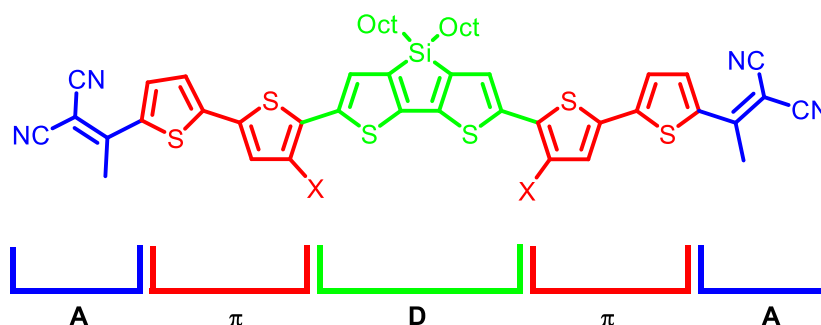


Figure 1 Target thiophene-based oligomers

The synthesis was achieved by a multi-step route, including the formation of the dithienosilole from 5-(trimethylsilyl) protected 2-bromothiophene by a one-pot halogen-dance – homocoupling sequence followed by cyclization with dichlorodioctylsilane and subsequent Suzuki coupling with the boron derivative of the β -functionalised thiophene. The final C-C bond was formed by Stille coupling.

References:

1. "Handbook of Thiophene-based materials", Vol.1, Ed: I.F.Perepichka, D.F.Perepichka, Wiley VCH, **2009**.
2. "Conjugated Polymers: Processing and Applications"; Skotheim, T. A., Reynolds, J., Eds; CRC Press: Boca Raton, **2007**.
3. Mishra, A. and P. Bauerle "Small Molecule Organic Semiconductors on the Move: Promises for Future Solar Energy Technology." *Angew. Chem., Int. Ed.*, **2012**, 51(9): 2020-2067.
4. L. Zhang, N. S. Colella, B. P. Cherniawski, S. C. B. Mannsfeld, and A. L. Briseno "Oligothiophene Semiconductors: Synthesis, Characterization, and Applications for Organic Devices", *ACS Appl. Mater. Interfaces*, **2014**, 6, 5327–5343.
5. N. S. Colella, B. P. Cherniawski, S. C. B. Mannsfeld, and A. L. Briseno, L. Zhang, Oligothiophene Semiconductors: Synthesis, Characterization, and Applications for Organic Devices. *Appl. Mater. Interfaces*, **2014**, 6, 5327–5343

Organic and biological materials for organic electronics: adding functionality

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Organic materials have shown very high potential in technological applications, such as their performance as active layers in OLEDs, (1) plastic solar cells, (2) organic field effect transistors and sensors (3) and so on. The field of organic electronics, continuously in progress, poses new challenges, including the fascinating opportunity to extend the functions of organic materials by integration with biological compounds. This is an extremely attractive perspective, opening access to relevant applications as multi-functional, bio-compatible and sustainable devices.

In this communication, different strategies for the combination of the functions of organic semiconductors with the additional features of biological molecules are presented.

The decoration of conjugated polymers and oligomers with small biomolecules, like L-phenylalanine and D-glucose, enables access to organic semiconductors that show interesting interaction with chiral environment and circularly polarized light. (4)

The bioconjugation of synthetic fluorophores with a photoenzyme, the Reaction Center (RC) from the bacterium *Rh. Sphaeroides*, (5) produces enzymatically active bio-hybrids with enhanced performances. (6) An analogous chemistry is used to anchor the RC photoenzyme and streptavidin (SA) onto evaporated organic pigments thin films. The full functionality of the solid state assembly is demonstrated by photosensitization of the organic films induced by the RC photoenzyme. (7)

As new perspective, the possibility to access environmentally harmless devices drawing fully from natural raw materials represents a frontier of great technological impact. Indeed, novel cellulose nanofibers freestanding thin films, known as "nanopaper", can be part of organic devices as substrates, putting aside some plastic derivatives from the equation "disposable and flexible organic devices = oil derivatives". Functionalization chemistry on the nanofibers, both in solution and in heterogeneous conditions, can be used to modulate surface properties of nanopaper and its environmental stability. Hydrophobization dramatically improves the water resistance yielding ideal substrates for various applications, including implantable devices. (8)

References: (1) Farinola, G.M.; Ragni, R. *Chem. Soc. Rev.*, 2011, 40, 3467-3482; (2) G. Marzano, C. V. Ciasca, F. Babudri, G. Bianchi, A. Pellegrino, R. Po, G. M. Farinola, *Eur. J. Org. Chem.* 2014, 6583– 6614; (3) Operamolla, A. Farinola, G. M. *Eur. J. Org. Chem.* 2011, 423–450; (4) Babudri, F., Farinola, G. M., Hassan Omar, O., Naso, F., Operamolla, A., Pedone, A., *Tetrahedron* 2011, 67, 486; Pescitelli, G., Hassan Omar, O., Operamolla, A., Farinola, G. M., Di Bari, L., *Macromolecules* 2012, 45, 9616. (5) Operamolla, A., Ragni, R., Milano, F., Tangorra, R. R., Antonucci, A., Agostiano, A., Trotta, M., Farinola, G. M., *J. Mater. Chem. C* 2015, 3, 6471. (6) Milano, F., Tangorra, R. R., Hassan Omar, O., Ragni, R., Agostiano, A., Operamolla, A., Farinola, G. M., Trotta, M., *Angew. Chem. Int. Ed.* 2012, 51, 11019; Hassan Omar, O., la Gatta, S., Tangorra, R. R., Milano, F., Ragni, R., Operamolla, A., Argazzi, R., Chiorboli, C., Agostiano, A., Trotta, M., Farinola, G. M., *Bioconj. Chem.* 2016, 27, 1614. (7) Glowacki, E. D., Tangorra, R. R., Coskun, H., Farka, D., Operamolla, A., Kanbur, Y., Milano, F., Giotta, L., Farinola, G. M., Sariciftci, N. S., *J. Mater. Chem. C* 2015, 3, 6554. (8) Project "SolarLeaf - Biodegradable organic solar cells supported on cellulose", financed by Regione Puglia within the program FutureInResearch

Molecular Tailoring of Hole-Transporting Materials for High-Performing Perovskite Solar Cells

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Organic-inorganic lead halide perovskites have emerged (1) as one of the most promising research field in photovoltaics, due to their excellent light-harvesting, ranging from the visible to the NIR region, their high extinction coefficients and long electron-hole diffusion lengths (2). In devices, the free photo-generated holes within the perovskite material need to be extracted and transported by suitable hole-transporting materials (HTMs). To date, the highest reported efficiency values (up to 20%) have been reached by using the expensive Spiro-OMeTAD (3). Aiming at providing convenient alternatives, we have planned and carried out the synthesis of novel phenothiazine-based HTMs (**PTZ1** and **PTZ2**) by binding the suitable donor groups (diarylamine or triarylamine) to a phenothiazine core through straightforward Buchwald-Hartwig and Suzuki-Miyaura cross-couplings, respectively. The higher oxidation potential measured for **PTZ2** could be favorable for obtaining high V_{OC} in perovskite solar cells, while the relatively lower oxidation potential of **PTZ1** could result in a faster hole transfer between the perovskite layer and the HTM (Figure 1). When employed as HTM in perovskite solar cells, however, a dramatic effect exerted by the presence of phenylene spacers was observed in the performances of the relevant devices. The power conversion efficiencies measured under AM 1.5 sun was boosted from 2.1% (**PTZ1**) to an outstanding 17.6% (**PTZ2**), a value closely rivaling the one obtained with the state-of-the-art Spiro-OMeTAD (17.7%). By combining spectroelectrochemistry and DFT investigation, this dramatic difference in photovoltaic performances exhibited by the two phenothiazine-based derivatives could be attributed to the modulation of electron density distribution, controlling the molecules stability during the charge transfer dynamics at the perovskite/HTM interface. These results can stimulate research on phenothiazine-based materials as readily available and cost-effective promising alternatives to Spiro-OMeTAD in perovskite solar cells.

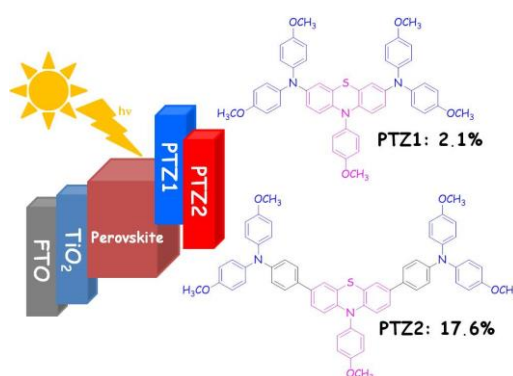


Figure 1. Energy level diagram of the perovskite solar cell components and molecular structures of **PTZ1** and **PTZ2**.

References: 1. A. Kojima, K. Teshima, Y. Shirai, T. Miyasaka, *J. Am. Chem. Soc.*, **2009**, *131*, 6050-51. 2. N. J. Jeon, J. H. Noh, W. S. Yang, Y. C. Kim, S. Ryu, J. Seo, S. I. Seok, *Nature*, **2015**, *517*, 476-80. 3. M. Saliba, S. Orlandi, T. Matsui, S. Aghazada, M. Cavazzini, J. P. Correa-Baena, P. Gao, R. Scopelliti, E. Mosconi, K.-H. Dahmen, F. De Angelis, A. Abate, A. Hagfeldt, G. Pozzi, M. Graetzel, M. K. Nazeeruddin, *Nat. Energy*, **2016**, *1*, 15017-23.

KuQuinones as photocatalysts in Light-driven water splitting

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Water splitting is a strongly endoergonic process, which requires the participation of four electrons and four protons and the formation of a new O–O bond. Consequently, it is characterized by important kinetic barriers, and the use of a catalyst is crucial to activate the splitting. Photosystem II constitutes in nature a successful model for water oxidation (1) indeed, the use of sunlight to perform water splitting appears to be a valid approach.

Few years ago, we developed a one-pot procedure for the synthesis of novel pentacyclic quinoid compounds, called KuQuinones (KuQs) (2), starting from easily available and cheap precursors. These compounds are able to harvest light in the visible region of the spectrum due to their pentacyclic and conjugated structure. Thanks to these interesting properties, we studied their ability to act as sensitive material in photoelectrochemical devices, using KuQs-functionalized ITO as working electrode and triethanolamine (TEOA) as sacrificial electron donor in solution (3). These features suggested the potential application of such novel compounds both as dyes and as electrons acceptor moiety also in the water-oxidation process. In this regard, a stable and high anodic photocurrent signal was detected in basic solution, according to the mechanism proposed in Figure 1. In this contribution, the general synthetic procedure of KuQuinones and preliminary results for the photoelectrochemical water oxidation will be presented.

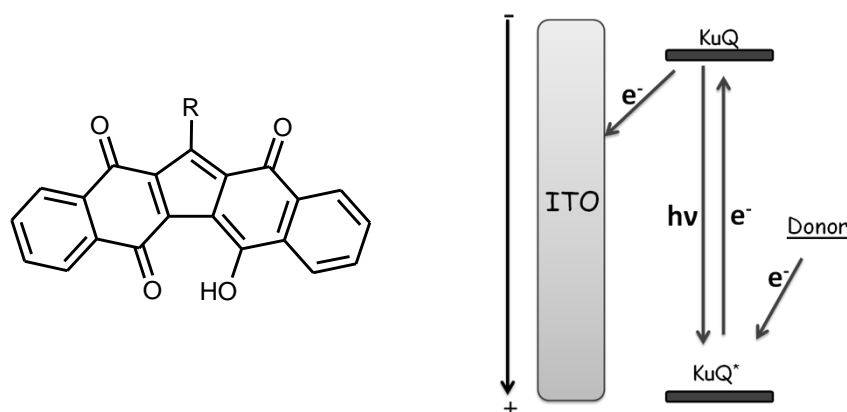


Figure 1. Structure of KuQs (left) and proposed mechanism for the photoelectrochemical cell (right).

- Herrero, C.; Lassalle-Kaiser, B.; Leibl, W.; Rutherford, A. W.; Aukauloo, A. *Coord. Chem. Rev.* **2008**, *252*, 456-468.
- Coletti, A.; Lentini, S.; Conte, V.; Floris, B.; Bortolini, O.; Sforza, F.; Grepioni, F.; Galloni, P. *J. Org. Chem.* **2012**, *77*, 6873-6879.
- Sabuzi, F.; Armuzza, V.; Conte, V.; Floris, B.; Venanzi, M.; Galloni, P.; Gatto, E. *J. Mat. Chem. C* **2016**, *4*, 622-629.

A quick and facile synthesis of stable, water-soluble CdSe/ZnS quantum dots.

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Core/shell Quantum Dots (QDs) are fascinating luminescent semiconductor nanomaterials characterized by a fine-tunable diameter size (ranging from 2 to 10 nm) (1). They display a wide range of unique and excellent electro-optical properties, such as broad absorption spectrum coupled with narrow emission band and a size-tunable photoluminescence in the visible spectral range (2). The possibility to functionalize their surface with organic molecules, allows to modulate their colloidal stability and to move their solubility from organic solvents to water environment. Water-soluble QDs can be achieved by grafting a corona of hydrophilic molecules on their surface. Ligand exchange, based on thiols containing small derivatives, is one of the most investigated approach to perform the phase-transfer step. In this regard, dihydrolipoic acid (DHLA) is the most investigating ligand to obtain water-soluble core-shell QDs, indeed, since it is bidentate, it provides quite stable interactions with QDs surfaces (3). Some examples of DHLA-based ligands have been reported to obtain water-soluble QDs, however, most of them suffer of short shelf lives: after few hours or days aggregation and precipitation phenomena take place by limiting some applications. In this framework, here is reported the efficient and reliable synthesis of hydrophilic thin coating grafted core/shell CdSe/ZnS QDs **1** (Figure 1) where the carboxylic group of a DHLA moiety was conjugated to the primary ammine group of an ethylenediamine-N,N-diacetic acid residue, named EDADA or UEDDA (4).

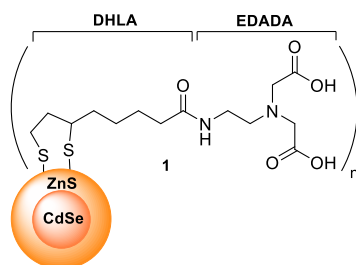


Figure 1. Core/shell CdSe/ZnS QDs **1**

In this presentation, the long term colloidal stability of water soluble QDs **1** in different pH buffer solutions, as function of the ionic strength of the media will be discussed. Then, by manipulating the later dicarboxylic groups of the EDADA-DHLA ligand, the surface of QDs **1** can be modified, making them useful tools for diverse applications. Finally, the preparation of hybrid polymer-QDs composites is discussed.

References:

1. Peng, X., Schlamp, M. C., Kadavanich, A. V., Alivisatos, A. P., *J. Am. Chem. Soc.* 119, **1997**, 7019
2. Norris, D.J., Bawendi, M.G., *Phys. Rev. B*, 53, **1996**, 16338.
3. Uyeda, H. T., Medintz, I. L., Jaiswal, J. K., Simon, S. M., Mattoussi H., *J. Am. Chem. Soc.*, 127, **2005**, 3870.
4. Pradeep, R., Varadwaj, A., Bih-Yaw, J., *Phys. Chem. Chem. Phys.*, 17, **2014**, 805.

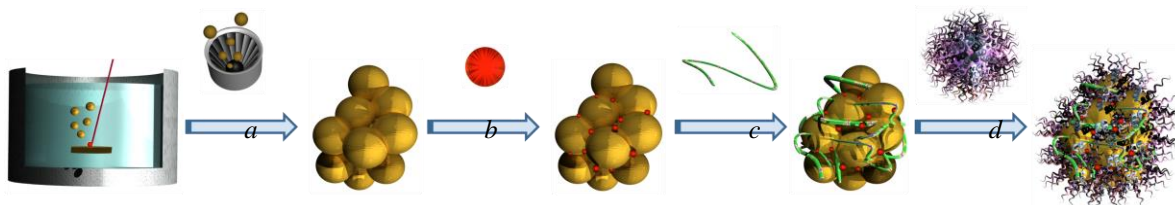
PreS1 Functionalized Gold Nanostructures for Liver Cancer Cells Targeting and Surface-Enhanced Raman Resonance Scattering Imaging

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The targeted delivery of biocompatible nanoparticles to malignant tumors has become a powerful tool in cancer nanomedicine for diagnostics and therapy. In particular, gold nanoparticles (AuNP) are one of the most employed nanomaterials because, besides displaying useful optical properties and a facile surface chemistry, are biocompatible, which is an essential requirement for biological application. AuNP can passively target tumors by the enhanced permeability and retention effect, but can also exhibit a high active targeting affinity and specificity when conjugated with biomolecular targeting agents, such as peptides, proteins or small molecules (1).

Recently the hepatitis B virus-preS1-(21-47) sequence has been identified as a specific ligand of



Synthetic steps for the preparation of the AuNP-nanostructures: after the laser ablation synthesis, the naked nanoparticles are aggregated by centrifugation (a); functionalized with the Raman reporter (b), and with PEG/peptide ligands (c). Finally BSA is used to complete the nanostructure (d).

Serpin B3, a member of the ovalbumin- family of serine protease inhibitor, frequently overexpressed in the majority of liver cancers (2). In this context, the aim of the present study was to synthesize preS1-functionalized gold nanostructures for targeting and detection of liver tumor cells. Nanostructures were prepared from naked AuNP obtained by Laser Ablation in Solution (3) and encoded with a Raman reporter, as shown in Figure, to achieve very intense Surface-Enhanced Raman Resonance Scattering (SERRS) signals (4,5). Peptides were synthesized on solid phase and, after deprotection and cleavage from the solid support, they were conjugated to nanoparticles, exploiting the affinity of gold for the thiol group of the ligand: a cysteine residue or a thiolated PEG chain added to the original peptide sequence. By synthesizing a few peptide analogues we were able to investigate the influence of different aspects important for Serpin B3 recognition, such as the peptide exposure and orientation on the nanostructures surface. Targeting of the nanostructures to hepatocellular carcinoma was checked on cells expressing or not Serpin B3, recording the SERRS signals cell by cell. Nanoaggregates covered with PEGs or with an anti-Serpin B3 antibody were used as negative and positive control, respectively. The results of tests *in vitro* and of a preliminary *in vivo* experiment will be presented.

References: 1. V.M. Rotello et al, *Adv Drug Deliv Rev* 60,11, 1307 (2008). 2. G. Fassina, *J. Biol. Chem*, 276, 36613 (2001) 3. V. Amendola, M. Meneghetti, *J. Mat. Chem*,17,44,4705 (2007) 4. Qian X. et al, *Nat. Biotech.* 83,1 (2008) 5. M. Meneghetti et al, *Small* 8, 3733 (2012).

Design and Synthesis of polyfunctional PNAs - A Biomolecular Engineering approach

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Peptide nucleic acids (PNAs) are polyamide analogues of nucleic acids, very effective in terms of affinity and selectivity in DNA/RNA recognition, and have been used for diagnostics, as well as for drug development.^{1,2} Appropriate design of modified PNAs allows to improve their properties and to increase their cellular uptake.³ This communication will describe our recent work, aimed to further improve the recognition properties of these compounds, aided by Molecular Dynamics and enhanced sampling Metadynamics (**Figure 1**).⁴ A series of synthetic modular strategies enabling a rational design of new PNA structures, and in particular poly-functional PNAs will be described.^{3,6} The synthesis of PNA able to undergo programmable group shift upon interaction with DNA or RNA, and rational interpretation of experimental data based on molecular models will be presented (**Figure 1a**); the application of this approach in understanding the effect of nucleobase modification will also be discussed (**Figure 1b**). This work was carried out in the frame of the H2020 ULTRAPLACAD project (grant agreement No 633937) aimed to improve the PNA performances for early diagnosis of colorectal cancer.

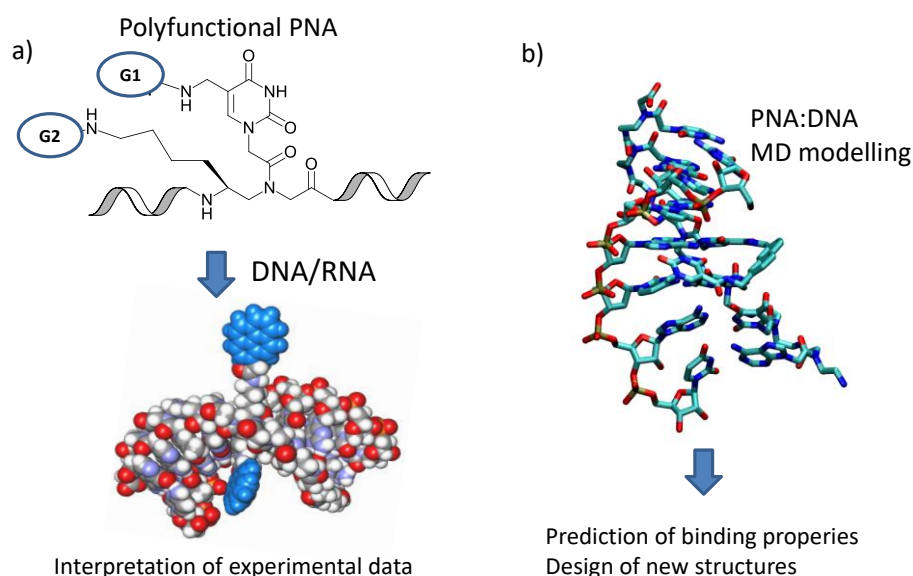


Figure 1. Present approaches for the interpretation and design of PNA properties for a) poly-functional PNA (modified base and backbone); b) PNA containing modified nucleobases.

References: 1. Nielsen, P. E. *Acc. Chem. Res.* **1999**, 32, 624–630. 2. Tonelli, R. et al. *Clinical Cancer Res* **2012**, 18, 796–807. 3. Manicardi, A.; Fabbri, E.; Tedeschi, T.; Sforza, S.; Bianchi, N.; Brognara, E.; Gambari, R.; Marchelli, R.; Corradini, R. *ChemBioChem* **2012**, 13 (9), 1327–1337. 4. Verona, M. D.; Verdolino, V.; Palazzesi, F.; Corradini, R. *Sci. Rep.* **2017**, 7, 42799. 5. Manicardi, A.; Guidi, L.; Ghidini, A.; Corradini, R. *Beilstein J. Org. Chem.* **2014**, 10, 1495–1503. 6. Manicardi A.; Bertucci, A.; Rozzi, A.; Corradini, R. *Org. Lett.* **2016**, 18, 5452–5455.

A Glycomimetic CHIP for microarray Screening of C-type Lectin Receptors

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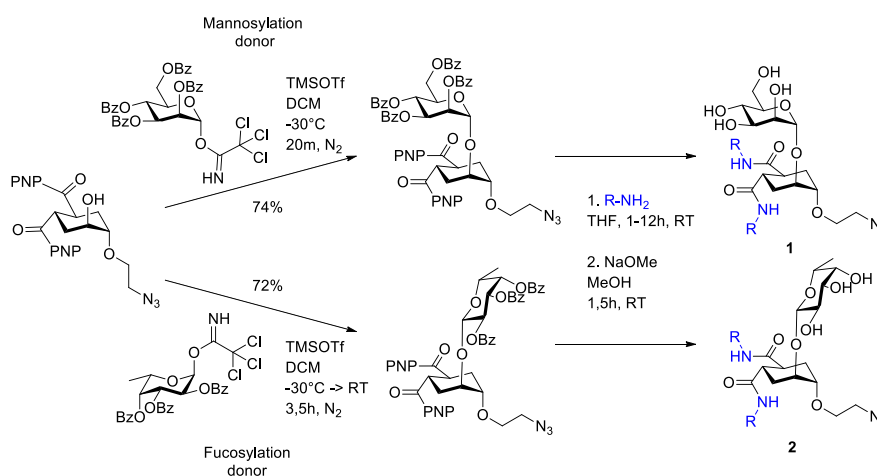
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Cell surfaces are covered by a large number of glycans (glycocalyx) which are docking sites for other cells, molecules and pathogens. Beside the sugars, these adhesion processes also involve carbohydrate-specific proteins – known as lectins, and the interactions between glycans and lectins are crucial for biological recognition and signal-initiation.

C-type lectin receptors (CLRs) were named after their Ca²⁺ requirement for binding carbohydrates and they play important roles in the immune response. CLR targeting can be an efficient strategy to steer the immune response toward a therapeutically desired effect. The Immunoshape European Training Network aims to develop potential lead structures for highly selective glycan-based multivalent immunotherapeutics for the treatment of cancer, autoimmune diseases and allergy.

Previous studies in our group (1) showed that mannoside mimics (**1**) are capable of efficiently targeting CLRs. Their inhibitory activity and selectivity depend on the nature of the two amide moieties attached to the cyclohexane ring. With the help of chemoinformatic tools, the mannose-based library was expanded, with the aim of identifying new high-affinity ligands for different CLRs. Additionally, β -fucosylated glycomimetics (**2**) were synthesized to exploit the mixed fucose-mannose selectivity of some CLRs.



The glycomimetics were printed on NHS-functionalized chips, with the help of a double-functionality linker and the resulting microarrays were screened at CIC biomaGUNE against human CLRs available through the Immunoshape consortium. The preparation of the microarrays was optimized and the covalently immobilized ligands were incubated with fluorescently labeled tetravalent lectins engineered at IBS. Quantification of the fluorescent signals allowed the estimation of the affinity of glycomimetic ligands towards the lectins and selected high-affinity binders were further studied by surface plasmon resonance (SPR) technique.

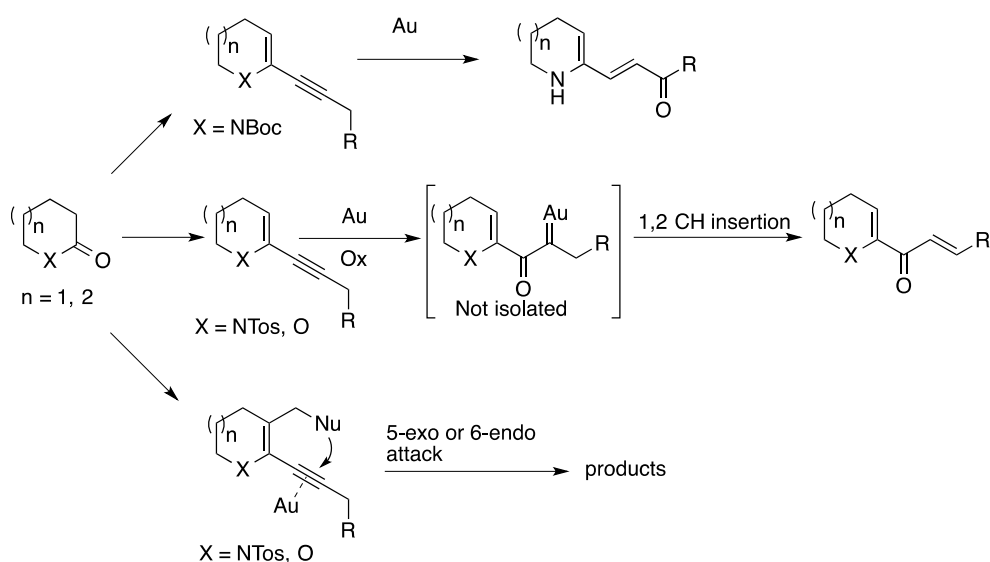
References: 1. N. Varga *et al.* Chem Eur. J., **2013**, 19, 4786-4797.

Gold(I)-catalyzed rearrangement of heterocycles derived 1,3-enynes

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We have previously demonstrated that the gold(I)-catalyzed reaction of *N*-Boc-protected 6-alkynyl-3,4-dihydro-2*H*-pyridines affords synthetically useful vinylogous amides (β -enaminones). The reaction has been studied in detail in order to optimize the reaction conditions, enlarge the scope and have insights into the mechanism and the structural features that selectively favor the 6-*endo dig* oxyuration of the triple bond.^{1,2} When the substrates are *N*-tosyl-protected 6-alkynyl-3,4-dihydro-2*H*-pyridines the intramolecular cyclization is prevented and an intermolecular reaction with external oxidants can be featured. Among various oxidants tested the most promising are pyridine-oxides derivatives. The oxidation of the triple bond occurs with high region and stereoselectivity, thus giving access to conjugated dienones.³ When the substrate enyne is suitably functionalized, an intramolecular trapping of the gold activated triple bond can be featured, paving the way to fused heterocycle systems.



References

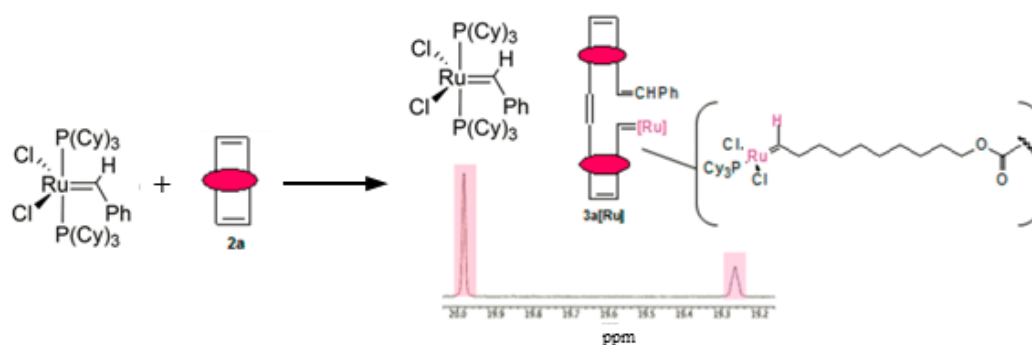
1. A. Oppedisano, C. Prandi, P. Venturello, A. Deagostino, G. Goti, D. Scarpi, E. G. Occhiato, *J. Org. Chem.* **2013**, 78, 11007-11016.
2. D. Scarpi, S. Begliomini, C. Prandi, A. Oppedisano, A. Deagostino, E. Gómez-Bengoa, B. Fiser, E. G. Occhiato, *Eur. J. Org. Chem.* **2015**, DOI: 10.1002/ejoc.201500205.
3. L. Zhang, *Acc. of Chem. Res.* **2013**, 47, 877-888.

Snapshot of Ruthenium–Carbene–Resorc[4]arene Complex in an Olefin Metathesis Reaction

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Previously, we envisaged the synthesis of resorc[4]arenes featuring eleven carbon side chains ending with a vinylidene group, in order to incorporate *via* metathesis reaction the macrocycles into polymeric architectures with intriguing mechanical properties.¹ Undecenyl resorc[4]arene **1a**, which featured the simplest pattern of substituent, was submitted to olefin metathesis using the second generation Grubbs complex as the catalyst. Depending on the reaction conditions, different products were isolated: a bicyclic alkene **2a**, a linear dimer **3a**, and a cross-linked homopolymer **P1a**.² With regard to the mechanistic pathway, we were able to detect for the first time the formation of a ruthenium-carbene-resorc[4]arene complex during the metathesis reaction of resorc[4]arene olefin **2a** with the first generation Grubbs catalyst in CDCl₃, by using high-resolution (600 MHz) ¹H, ³¹P NMR and DOSY spectroscopy.³ We developed an NMR analytical protocol, which proved capable of yielding both qualitative and quantitative information. In the first case, we were able to identify the complex **3a[Ru]** as a key intermediate in the ROM-CM sequence of reactions, giving us a definitive proof of the previously hypothesized mechanism. As a further feedback of the pathway, we performed a quantitative analysis using benzene in the place of CDCl₃, due to the poor stability of the catalyst in such a solvent. The reaction allowed the isolation of decomposition products of the **2a[Ru]** complex, which, due to the presence of still reactive alkene functions, proved to behave as propagating alkylidene species leading to further decomposition products.



References:

1. Christopher W. Bielawski, Robert H. Grubbs, *Progress in Polymer Science*, **2007**, 32, 1-29.
2. Francesca Ghirga, Ilaria D'Acquarica, Giuliano Delle Monache, Sara Toscano, Luisa Mannina, Anatoly P. Sobolev, Franco Ugozzoli, Domenico Crocco, Riccarda Antiochia, Bruno Botta, *RSC Advances*, **2013**, 3, 17567-17576.
3. Federica Aiello, Federica Balzano, Francesca Ghirga, Ilaria D'Acquarica, Bruno Botta, Gloria Uccello-Barretta, Deborah Quaglio, *European Journal of Organic Chemistry*, 2407-2415.

Efficient Suzuki-Miyaura micellar Cross-Coupling in water, at room temperature and under aerobic atmosphere. Organic materials going green.

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Micellar coupling enables carrying out popular and versatile reactions like Suzuki-Miyaura, Sonogashira, Stille, Buchwald-Hartwig, aromatic nucleophilic substitution and many more in water environment and very frequently at room temperature, unregarding to the water solubility of reagents and products.(1) Literature reports an increasing number of “designer” surfactant specifically engineered to perform such kind of reaction.(2) Alongside, authors also explored the potentials of well established industrial surfacts like Triton X-100 and the Tween/Span series with comparable results. So far micellar coupling enabled a dramatic reduction of the overall E factor in synthetic pathways relevant for the synthesis of natural products and drugs. It is only very recently that the field of organic conjugated materials began to take into account concepts like sustainability, atom economy and E-factor. Motivated by our experience with both the encapsulation of organic fluorophores in micelles (3) and by our established experience in the field of organic semiconductors, we here present very efficient protocols for Suzuki-Miyaura, Stille and Buchwald Hartwig amination reactions representing the key steps for the preparation of molecular and polymeric semiconductors. Notably, all protocols we developed are oxygen insensitive, require moderate heating or no heating at all and feature strongly reduced reaction times with respect to the standard organic solvents enforced protocols. Reactions can be easily scaled up from hundreds of milligrams to tens of grams without relevant changes in conditions. Alongside with the demonstration of the reactions scope and efficiency, we will also discuss the very peculiar aspects ruling the kinetics and in some cases the chemo selectivity of the processes we developed.

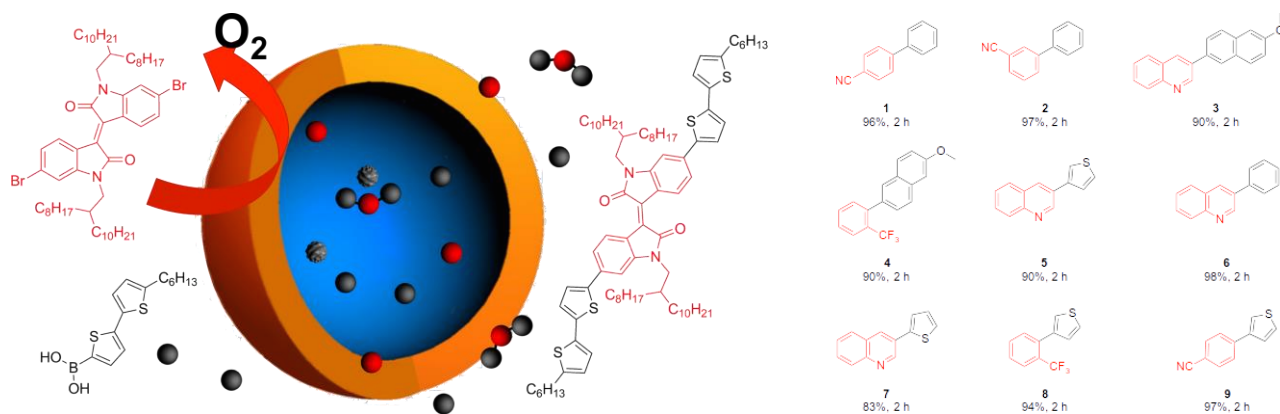


Figure 1. Schematic representation of an oxygen insensitive, water based micellar coupling. Examples of reactions performed (red for the fragment originally carrying the halogen and black for the boronic derivative)

References: 1). Lipshutz, B.H., 2017. When Does Organic Chemistry Follow Nature’s Lead and “Make the Switch?” The Journal of Organic Chemistry, 82(6), pp.2806–2816. 2). Lipshutz, B.H., 2012. “Designer-”Surfactant-Enabled Cross-Couplings in Water at Room Temperature. Aldrichimica acta, 45(1), p.3. 3). Mattiello, S. et al., 2016. Self-Assembled Dual Dye-Doped Nanosized Micelles for High-Contrast Up-Conversion Bioimaging. Advanced Functional Materials. 4) Mattiello, S. et al., 2017. Suzuki–Miyaura Micellar Cross-Coupling in Water, at Room Temperature, and under Aerobic Atmosphere. Organic Letters, 19(3), pp.654–657

TiCl₄-Assisted Protocols in Organic Synthesis: the Case of Amides and β -Enaminones

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Titanium tetrachloride (TiCl₄) is a Lewis acid largely used in organic synthesis that has a strong affinity for oxygen-containing organic compounds.(1)

In our research activity, we had the opportunity to observe how TiCl₄ is able to coordinate to the oxygen atom by increasing the reactivity of carbonyl-containing compounds towards nucleophiles or forming a good leaving group.(2)

TiCl₄ was used to achieve the direct one-pot conversion of aldehydes and hydroxylamine into nitriles (3) and for condensing carboxylic acids with amines to obtain the corresponding amides.

TiCl₄ can also be used in combination with a tertiary amine (NR₃), thus forming the TiCl₄/NR₃ reagent system widely used for the preparation of titanium enolates for applications in aldol and related reactions in organic synthesis.(4)

The TiCl₄/NR₃ reagent system can easily generate an iminium ion that can evolve forming an organotitanium compound useful in the formation of carbon-carbon bonds.

The reaction of variously substituted aromatic acyl chlorides in methylene chloride with triethylamine and TiCl₄, by using two different experimental procedures (Method A and Method B), afforded alternatively the corresponding amides or β -enaminones as unique or major products.

The reaction occurs through the formation of the TiCl₄/NR₃ reagent system that, depending on the adopted experimental procedure, evolves differently generating two alternative reaction paths that provide the amide or β -enaminone, both important building blocks in organic synthesis.

The two developed protocols were also applied successfully to a series of tertiary amines. The reactions, modulated by the presence of TiCl₄, provided the corresponding amides or β -enaminones with satisfactory yields.

1. a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789-2834; (b) Mukaiyama, T. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 817-826.
2. a) Di Gioia, M. L.; Leggio, A.; Le Pera, A.; Liguori, A.; Siciliano, C. *Eur. J. Org. Chem.* **2004**, 463-467; b) Di Gioia, M. L.; Leggio, A.; Le Pera, A.; Liguori, A.; Pitrelli, A. F.; Siciliano, C. *Protein and Peptide Letters* **2005**, *12*, 357-362; c) Di Gioia, M. L.; Belsito, E. L.; Leggio, A.; Leotta, V.; Romio, E.; Siciliano C.; Liguori, A. *Tetrahedron Lett.* **2015**, *56*, 2062-2066; d) Di Gioia, M. L.; Leggio, A.; Guarino, I. F.; Leotta, V.; Romio, E.; Liguori A. *Tetrahedron Lett.* **2015**, *56*, 5341-5344.
3. A. Leggio, E. L. Belsito, S. Gallo and A. Liguori; *Tetrahedron Letters*, **2017**; 58:1512-1514.
4. a) Periasamy. M *Arkivok* **2002**, 151-166.

Which reaction step controls regio selectivity in CuCl₂-catalyzed cyclization of alkynyl-substituted ureas and carbamates?

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One among the most powerful methods for the synthesis of biologically important heterocycles from simple unsaturated precursors is transition metal-catalyzed intramolecular cyclization (1). In this context, copper catalysts are very attractive thanks to their low cost, tolerance toward many reactive functional groups and convenient reaction conditions. Recently, three of the Authors (EMB, SG, and GB) developed a simple and efficient method of alkoxyhalogenation of alkynyl ureas involving Cu(II) salts (2) as a catalyst in the presence of N-halosuccinimides. Spurred by such results, we wished to extend the methodology toward the synthesis of haloalkylidene-substituted heterocycles with carbamates as precursors: at variance with our expectation, however, the cycles tend to close on the nitrogen, meaning that electronic effects control the reaction regiochemistry.

With the aim of elucidating the reaction mechanism and the motivations behind the stereochemical control and change in regiochemistry, Gibbs energy cyclization profiles are explored via DFT calculations. Four possible pathways arising from possible complexes between phenyl urea and CuCl₂ are followed leading to non trivial results; while the formation of urea dimers inhibits catalysis if CuCl₂ coordinates to the carbonyl oxygen, imposes coordination to the alkyne and controls the stereo selectivity, the relative energetic behavior of the two remaining paths rationalizes the regio selectivity. A parallel investigation is also carried out for phenyl and tosyl carbamate: it emerges that the tosyl group markedly influences the total energetics and that a detailed consideration of the possible acid-base equilibria is required to rationalize the region and stereo selectivity of the products.

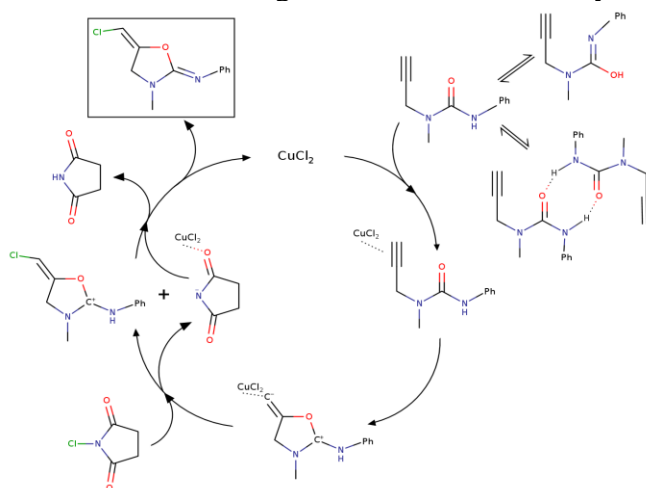


Figure 1: Proposed mechanism of the Cu(II)-catalyzed reaction on urea. The mechanism consists of: preequilibrium, cyclization, chloruration from NCS, deprotonation.

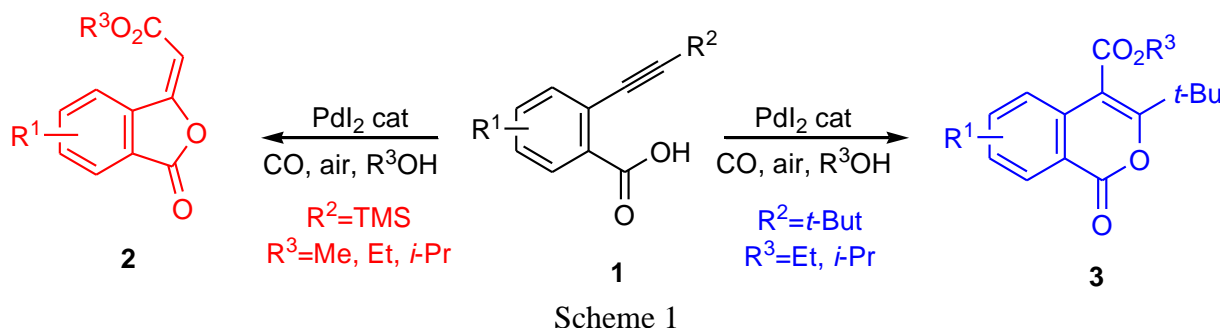
1. Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, 96, 49. 2. Gazzola S.; Beccalli, E. M.; Borelli, T.; Castellano, C.; Chiacchio, M. A.; Diamante, D.; Brogini, G. *J. Org. Chem.* **2015**, 80 (14), 7226.

Divergent Syntheses of (*E*)-3-Isobenzofuran-1-(3*H*)-one and (1*H*)-Isochromen-1-one Derivatives by Palladium-Catalyzed Carbonylation of 2-Alkynylbenzoic Acids

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PdI₂-catalyzed oxidative carbonylation of acetylenic substrates bearing a suitably placed nucleophilic group is a powerful methodology for the direct synthesis of carbonylated heterocycles¹. We report here a novel method for the synthesis of functionalized (*E*)-isobenzofuranone **2** and isochromenone **3** derivatives based on PdI₂-catalyzed oxidative heterocyclization-carbonylation of 2-alkynylbenzoic acids **1** (Scheme 1).



Scheme 1

Reactions were carried out at 100°C and under 20 atm of 4:1 mixture of CO-air, in the presence of catalytic amount of PdI₂ (1 mol %) in conjunction with KI (10 mol %).

We have found that the regiochemical output of the process may be modulated by the nature of substituents on the triple bond and by the nature of alcoholic solvents.

In particular, a TMS group on the triple bond tended to promote the 5-*exo* cyclization mode, with sole formation of desilylated (*E*)-3-isobenzofuran-1-(3*H*)-ones **2**, while a *tert*-butyl group, with EtOH or *i*-PrOH as the solvent, favored the 6-*endo* cyclization mode, with exclusive formation of (1*H*)-isochromen-1-ones **3**. Products were obtained in good isolated yields (60-95%), and the structure of some representative products were confirmed by XRD analysis.

The heterocyclic derivatives synthesized in this work belong to particularly important classes of heterocycles, known to possess a wide range of biological activities.

1. (a) Wu, X.-F.; Neumann, H.; Beller, M. *Chem Rev.* **2013**, *113*, 1-35. (b) Gabriele, B.; Mancuso, R.; Salerno, G. *Eur. J. Org. Chem.* **2012**, 6825-6839

Eliciting specific humoral and cellular immune response by self-adjuvanting gold nanoparticles carrying tumor-associated MUC1 glycopeptides

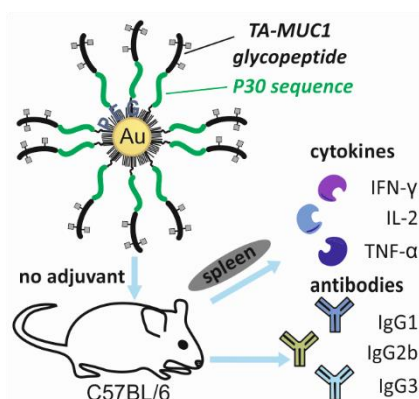
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The extracellular, variable number tandem repeat (VNTR) domain of the MUC-1 (MUC1) glycoprotein is an attractive target for the development of therapeutic cancer vaccines.(1, 2) Tumor-associated MUC1 (TA-MUC1) is found markedly underglycosylated compared to MUC1 on healthy cells, which results in the display of new peptide and carbohydrate epitopes. Furthermore, TA-MUC1 is found overexpressed on cancer cells.(3, 4) Although a number of vaccine design strategies have been pursued, successful anticancer vaccines are yet to be obtained.(5)

We are developing multivalent, TA-MUC1 vaccine candidates based on PEGylated gold nanoparticles (AuNPs)(6) as the antigen carrier and we have shown that they can induce specific antibodies directed against TA-MUC1.(7)

In this contribution we describe the preparation and characterization of novel AuNP-based vaccine candidates. We show that they elicit not only a robust humoral immune response but also a cellular immune response in wild-type mice without the need of any additional adjuvant. We also show that the antisera of vaccinated animals strongly react with several types of human cancer cells demonstrating recognition of TA-MUC1 antigens in the context of human cells. Antisera binding profile demonstrates that antigen delivery via AuNP-based formulations does not affect antigen processing by the immune system. Altogether these results show the great potential of TA-MUC1 vaccine candidates based on PEGylated AuNPs, especially considering their good immunogenicity and self-adjuvanting properties.



1. K. Pillai, M. H. Pourgholami, T. C. Chua, D. L. Morris, *Am. J. Clin. Oncol.* **2015**, *38*, 108-118.
2. M. A. Cheever, J. P. Allison, A. S. Ferris, O. J. Finn, B. M. Hastings, T. T. Hecht, I. Mellman, S. A. Prindiville, J. L. Viner, L. M. Weiner, L. M. Matrisian, *Clin. Cancer. Res.* **2009**, *15*, 5323-5337.
3. S. Nath, P. Mukherjee, *Trends Mol. Med.* **2014**, *20*, 332-342.
4. M. A. Hollingsworth, B. J. Swanson, *Nat. Rev. Cancer* **2004**, *4*, 45-60.
5. K. M. Hossain, A. K. Wall, *Vaccines* **2016**, *4*, doi:10.3390/vaccines4030025.
6. L. Maus, O. Dick, H. Bading, J. P. Spatz, R. Fiammengo, *ACS Nano* **2010**, *4*, 6617-6628.
7. H. Cai, F. Degliangeli, B. Palitzsch, B. Gerlitzki, H. Kunz, E. Schmitt, R. Fiammengo, U. Westerlind, *Biorg. Med. Chem.* **2016**, *24*, 1132-1135.

Natural compounds in cancer prevention: effect of coffee extracts and their main polyphenolic component 5-CQA on oncogenic Ras proteins

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Recent epidemiological studies demonstrate that consumption of healthy foods, especially rich in polyphenols content, might reduce the incidence of cancer and degenerative diseases(1).

In particular, chlorogenic acids (CGAs), esters formed between hydroxycinnamic acids (mainly caffeic and ferulic) and quinic acid occur ubiquitously in food, being 5-caffeoylquinic acid (5-CQA) the most abundant polyphenols in the human diet.(2)

A number of beneficial biological effects, including anti-inflammatory activity, anti-carcinogenic activity and protection against neurodegenerative diseases have been described for CGAs.(3) However, the molecular mechanisms at the basis of these biological activities have not yet been investigated in depth.

Here we reports ours contribute to the elucidation of the molecular mechanism through which 5-CQA carry out its potential as chemoprotective supplements against carcinogenesis. In particular, we evaluated: 1) the molecular interaction between 5-CQA and the proto-oncogenic human protein h-Ras by mean of molecular docking and STD-NMR spectroscopy; 2) the effect of 5-CQA binding on Ras ability to switch-on the proliferative signalling; 3) the biological effects of 5-CQA in *ex vivo* assay using MDA-MB-231 (Breast cancer, Ras^{G13D}) and of SW48 (colon rectal adenocarcinoma) cell lines; 4) the biological effects of enriched CGAs natural extracts obtained from green and roasted coffee beans.

References

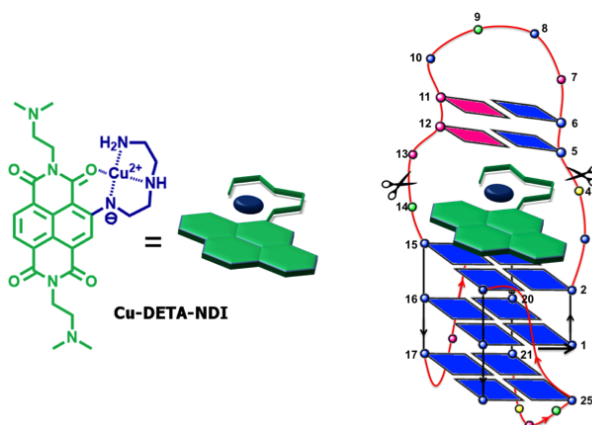
- 1 C.-J. Weng and G.-C. Yen, *Cancer Treatment Reviews*, 2012, **38**, 76.
- 2 M. N. Clifford, *Journal of the Science of Food and Agriculture*, 2000, **80**, 1033.
- 3 (a) R. Feng, Y. Lu, L. L. Bowman, Y. Qian, V. Castranova and M. Ding, *Journal of Biological Chemistry*, 2005, **280**, 27888; (b) H. S. Shin, H. Satsu, M.-J. Bae, Z. Zhao, H. Ogiwara, M. Totsuka and M. Shimizu, *Food Chemistry*, 2015, **168**, 167; (c) L. Amigoni, M. Stuknytė, C. Ciaramelli, C. Magoni, I. Bruni, I. De Noni, C. Airoidi, M. E. Regonesi and A. Palmioli, *Journal of Functional Foods*, 2017, **33**, 297; (d) G. Oboh, O. Agunloye, A. Akinyemi, A. Ademiluyi and S. Adefegha, *Neurochem Res*, 2013, **38**, 413.

Synthesis and Binding Properties of a new Selective Scissoring Tool for Quadruplex Nucleic Acids.

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It has been shown that G-quadruplex structures (G4s) have regulatory functions for telomere extension and maintenance, playing an important role in cancer biology. In addition, G4s involved in the life cycle of different viruses have been reported. Consequently, G4 selective ligands represent potential anticancer and antiviral agents. To date, more than seven thousands stabilizing G4 ligands have been published, but the fairly selective cleavage of G4s has only been achieved once, on intramolecular telomeric G4s. (1) Nowadays, no effective and selective G4s-scissoring agents have been reported. In this frame, we synthesized and characterized a tri-substituted naphthalene diimide (NDI) embedding a diethylenetriamine (DETA) substituent (named **Cu-DETA-NDI**), which selectively coordinates Cu(II) at physiological pH with a very high apparent binding constant ($\log\beta = 17.3$). (2)



Tri-substituted naphthalene diimides (NDIs) are known as potent G4 binding small molecules, with high affinity and reversibility, while the copper complexes are well known as catalytic metallodrug, (3) also targeting G4 nucleic acids. The selective oxidation is a ROS mediated process catalysed by Cu(II) under oxidative stress. In the present study, we have investigated ligand stability using ascorbate (1 equiv.) and H₂O₂ (4 eq.) at neutral pH, confirming that **Cu-DETA-NDI** binding with G4 is fundamental to maintain the ligand undamaged. Thanks to his copper complex moiety directly embedded on the NDI core, it delivers the copper coordination sphere in close proximity to G4s, opening the opportunity to achieve an effective and site-selective cleavage.

Acknowledgment: This work was supported by ERC Consolidator (grant No. 615879)

References:

1. Yu, Z.; Han, M.; Cowan, J. A., *Angew. Chem. Int. Ed.* **2015**, 54 (6), 1901-1905.
2. Yu, Doria, F.; Amendola, V.; Grande, V.; Bergamaschi, G.; Freccero, M., *Sensors and Actuators B: Chemical* **2015**, 212, 137-144.
3. Yu, Qin, X. Y.; Liu, Y. N.; Yu, Q. Q.; Yang, L. C.; Liu, Y.; Zhou, Y. H.; Liu, J., *ChemMedChem* **2014**, 9 (8), 1665-71.

Amino- and guanidinoglycoside based vectors for cell transfection

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The development of efficient alternatives to viral vectors is a hot subject for the uptake of high molecular weight biomolecules like peptides, proteins and genes that can't spontaneously cross the cell membrane. Aminoglycosides, such as neomycin (Neo, structure A in Figure 1) are a class of naturally occurring antibiotics while guanidinoglycosides, such as guanidinoneomycin (GNeo, structure B in Figure 1) are aminoglycosides where all the amino groups are converted into guanidino

groups. The group of Prof. Tor has shown that guanidinoglycosides are very efficient molecular transporters facilitating the intracellular delivery of high molecular weight cargos at nanomolar concentrations by binding selectively cell surface heparan sulfate proteoglycans¹.

Recently, our group has been involved in the synthesis of aminoglycoside and guanidinoglycoside-based vectors for

an efficient gene and drug delivery^{2,3}. Since then different carriers have been developed including cationic lipids systems (using calix[4]arenes and cyanuric chloride as scaffolds) and colloids such as PEG-PEI nanogels decorated with Gneo. The synthetic part along with biological tests on cell viability and transfection efficiency will be reported.

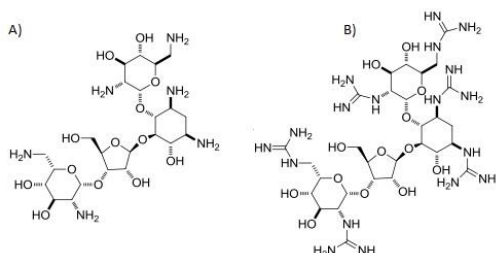


Fig 2 A) Neomycin (Neo) and

B) guanidinoneomycin (GNeo)

References:

- 1) Sarrazin, S.; Wilson, B.; Sly, W.S.; Tor, Y.; Esko J.D. *Molecular Therapy*, 2010, 18, 1268
- 2) Ghilardi, A.; Pezzoli, D.; Bellucci, M.C.; Malloggi, C.; Negri, A.; Sganappa A.; Tedeschi, G.; Candiani, G.; Volonterio, A., *Bioconj. Chem.*, 2013, 24, 1928
- 3) Sganappa, S.; Wexselblatt E.; Bellucci M.C.; Esko J.D.; Tedeschi G.; Tor Y.; Volonterio A.; *ChemBioChem*, 2017, 1, 119

Discovery of a new class of GPBAR1 modulators

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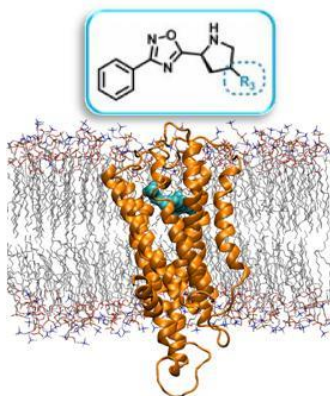
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Since the discovery of the G-protein-coupled bile acid receptor GPBAR1 (also known as TGR5), there has been an increased interest to pharmacologically modulate this target involved in lipids and glucose metabolism disorders such as nonalcoholic steatohepatitis, hypercholesterolaemia, hypertriglyceridaemia, and type 2 diabetes mellitus (1,2).

Most of our previous research programs were focused to explore the chemical space of the bile acids, the endogenous GPBAR1 ligands (3-7). However, the specificity of bile acid derivatives is not restricted to this receptor and their clinical use can undergo some limitations exerting a variety of pathophysiological and pharmacological activities (8). Thus, recently, our investigations have been shifted towards the development of GPBAR1 non-bile acid modulators, with the final aim of identifying privileged chemical scaffolds able to exert a fine-tuning modulation of this receptor. In this context, using a rational structure-based design and a multidisciplinary approach, we have developed a library of novel active GPBAR1 ligands, that might provide new opportunities in the treatment of several metabolic disorders.



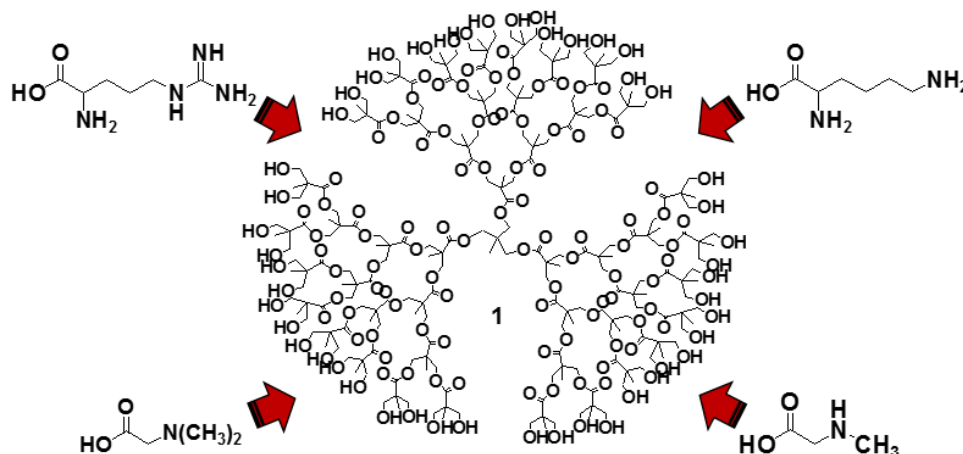
References: 1. Fiorucci, S., Cipriani, S., Baldelli, F. & Mencarelli, A. *Prog. Lipid Res.* **2010**, 49, 171–185. 2. Tiwari, A. & Maiti, P. *Drug Discovery Today* **2009**, 14, 523–530. 3. Sepe S. V.; Renga, B.; Festa, C.; D'Amore, C.; Masullo, D.; Cipriani, S.; Di Leva, F. S.; Monti, M. C.; Novellino, E.; Limongelli, V. et al *J. Med. Chem.* **2014**, 57, 7687–7701. 4. Festa C. Renga, B.; D'Amore, C.; Sepe, V.; Finamore, C.; De Marino, S.; Carino, A.; Cipriani, S.; Monti, M.C.; Zampella, A.; Fiorucci, S. *J. Med. Chem.* **2014**, 57, 8477–8495. 5. Di Leva; F. S.; Festa, C.; Renga, B.; Sepe, V.; Novellino, E.; Fiorucci, S.; Zampella, A. Limongelli, V. *Scientific Reports*, **2015**, 5, 16605. 6. Sepe, V.; Renga, B.; Festa, C.; Finamore, C.; Masullo, D.; Carino, A.; Cipriani, S.; Distrutti, E.; Fiorucci, S.; Zampella, A. *Steroids*, 2015, 105, 59-67. 7. Finamore, C.; Festa, C.; Renga, B.; Sepe, V.; Carino, A.; Masullo, D.; Biagioli, M.; Marchiano, S.; Capolupo, A.; Monti, M. C.; Fiorucci, S.; Zampella, A. *Scientific Reports*, 2016, 6, 29320. 8. Xu Y. *J. Med. Chem.* **2016**, 59(14):6553-79.

New promising vectors for gene delivery by a step-wise functionalization of a polyester-based non toxic dendrimer with *N,N*-dimethylglycine, *N*-methylglycine, lysine and arginine

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Polycationic dendrimers are able to electrostatically bind genetic material forming nanosized complexes (polyplexes). They result very appealing for applications as non-viral vectors to bring DNA or RNA within genetically defective cells for treating or solving several diseases including cancer. Commonly used cationic polymers (*b*PEI) or dendrimers (PAMAM), thanks to a good buffer capacity due to the several weakly basic amines in their structure, once in the cell, induce an osmotic swelling of endosomes that contain the polyplexes leading to content release (1). For this reason *b*PEI and PAMAM are endowed with high transfection efficiencies (2) but, if not chemically modified do not find real applications in gene therapy because of their cytotoxicity. It is also known that dendrimers containing arginine improve *si*RNA cellular uptake (3) and are equipped with higher efficiency of transfection and reduced toxicity (4, 5). In respect of this background in this communication we report the setting up of versatile protocols to introduce on the hydrolysable polyester-based fourth generation dendrimer (**1**) previously prepared, a mixture of *N,N*-dimethylglycine, *N*-methylglycine, lysine, and arginine. The synergic presence of nitrogen atoms with different pK_a and the arginine moiety should have promoted the cellular up-take and should have contributed to an optimal buffering capacity enhancing the endosomal escape and improving transfection activity.



The obtained products in the hydrochloride forms were subjected to volumetric titration to determine experimental molecular weight and to NMR analysis to confirm the structures. Potentiometric titration to calculate the buffer capacity (β) and then the average buffer capacity and the NMR characterization of all the intermediates were also performed.

References: 1. Behr, J. P. *Chimia* **1997**, *51*, 34-36. 2. Akinc, A.; Thomas, M.; Klibanov, A. M.; Langer, R. *J Gene Med.* **2005**, *7*, 657-663. 3. Liu, X.; Liu, C.; Zhou, J.; Chen, C.; Qu, F.; Rossi, J. J.; Rocchi, P.; Peng L. *Nanoscale* **2015**, *7*, 3867-3875. 4. Kim, T.; Bai, C. Z.; Nam, K.; Park, J. *J. Control. Release* **2009**, *136*, 132-139. 5. Peng, Q.; Zhu, J.; Yu, Y.; Hoffman, L.; Yang, X. *J. Biomater. Sci. Polym. Ed.* **2015**, *26*, 1163-1177.

New polymethine dyes for photodynamic therapy

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Photodynamic therapy (PDT) (1) is an emerging non-invasive technique for the treatment of cancer. It involves the systemic or topic administration of a photosensitizer (PS) that, after its excitation with light at a specific wavelength, is able to produce reactive oxygen species (ROS), causing damage to targeted cancer cells. An ideal PS should fulfil specific, clinically relevant requirements: i) sharp, intense absorption in the biological tissues' transparency window (600-900 nm), ii) good solubility in the biological environment, iii) low dark toxicity but strong photo-cytotoxicity and iv) a high ROS sensitization quantum yield. Moreover, an ideal PS should possess a high specificity for cancer tissues and be easily and rapidly removed from the body post-treatment.

Even if some important developments have been achieved and some porphyrin-based PSs are already commercially available and clinically used (2), some problems still exist. Haematoporphyrin derivative-mediated PDT has several clinical disadvantages, including prolonged skin photosensitivity (4 weeks), relatively low quantum yield of singlet oxygen, and a limited depth of associated tissue damage of 2-5 mm. Consequently, there has been extensive research into the design of improved alternative PSs aimed at overcoming these drawbacks. Polymethine dyes (3) deserve to be counted among the innovative potential PS classes for PDT for their strong absorption in the tissue transparency window (600-800 nm).

In this work we designed and synthesised a new series of near infra-red (NIR) absorbing polymethine dyes with different substitution groups in order to investigate how the structure may influence the capacity of these molecules to produce ¹O₂. The oxygen-generation ability of the new dyes was accessed *in vitro* by the 1,3-diphenylbenzofuran (DPBF) quenching method (4), envisioning their potential use as sensitizers for PDT. On the most promising PSs, ROS generation, cytotoxicity, cell death and DNA damage analyses were performed after the photodynamic treatment. Here we present the results obtained along with a structure-activity relationship discussion of these new potential photosensitizers for PDT. In particular, two of these squaraine dyes showed very interesting PDT performances as well as co-localization in mitochondria (5).

References: 1. A.M. Rkein, D.M. Ozog. *Dermatol. Clin.* 32 (2014) 415–425. 2. R.R. Allison, C.H. Sibata. *Photodiagn. Photodyn. Ther.* 7 (2010) 61–75. 3. R.R. Avirah, D.T. Jayaram, N. Adarsh, D. Ramaiah. *Org. Biomol. Chem.* 10 (2012) 911–920. 4. Y. Prostota, O.D. Kachkovsky, L.V. Reis, P.F. Santos. *Dyes Pigment* 96 (2013) 554-562. 5. L. Serpe, S. Ellena, N. Barbero, F. Foglietta, F. Prandini, M. P. Gallo, R. Levi, C. Barolo, R. Canaparo, S. Visentin. *Eur. J. Med. Chem.* (2016), 113, 187-197.

From Melanins to OLED Devices: Taking Inspiration from the Black Human Pigments for the Design of Innovative Electroluminescent Materials.

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The growing expansion and impact of OLED devices in our everyday life have stimulated the synthesis of a wide plethora of electroluminescent materials with the aim of improving the efficiency and the life-time of the device as well as of selectively tuning the wavelength of the emitting light. In the frame of our research activity aimed at exploring the role of melanins, the dark pigments found in mammalian skin, hair and eyes, as soft organic semiconductors in bio-electronic devices (1), we have undertaken a new challenge: to obtain innovative electroluminescent compounds from black melanin pigments.

The strategy of this research activity has been based on the use of melanin precursors, such as 5,6-dihydroxyindole and dopamine, as starting compounds for the synthesis of fluorescent or phosphorescent materials for applications as emitting layer in OLED devices (2).

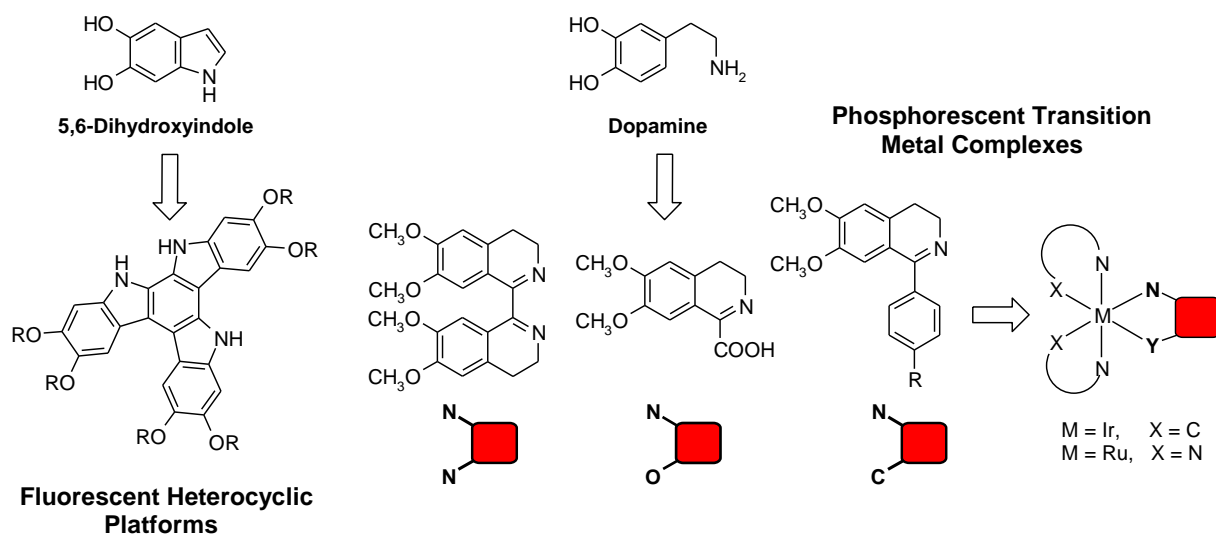


Figure 1

In this communication we will discuss the synthesis of a set melanin-inspired electroluminescent compounds; we will report on their photo-physical and electrical properties; the fabrication and characterization of the corresponding OLED devices will also be presented.

References

- (1) Pezzella, A.; Barra, M.; Musto, A.; Navarra, A.; Alfé, M.; Manini, P.; Parisi, S.; Cassinese, A.; Criscuolo, V.; d'Ischia, M. *Mater. Horiz.* **2015**, *2*, 212.
- (2) Manini, P.; Criscuolo, V.; Ricciotti, L.; Pezzella, A.; Barra, M.; Cassinese, A.; Crescenzi, O.; Maglione M.G.; Tassini, P.; Minarini, C.; Barone, V.; d'Ischia, M. *ChemPlusChem*, **2015**, *80*, 919.

Modification of biopolymers in ionic liquids (ILs) media to access added value materials

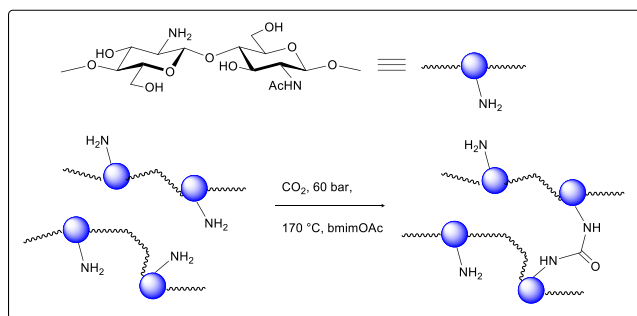
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Ionic liquids (ILs) are low-melting organic salts, generally composed of an organic cation and a wide range of anions. ILs are characterized by unique physicochemical properties comprising of negligible vapor pressure under ambient conditions, wide liquid range, low flammability, high ionic and thermal conductivity, wide electrochemical potential window, excellent thermal, chemical and radiochemical stability.

Thanks to the variability of the constituent ions, it is possible to tune these properties, and this is the reason why they are often referred to as designer solvents. In particular, some ILs are able to disrupt the hydrogen bonding pattern present in native biopolymers. Since the pioneering work from Rogers *et al.* (1), ionic liquids (ILs) have become a potential new medium to dissolve biopolymers (eg chitin, cellulose). For instance, ILs permitted the dissolution of cellulose up to 22% w/w. Several works employed ILs and biomass, and allowed for the preparation of some new materials in the form of films, microspheres, nanofibers, hydrogels, composites, or functionalized derivatives (2).

Among the biopolymers, chitosan is an aminopolysaccharide consisting of beta-(1→4)-linked D-glucosamine units and is directly obtained by de-*O*-acetylation of chitin. Chitosan is biodegradable and non-toxic, and displays remarkable intrinsic properties such as antifungal, mucoadhesive and haemostatic properties, and antibacterial activity, all making chitosan and chitosan-based materials of interest for developing future biomedical applications (3). Cross-linking the



Scheme 1 – Chitosan crosslinking reaction.

chitosan backbone is one way to obtain variation of the pristine biopolymer, and we investigated this kind of modification in ILs by using CO₂ as a safe, non toxic, economical C1 cross-linking agent (Scheme 1). (4) Herein, the results of this cross-linking of chitosan, a reaction which can't be performed in aqueous media, are reported, as well as the fundamental role played by the IL. Also, our latest results in the area of obtaining new materials from the bio-feedstock by modifying them in ILs, are presented.

References: 1. Swatloski R. P., Spear S. K., Holbrey J. D., Rogers R. D. *J.A.C.S.* **2002**, 124, 4974. 2. Silva S.S., Mano F.J., Reis R.L. *Green Chem.* **2017**, 19, 1208. 3. LogithKumar R., KeshavNarayan A., Dhivya S.; Chawla A., Saravanan S., Selvamurugan N. *Carbohydr. Polym.*, **2016**, 151, 172. 4. Mezzetta A., Guazzelli L., Chiappe. C. *Green Chem.* **2017**, 19, 1235.

Towards Integrated Continuous-Flow Fractionation and Functionalisation of Technical Lignins

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Lignin is the second-most abundant renewable polymer, contributing as much as 30% of the weight, and as much as 40% of the energy content of lignocellulosic biomass.(1,2) Sustainable and efficient biorefinery processes should not only aim at the valorization of lignin in form of fuels, but also in form of a versatile resource for oligo- and polymeric starting materials for the chemical industries.(2) Isolated lignins are highly complex polyphenols, exhibiting plant-specific compositions and linkage motifs as well as isolation-depending linear or branched polymer chains. The lack of a uniform defined primary structure, and the rather random arrangement of phenyl-propanoid (C9) polyphenols, prevents easy adoption of lignin, or modified lignins, as substitutes for oil-based polymers.(1) The rather broad distribution of molecular weights of the oligomers and polymers that generally characterizes most lignins presents another significant drawback to applications. However, regardless of the plant specific structural variations, lignin can be seen as naturally available, 'functionally decorated' polystyrene-polypropylene composite.

Fractionating lignin using physico-chemical principles(3) or filtration techniques(4), and immediately chemically re-functionalizing the (fractionated) lignin in a way that derivatives are obtained which show a more homogenized functional group profile with respect to both their 'nature'-specific and their isolation-specific differences will facilitate, or even permit for the first time, the exploitation of new fields of application of lignin.

In one of our current research line, we have conceptually designed a new segmented continuous-flow-inspired set-up for the fractionation of lignins and the subsequent chemical functionalisations of the low polydispersity lignin fractions without un-handling steps.

Up to date, two important types of industrially available lignins, *i.e.*, wheat straw organosolv lignin and softwood Kraft lignin, have been fractionated under optimized segmented flow conditions, adopting insights from non-scalable batch versions.(3) Moreover, based on advanced analytical data(5,6), selected fractions have been used for the production of structurally homogenized lignin oligomers selectively targeting the various types of hydroxyl groups in the lignin backbone. Fractionated and chemically tailored lignins - also in form of tailor-made combinations of fractions - are currently optimized for exploitation in stimuli-responsive polymers,(7,8) industrial coatings and fiber production.

The presentation thus highlights the crucial features of the continuous-flow-based fractionation-functionalization set-up, as well as the flow-compatible chemistries used for targeted functionalization of oligo- and polymeric lignins.

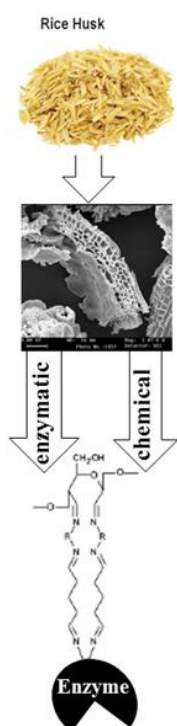
References: 1. M. Aresta, A. Dibenedetto and F. Dumeignil, *Biorefineries, An Introduction*. De Gruyter, Berlin, Boston, **2015**. 2. T. Q. Hu, *Chemical Modification, Properties, and Usage of Lignin*. Kluwer Academic/plenum Publishers, New York, **2002**. 3. H. Lange, P. Schiffels, M. Sette, O. Sevastyanova and C. Crestini, *ACS Sustain. Chem. Eng.* **2016**, *4*, 5136–5151. 4. O. Sevastyanova, M. Helander, S. Chowdhury, H. Lange, H. Wedin, L. Zhang, M. Ek, J. F. Kadla, C. Crestini and M. E. Lindström, *J. Appl. Polym. Sci.* **2014**, *131*, e40799. 5. M. Sette, H. Lange and C. Crestini, *Comput. Struct. Biotechnol. J.* **2013**, *6*, 1–7. 6. H. Lange, F. Rulli and C. Crestini, *ACS Sustain. Chem. Eng.* **2016**, *4*, 5167–5180. 7. A. Duval, H. Lange, M. Lawoko and C. Crestini, *Green Chem.* **2015**, *17*, 4991–5000. 8. A. Duval, H. Lange, M. Lawoko and C. Crestini, *Biomacromolecules* **2015**, *16*, 2979–2989.

Chemo-enzymatic strategies for the synthesis and functionalization of renewable polymers and composite materials

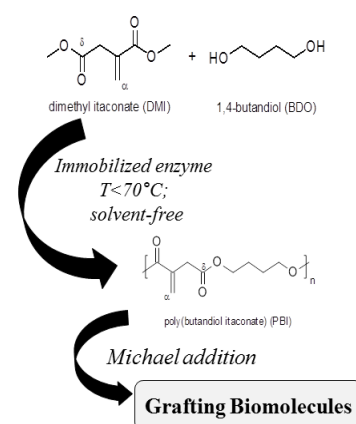
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Enzymes are not only renewable and sustainable catalysts but they are also endowed with unique selectivity and activity under mild conditions that enable the fine tuning of chemical structure and function of target products. In the present study, hydrolases (lipases and cutinases) were applied for the synthesis of polyesters (1,2,3) under mild conditions (50-70°C) and in solvent-free systems, while oxido-reductases (laccases) were exploited for the targeted modification of the surface of natural composite materials (e.g. rice husk). (5) The two hydrolases enabled the polycondensation of itaconic acid, a monomer displaying a C=C bond that undergoes isomerization and radical cross linking under the conditions used in conventional chemical polycondensations (T > 150 °C). A number of



renewable monomers (e.g. itaconic acid, azelaic acid, adipic acid, glycerol, 1,4-butanediol, CHDM) were used for the synthesis of polymers and terpolymers with controlled architecture. The resulting polyesters have MW < 2000 Da, a desired properties for functional polyesters used in dermatologic applications or for further chemical elongation. The C=C pendant was fully conserved throughout the polycondensation and prone to further chemical modification through Michael addition. Mild and solvent-free functionalization paved the way to different synthetic routes for anchoring biomolecules on the bio-based polyesters.



Laccases enzymes were used oxidize the cellulose component of rice husk, a widely available composite material made by cellulose, hemicellulose, lignin and SiO₂. The laccase enzymes allowed the introduction of chemical functionalities under mild conditions while preserving the bulk structure of the material. The functionalized matrix was used as solid support (4) for the anchoring of 6 different enzymes that maintained their activities and were successfully applied in the synthesis of esters, polyesters, as well as in the hydrolysis of proteins and oligosaccharides. The same material can be used for the removal of toxic components from effluents.

References:

1. A. Pellis et al. A "Fully renewable polyesters via polycondensation catalyzed by *Thermobifida cellulosilytica* cutinase 1: an integrated approach". *Green Chem.*, 2017, **19**, 490-502.
2. L. Corici et al. L., "Understanding potentials and restrictions of solvent-free enzymatic polycondensation of itaconic acid: an experimental and computational analysis". *Adv. Synth. Cat.*, 2015, **357**, 1763-1774.
3. A. Pellis et al., "Towards feasible and scalable solvent-free enzymatic polycondensations: integrating robust biocatalysts with thin film reactions". *Green Chem.*, 2015, **17**, 1756-1766
4. L. Corici et al., "Large scale applications of immobilized enzymes call for sustainable and inexpensive solutions: rice husk as renewable alternative to fossil-based organic resins." *RSC Adv.*, 2016, **6**, 63256-63270.

Chemical Modifications for the Valorization of Lignin

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Lignin is the most abundant renewable source of poly-aromatic moieties as its annual production is second only to cellulose. This aromatic polymer is biosynthesized for structural purposes in the plant cell walls through oxidative coupling of phenoxy radicals leading to the formation of an extremely complex three-dimensional network. The peculiar chemical nature makes lignin a potential candidate for the replacement of fossil resources. In fact large quantities of lignin by-product are made available yearly from pulping processes, as well as bio-ethanol digestion and saccharification processes. Great research efforts are made worldwide to develop physical, chemical and biological methodologies to exploit lignin as a possible substitute of petroleum-based chemical intermediates. Nevertheless, lignin valorization and upgrade to co-product status is often hindered by its complex and heterogeneous chemical and morphological structure which is strongly influenced by numerous factors, such as the botanical source and the extraction process.

(1)

In this presentation we would like to summarize our results concerning lignin valorization, which mainly focuses on different chemical modification. The valorization of lignin through integrated approaches is of crucial importance to match the requirements of the biorefinery concept, which is a comprehensive utilization of all those lignocellulosic materials consisting of the residual non-food parts of current crops or other non-food sources (known as second-generation feedstock) by converting these biomasses into fuels, energy, chemicals and materials. (2)

The more interesting chemical modifications studied have been:

- i. Allylation: the allylation reaction and the aromatic Claisen rearrangement of the allyl group on lignin as chemical modifications were investigated. This approach is aimed at the development of new lignin-based materials and the improvement of its compatibility and ease of processing. The allylated lignin was used for partial replacement of carbon black in tires industry. (3, 4)
- ii. Epoxidation: oxirane ring were inserted on the phenolic functionalities of lignin by reaction in alkaline water with epichlorohydrin. (5) Epoxidized lignin has been used as bio-based reticulating agent in epoxy resin formulation.
- iii. Carbonation: epoxide groups on lignin were converted into cyclic carbonates by the addition of CO₂ to oxirane rings in ionic liquid. Imidazolium based ionic liquids, acting as both solvents and catalysts, were successfully employed in the carbonation reaction. Moreover, the ionic liquid was reused up to three times without significant loss in activity. (5) Cyclocarbonate lignin was used as bio-based cross-linking agent in polyhydroxyurethane formulation. (6)

References: 1. B.M. Upton, A.M. Kasko. "Strategies for the conversion of lignin to high-value polymeric materials: Review and perspective". *Chemical reviews*, **2015**, 116(4), 2275-2306. 2. S. Fernando, S. Adhikari, C. Chandrapal, N. Murali. "Biorefineries: Current Status, Challenges, and Future Direction". *Energy Fuels*, **2006**, 20(4), 1727-1737. 3. L. Zoia, A. Salanti, P. Frigerio, M. Orlandi. "Exploring Allylation and Claisen Rearrangement as Novel Chemical Modification of Lignin". *BioResources*, **2014**, 9(4), 6540-6561. 4. T. Hanel, L. Castellani, M. Orlandi, P. Frigerio, L. Zoia **2013** "Tyre for vehicle wheels". *Patent No.* US 2013-61803275. 5. A. Salanti, L. Zoia, M. Orlandi. "Chemical modifications of lignin for the preparation of macromers containing cyclic carbonates". *Green Chem.*, **2016**, 18, 4063-4072. 6. A. Salanti, L. Zoia, M. Orlandi. "Utilization of cyclocarbonated lignin as a bio-based cross-linker for the preparation of poly(hydroxy urethane)s". *RSC Advances*, **2017**, 7, 25054-25065.

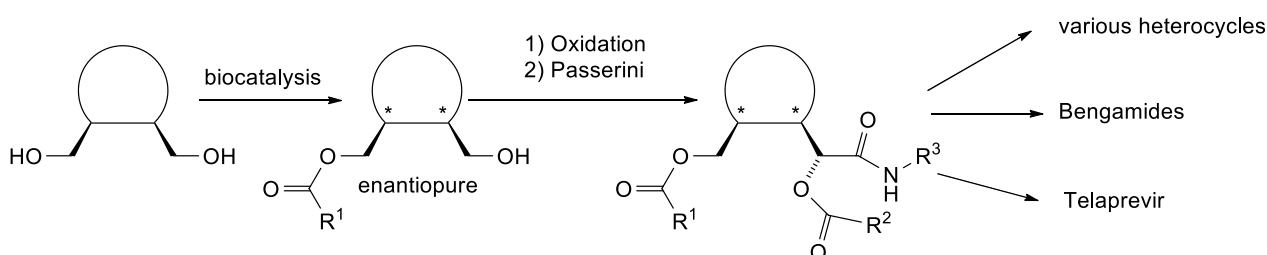
Multicomponent reactions on biocatalytically produced substrates

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Isocyanide-based multicomponent reactions represent a very useful tool for the fast generation of libraries of drug-like substances. However, stereochemical control is still an important and mostly unsolved issue. Due to this problem, and also to the limited availability of chiral starting components, often MCR products are obtained in racemic form. In this lecture I will describe an original approach to enantiopure MCR-derived products, based on the biocatalytic generation of chiral inputs and on their use in diastereoselective multicomponent reactions (1), followed by cyclization reaction (2). In this way, a fast access to interesting polyfunctionalized products and/or unusual heterocycles (3,4) was accomplished.

In particular we have used some chiral, enantiopure, monoesters derived from desymmetrization of cyclic *meso*-diols, as inputs for diastereoselective Passerini reactions mediated or catalysed by Lewis acids. Most of these *meso* diols are bio-based, since they can be derived from renewable biomass. Application to the total synthesis of Telaprevir (5) and Bengamides (6) will also be discussed.



1. Banfi, L.; Basso, A.; Moni, L.; Riva, R., *Eur. J. Org. Chem.* **2014**, 2014, 2005-2015.
2. Banfi, L.; Riva, R.; Basso, A., *Synlett* **2010**, 23-41.
3. Moni, L.; Banfi, L.; Basso, A.; Martino, E.; Riva, R., *Org. Lett.* **2016**, 18, 1638-1641.
4. Moni, L.; Banfi, L.; Basso, A.; Bozzano, A.; Spallarossa, M.; Wessjohann, L.; Riva, R., *Molecules* **2016**, 21.
5. Moni, L.; Banfi, L.; Basso, A.; Carcone, L.; Rasparini, M.; Riva, R., *J. Org. Chem.* **2015**, 80, 3411-3428.
6. Garcia-Ruiz, C.; Sarabia, F., *Marine Drugs* **2014**, 12, 1580-1622.

Photocatalytic Radical Alkylation of Electrophilic Olefins by Benzylic and Alkyl Zinc-Sulfinates

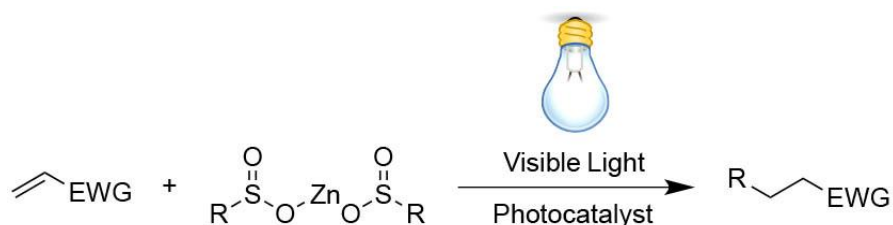
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The decarboxylative coupling of carboxylic acids has numerous applications in photoredox catalysis.(1) In these reactions, monoelectronic oxidation of carboxylate anions, followed by carbon dioxide evolution from the so formed RCOO•, gave entry to nucleophilic radicals (R•) that were found to react with electrophilic alkenes.(2) An interesting alternative for the generation of radical species can be based on sulfinic acids or sulfinates,(3) with the advantage that the oxidation potentials of sulfinates are lower compared to carboxylate anions. A radical-based functionalization strategy that involves the use of sodium and zinc bis(alkylsulfinate) reagents has already been developed by Baran.(4)

Herein we describe a new procedure to accomplish the difficult radical alkylation of electrophilic alkenes using benzylic and alkyl sulfinates in combination with commercially available photocatalysts and visible light irradiation.

Moreover, it is shown that zinc sulfinates can be used for facile not-radical sulfonation reactions with highly electrophilic Michael acceptors.



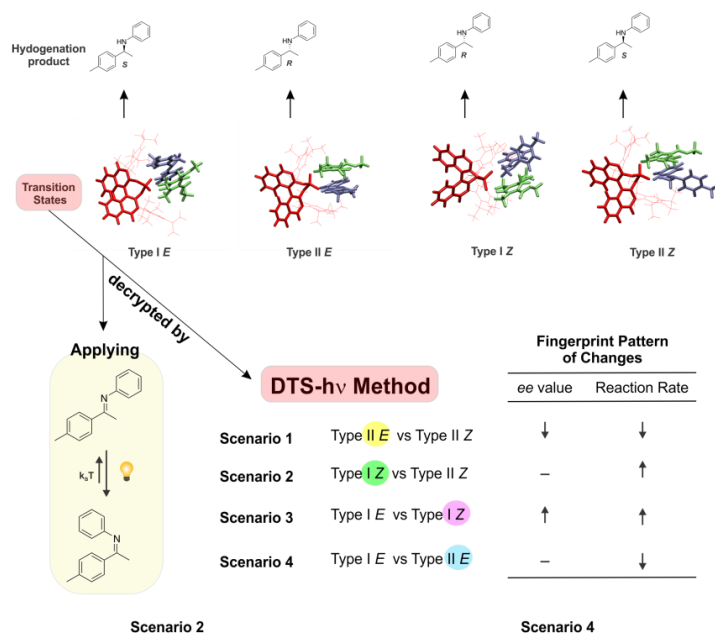
References: 1. (a) Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 5257; (b) Nawrat, C. C.; Jamison, C. R.; Slutskyy, Y.; MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **2015**, *137*, 11270; (c) McCarver, S. J.; Qiao, J. X.; Carpenter, J.; Borzilleri, R. M.; Poss, M. A.; Eastgate, M. D.; Miller, M.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2017**, *56*, 728. 2. (a) Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 10886; (b) Slutskyy, Y.; Jamison, C. R.; Lackner, G. L.; Müller, D. S.; Dieskau, A. P.; Untiedt, N. L.; Overman, L. E. *J. Org. Chem.* **2016**, *81*, 7029. 3. For a review, see: Aziz, J.; Messaoudi, S.; Alami, M.; Hamze, A. *Org. Biomol. Chem.* **2014**, *12*, 9743. 4. (a) Ji, Y.; Brueckl, T.; Baxter, R.D.; Fujiwara, Y.; Seiple, I.B.; Su, S.; Blackmond, D.G.; Baran, *PNAS*, **2011**, *108*, 14411; (b) Fujiwara, Y.; Dixon, J.A.; Rodriguez, R.A.; Baxter, R.D.; Dixon, D.D.; Collins, M.R.; Blackmond, D.G.; Baran, P.S. *J. Am. Chem. Soc.* **2012**, *134*, 1494; (c) Fujiwara, Y.; Dixon, J.A.; O'Hara, F.; Daa Funder, E.; Dixon, D.D.; Rodriguez, R.A.; Baxter, R.D.; Herlé, B.; Sach, N.; Collins, M.R.; Ishihara, Y.; Baran, P.S. *Nature* **2012**, *492*, 95.

Decrypting Transition States by Light (DTS-hv) in Brønsted Acid Catalysis

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In the field of Brønsted acid catalysis, chiral phosphoric acids have been recognized as one of the most prominent class of catalysts because they combine high substrate tolerance with high activity and stereoselectivity (1). Despite their wide applicability (more than 400 asymmetric transformations published), experimental insight into the transition states is very rare and most of the mechanistic knowledge is gained by theoretical calculations.

In the context of our work on the NMR mechanistic investigation on phosphoric acids catalyzed addition of nucleophiles to imines, we sought an alternative method to go deeper into the reaction mechanism. For these transformations ternary complexes are postulated as active transition states. Four different stereochemical arrangements, denominated as Type I Z, Type I E, Type II Z, Type II E are possible considering that the imine can adopt an E- or Z-configuration and the nucleophilic attack can occur from the top (Type II) or the bottom (Type I) of the imine/catalyst binary complex (2,3).



With this background we questioned whether the photoisomerization of double bonds might be used as a mechanistic tool (4). Upon illumination, in the presence of a double bond that can be isomerized without significant photodegradation, with no change in the principal reaction mechanism and when the isomerization is slow or comparable to the enantioselective step, the photoisomerization is affecting only the E/Z-imine ratio with a direct effect on the reaction rate and enantioselectivity. The changes obtained for these values with respect to a dark reaction create a characteristic fingerprint pattern, which can be read directly in terms of transition states. Two model systems were investigated. For the asymmetric transfer hydrogenation of imines the

characteristic fingerprint pattern of changes obtained (increase on reaction rate, no change on enantioselectivity) upon illumination showed the competition between the two Z-transition states (Scenario 2). According to the configuration of the major product the nucleophilic attack to the Z-imine occurs from the bottom side (Type I Z). Whereas, for the nucleophilic addition of acetylacetone to N-Boc protected imines, Type I E and Type II E were identified as the active transition states. The isomerization to the corresponding Z-imine was in fact detrimental for the reaction rate whereas the enantioselectivity was not affected (Scenario 4).

References: 1. Rueping, M.; Parmar, D.; Sugiono E. *Asymmetric Brønsted Acid Catalysis*; Wiley-VCH: Weinheim, 2005. 2. Simón, L.; Goodman, J. M. *J. Am. Chem. Soc.* 2008, 130, 8741-8747. 3. Marcelli, T.; Hammar, P.; Himo, F. *Chem. Eur. J.* 2008, 14, 8562-8571. 4. Renzi, P.; Hioe, J.; Gschwind R. M. *J. Am. Chem. Soc.* 2017, accepted.

Structural and Medium Effects in the Hydrogen Atom Transfer Processes Promoted by Short-Lived Aminoxyl Radicals

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Hydrogen atom transfer (HAT) processes from organic substrates to short-lived aminoxyl radicals such as the phthalimide-*N*-oxyl radical (PINO) are strongly influenced by structural and medium effects. For example we have found that addition of Brønsted or Lewis acids determines a significant deactivation of C-H bonds α to the nitrogen in amides (Figure 1) (1).

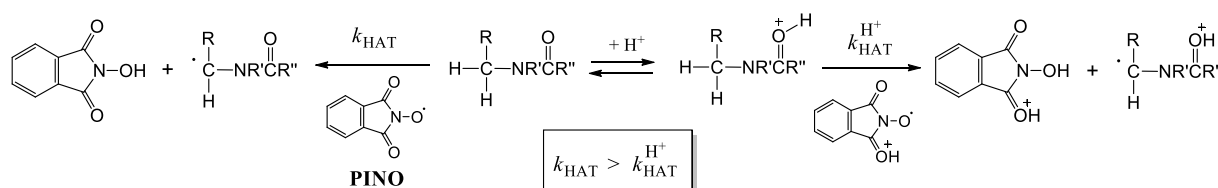


Figure 1

In the HAT from 4-alkyl-*N,N*-dimethylbenzylamines to PINO a change in regioselectivity has been observed by effect of protonation. This change has been successfully applied for selective functionalization of the less activated benzylic C-H bonds *para* to the $\text{CH}_2\text{N}(\text{CH}_3)_2$ group in the aerobic oxidation of 4-alkyl-*N,N*-dimethylbenzylamines catalyzed by *N*-hydroxyphthalimide in acetic acid (Figure 2).

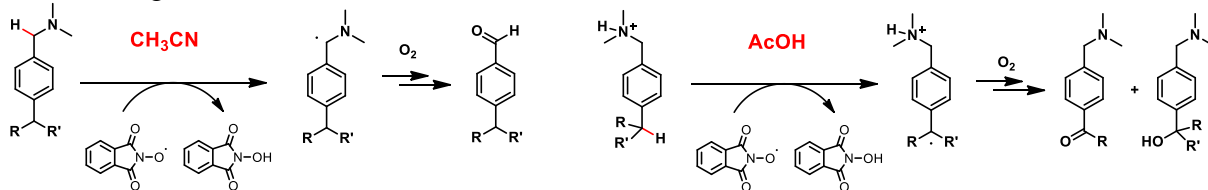


Figure 2

An increase of the HAT reactivity by addition of Brønsted or Lewis acids was instead observed with the quinolinimide-*N*-oxyl radical (QINO) by effect of the protonation or complexation with the Lewis acid of the pyridine nitrogen that leads to a significant decrease of the electron density in the *N*-oxyl radical (Figure 3).

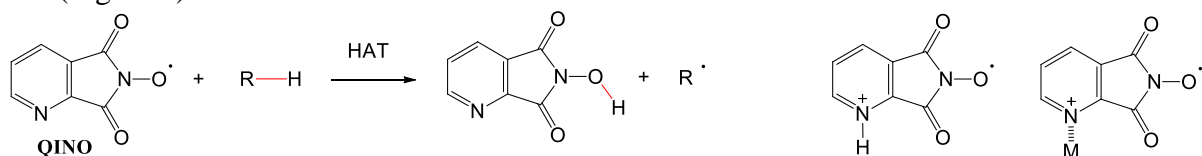


Figure 3

Thus, by changing the structure of the aminoxyl radical or the reaction medium it is possible to carefully control the reactivity and selectivity in the aerobic oxidations catalyzed by the *N*-hydroxyimides widening the synthetic versatility of the HAT process.

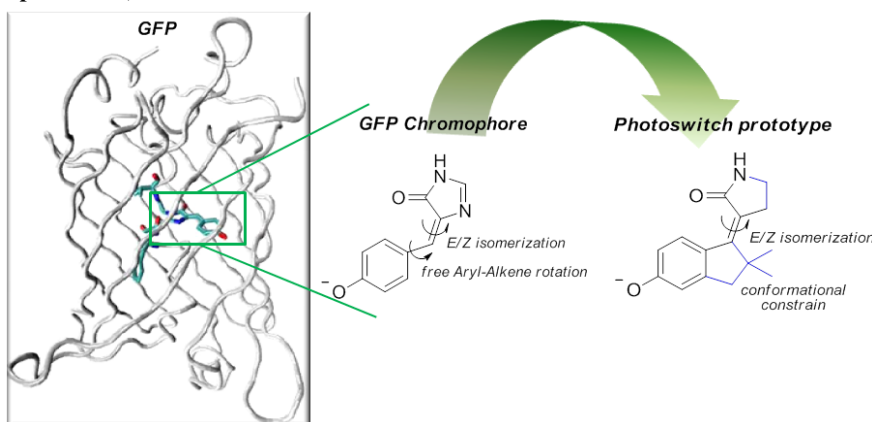
References: 1. M. Bietti, V. Forcina, O. Lanzalunga, A. Lapi, T. Martin, M. Mazzonna, M. Salamone, *J. Org. Chem.* **2016**, *81*, 11924-11931.

An Ultrafast Molecular Photoswitch Bio-inspired by Green Fluorescent Protein Fluorophore

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Light-driven molecular switches and motors are based on the conversion of light energy into molecular motion.(1) Single-molecule rotary devices are capable of funneling the energy of a photon into E/Z isomerization modes putting in motion a rotor moiety with respect to a stator framework.(2) In the past years, we have shown a practicable strategy for achieving alternative light-driven rotary devices based on mimicking strictly the photoisomerization of biological chromophores. Indeed, we have reported the design and synthesis of a series of positively charged N-alkylated indanylidene pyrroline Schiff bases (NAIPs) structures which replicate the reactivity of the retinal chromophore of visual pigments. NAIPs have been shown to undergo a regioselective subpicosecond double bond photoisomerization similar to that observed for the protein embedded chromophore of animal and microbial rhodopsins.(3,4) Recently, our biomimetic strategy has been reemployed to design and prepare a molecular photoswitch mimicking the radiationless photoisomerization of the green fluorescent protein (GFP) fluorophore: the *para*-4-hydroxybenzylidene-2,3-dimethylimidazolinone (*p*-HBDI) anion.



The *p*-HBDI fluorophore of GFP is hosted in a tight β -barrel cavity, which locks its central double bond and the adjacent single bond, yielding a photochemically nonreactive molecule and, consequently, an efficient emitter.(5) The chromophore, isolated from the protein, extremely loses its fluorescence in solution due to a rapid twisting of the *p*-HBDI

central bonds lead to radiationless deactivation via decay at a conical intersection between the first singlet excited state (S1) and the ground state (S0) of the molecule.(6) In light of this we designed a *p*-HBDI mimic structure which could undergo the type of regioselective double bond isomerization required for building a rotary photoswitches. We report on the computational design, preparation, and spectroscopic characterization of a synthetic *p*-HBDI mimic bearing a single exocyclic and ultrafast photoisomerizable E/Z double bond that connect two rigid units.(7)

References: 1. Browne, W. R.; Feringa, B. L. *Nat. Nanotechnol.* **2006**, *1*, 25–35. 2. Pollard, M. M.; Klok, M.; Pijper, D.; Feringa, B. L. *Adv. Funct. Mater.* **2007**, *17*, 718–729. 3. Lumento, F.; Zanirato, V.; Fusi, S.; et al. and Olivucci, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 414–420. 4. Léonard, J.; Schapiro, I.; Briand, J. et al. and Haacke, S. *Chem. - Eur. J.* **2012**, *18*, 15296–15304. 5. Subach, F. V.; Verkhusa, V. V. *Chem. Rev.* **2012**, *112*, 4308–4327. 6. Olsen, S.; Lamothe, K.; Martínez, T. J. *J. Am. Chem. Soc.* **2010**, *132*, 1192–1193. 7. Paolino, M.; Gueye, M.; Pieri, E.; et al. and Olivucci, M. *J. Am. Chem. Soc.* **2016**, *138*, 9807–9825.

Highly selective arylation protocols to prepare bioactive and fluorescent imidazole-based compounds.

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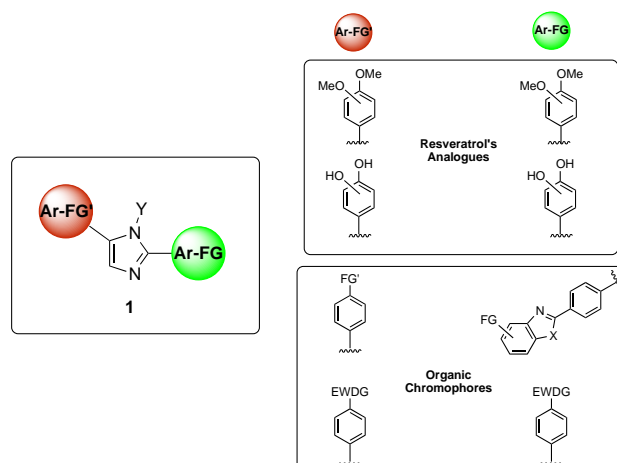
Arylimidazoles are frequently used in different fields of chemistry. Particularly, arylimidazole units are found in compounds having biological activity (i.e. natural products, pharmaceuticals, agrochemicals), and in precursors used for the preparation of organic functional materials.

Due to their widespread applications, the improvement of synthetic protocols aimed to decorate selectively and under mild conditions the imidazole core is a challenging target in organic chemistry. In this context, the transition metal-catalyzed direct arylation reactions of imidazole (or azoles in general) with aryl halides have emerged as an attractive strategy for the effective construction of aromatic Csp²–Csp² bonds. These reactions, unlike the traditional metal-catalyzed cross-coupling procedures involving the use of preformed organometallics, enable the direct elaboration of heteroaromatic cores without the pre-activation of both the coupling partners.

In the last years, our research's group efforts have been focused on the development of new and efficient Pd-catalyzed arylation methods involving imidazoles and (hetero)aryl halides, able to tolerate a wide range of organic functional groups. (1, 2, 3, 4)

Our results underline that it is possible to carry out highly selective direct arylations on imidazole derivatives under relative mild conditions using a proper combination of Pd precatalyst/precursor/Base/solvent.

In this talk we will show the application of our synthetic protocols to the preparation of new biological active imidazole derivative (Resveratrol analogues) and of novel imidazole-based fluorescent dyes of general formula **1**. (5, 6)



We will also present and discuss the anti-cancer properties of our new resveratrol analogues, and the peculiar optical properties of the newly synthesized imidazole-based dyes. (7, 8)

References: 1. Bellina F. et al. *Eur.J. Org. Chem.*, **2006**, 693. 2. Bellina F. et al. *Eur.J. Org. Chem.*, **2008**, 5436. 3. Bellina F. et al. *Tetrahedron*, **2008**, 6060. 4. Bellina F. et al. *Eur.J. Org. Chem.*, **2013**, 5621. 5. Bellina F. *ChemPlusChem*, **2014**, 366. 6. Bellina F. et al. *Tetrahedron*, **2015**, 2298. 7. Pucci A. et al. *Dyes and Pigments*, **2016**, 118. 8. Vergara D. *Mol.BioSyst.* **2017** Advanced Article DOI: 10.1039/C7MB00128B

Short Build/Couple/Pair Approaches for the Synthesis of Novel Glyco- and Peptidomimetic Scaffolds

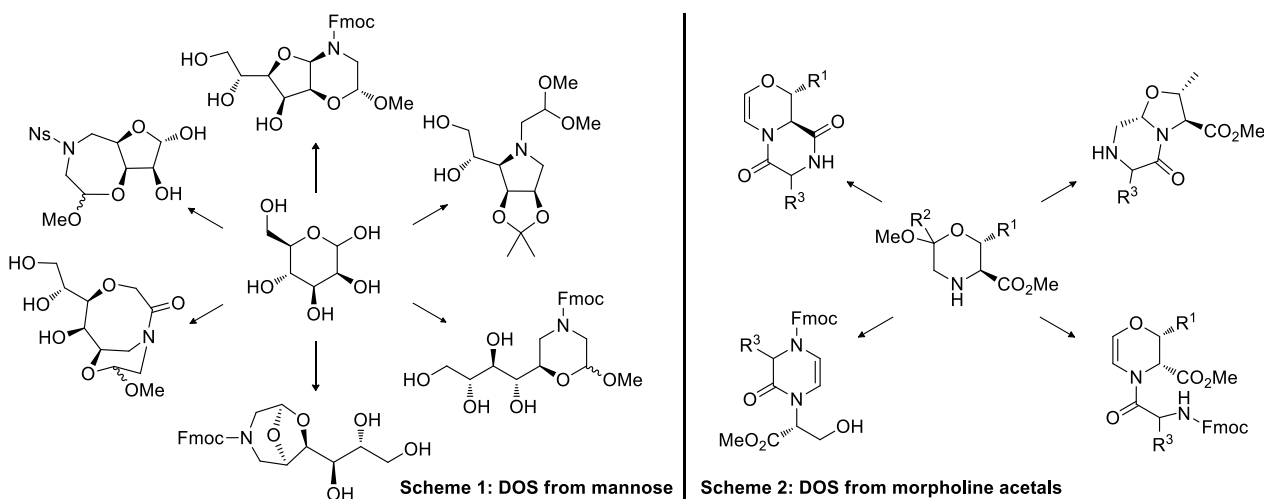
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The generation of large compound libraries is strictly necessary to increase the chance of finding new lead compounds for drug discovery programmes. In this context, Diversity-Oriented Synthesis (DOS) is one of the major opportunities for organic chemists to produce high-quality chemical libraries (1). However, considering that the synthetic efforts are not directed through a validated target, DOS synthetic strategies have to be versatile, efficient and consisting of no more than four/five economic steps. In this context, Build/Couple/Pair strategy is a powerful approach in DOS, even if, by far, only few examples of the application of this strategy starting from carbohydrates and amino acids have been reported.

However, we found that the exploitation of acetals chemistry allowed to obtain novel heterocyclic structures without the need of transitional protection/deprotection stages. Assembling D-mannose with glycine-derived aminoacetaldehyde six novel skeletally different scaffolds were achieved (Scheme 1) (2). The application of a cell-based phenotypic assay on these compounds allowed for the selection of the hexahydro-2*H*-furo[3,2-*b*][1,4]oxazine as a new biologically active scaffold, capable of inducing MDA-MB-231 cell growth inhibition (3).

In addition, four different morpholine-derived heterocyclic structures were obtained through the rearrangement of the intermediate resulting from the coupling between morpholine acetals and α -amino acids (Scheme 2) (4). Finally, new processes for the synthesis of novel skeletally different morpholine-based scaffolds using Petasis multicomponent reactions in the coupling step, are currently under development in our laboratories.



References: 1. (a) "Diversity-Oriented Synthesis: Basics and Applications in Organic Synthesis, Drug Discovery, and Chemical Biology", Trabocchi, A., Ed.; Wiley and Sons, **2013**; (b) Schreiber, S. L. *Science* **2000**, *287*, 1964; 2. Lenci, E.; Menchi, G.; Guarna, A.; Trabocchi, A. *J. Org. Chem.* **2015**, *80*, 2182; 3. Lenci, E.; Innocenti, R.; Biagioni, A.; Menchi, G.; Bianchini, F.; Trabocchi, A. *Molecules* **2016**, *21*, 1405; 4. Lenci, E.; Innocenti, R.; Menchi, G.; Faggi, C.; Trabocchi, A., *Org. Biomol. Chem.* **2015**, *13*, 7013.

A New Antibacterial Cyclic Peptide from Hot Springs

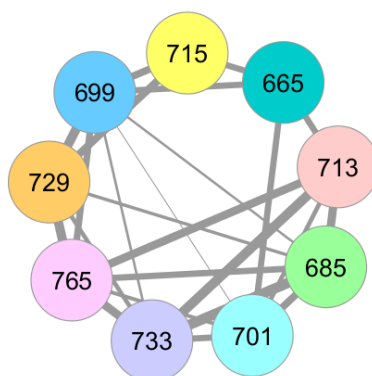
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The increasing incidence of bacterial infections and the rise of antibiotic-resistant bacterial strains have urged the need for novel antibiotics.

Marine environment is a unique source of bioactive chemical compounds that can lead to new drugs candidates and/or inspire the development of new medicinally relevant scaffolds. Microorganisms living in specialized ecological niche, such as submarine geothermal areas are a still untapped source of novel lead compounds in drug discovery. A strain of the thermophilic bacterium *Thermoactinomyces vulgaris*, has been isolated from Icelandic marine hot springs. The extract has been studied following a new approach that combines liquid chromatography-high resolution mass spectrometry (LC-HRMS) with automated data analysis through molecular networking (1). Molecular networking is a visual representation of molecular relationships, due to structure similarity, of any given set of molecules as determined by tandem mass spectrometry (MS/MS) data (2). In a network, a single chemical species is represented as a node, and the relatedness between compounds is represented by an edge.

The molecular network of *T. vulgaris* extract contained a cluster composed by nine nodes, indicating the presence of nine closely related compounds. MS-guided purification from the extract of the most abundant compound in the cluster yielded a new antibacterial cyclic hexapeptide. The structure of the new compound was fully determined by HRMS and HRMS/MS, 1D and 2D NMR, and a modified version of Marfey's method was applied to assess the configuration of each amino acid. The new cyclopeptide showed a remarkable antibacterial activity against *S. aureus*. Eight minor analogues were also isolated, whose structures were partly elucidated by MS/MS.



The cyclopeptide cluster from *T. vulgaris* extract. Nodes are labeled with parent m/z ratio. Edge thickness is related to similarity score.

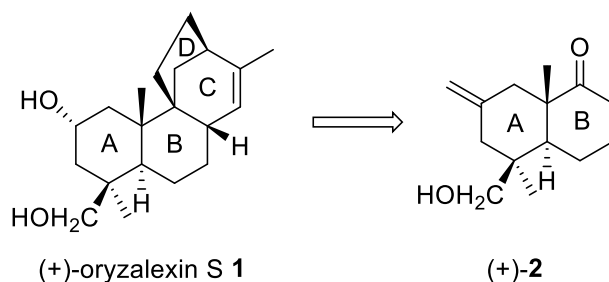
1. Teta, R.; Della Sala, G.; Glukhov, E.; Gerwick, L.; Gerwick, W.H.; Mangoni, A.; Costantino, V. *Environ. Sci. Technol.*, 2015, 49 (24), 14301–14310.
2. Watrous, J.; Roach, P.; Alexandrov, T.; Heath, B. S.; Yang, J. Y.; Kersten, R. D.; van der Voort, M.; Pogliano, K.; Gross, H.; Raaijmakers, J. M.; Moore, B. S.; Laskin, J.; Bandeira, N.; Dorrestein, P.C. *Proc. Natl. Acad. Sci. U.S.A.* 2012, 109, E1743-E1752.

Recent advances in the synthesis of stemarane diterpenoids

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Stemarane diterpenoids, characterized by the presence of a unique bicyclo[3.2.1]octane C/D ring system within a tetracyclic skeleton, were isolated in Central and South America from plants of the genus *Stemodia* (1) and *Calceolaria* (2) respectively, and in Japan from the fungus *Phoma Betae* (3). Besides, a stemarane diterpenoids, (+)-oryzalexin S **1**, was also isolated from *Oryza sativa* which produces it when attacked by the fungus *Pyricularia oryzae* or when exposed to UV radiations (4) or when irradiated by ultraviolet light.



Its structure was elucidated by means of 2-D NMR experiments but the absolute configuration assignment is still unknown. The (+)-oryzalexin S **1** is the first stemarane type phytoalexin to be reported and it has not yet been synthesized.

Continuing our efforts in the synthesis of stemarane diterpenoids (5), whose C/D ring system can now be efficiently obtained (6), we wish now to describe the enantioselective synthesis of the key building block (+)-**2**, in which three out of the seven stereogenic centers of (+)-oryzalexin S **1** are correctly installed.

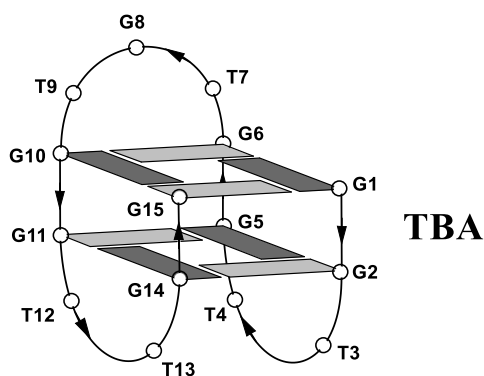
References: 1. Manchand, P. S.; Blount, J. F. *J. Chem. Soc., Chem. Commun.*, **1975**, 894-895. 2. (a) Chamy, M. C.; Piovano, M.; Garbarino, J. A.; Miranda, C.; Gambaro, V. *Phytochem.*, **1990**, *29*, 2943-2946; (b) Garbarino, J. A.; Molinari, A. *Phytochem.*, **1990**, *29*, 3037-3039; (c) Garbarino, J. A.; Molinari, A. *Phytochem.*, **1990**, *29*, 3040-3041; (d) Chamy, M. C.; Piovano, M.; Garbarino, J. A.; Gambaro, V. *Phytochem.*, **1991**, *30*, 3365-3368. 3. Oikawa, H.; Toshima, H.; Ohashi, S.; König, W. A.; Kenmoku, H.; Sassa, T. *Tetrahedron Lett.*, **2001**, *42*, 2329-2332. 4. Kodama, O.; Tamogami, W. X.; Akatsuka, T. *Biosci. Biotechn. Biochem.*, **1992**, *54*, 1002-1003; Tamogami, S.; Mitani, M.; Kodama, O.; Akatsuka, T. *Tetrahedron*, **1993**, *49*, 2025-2032. 5. (a) Marini Bettolo, R.; Migneco, L. M.; Moretti, P.; Scarpelli, R. *J. Prakt. Chem.* **1999**, *341*, 687-690; (b) Di Stefano, S.; Leonelli, F.; Garofalo, B.; Mandolini, L.; Marini Bettolo, R.; Migneco, L. M. *Org. Lett.* **2002**, *4*, 2783-2785; (c) Leonelli, F.; Borocci, S.; Migneco, L. M.; Marini Bettolo, R.; Lamba, D. *Helv. Chim. Acta* **2002**, *85*, 2817-2826; (d) Leonelli, F.; Caschera, B.; Silvestri, L.; Prastaro, A.; Corso, G.; Ceccacci, F.; La Bella, A.; Migneco, L. M.; Marini Bettolo, R. *Helv. Chim. Acta* **2008**, *91*, 598-607; (e) Leonelli, F.; Latini, V.; Trombetta, A.; Bartoli, G.; Ceccacci, F.; La Bella, A.; Sferrazza, A.; Lamba, D.; Migneco, L. M.; Marini Bettolo, R. *J. Nat. Prod.* **2012**, *75*, 1944-1950; (f) Leonelli, F.; Mostarda, A.; De Angelis, L.; Lamba, D.; Demitri, N.; La Bella, A.; Ceccacci, F.; Migneco, L. M.; Marini Bettolo, R. *J. Nat. Prod.* **2016**, *79*, 1155-1159; (g) La Bella, A.; Leonelli, F.; Migneco, L. M.; Marini Bettolo, R. *Molecules* **2016**, *21*, 1197-1216. 6. Leonelli, F.; Blesi, F.; Dirito, P.; Trombetta, A.; Ceccacci, F.; La Bella, A.; Migneco, L. M.; Marini Bettolo, R. *J. Org. Chem.* **2011**, *76*, 6871-6876;

Easy chemical modifications to explore the ‘Janus face’ of TBA: anticoagulant vs antiproliferative properties.

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RNA and DNA aptamers can be defined as short synthetic ribo- and deoxyribonucleic acids able to bind with high affinity and specificity a broad range of molecular targets as small molecules, proteins and other nucleic acids (1). Under certain conditions and in aqueous solution, aptamers are able to fold in stable three-dimensional structures conferring on them the ability to bind their cognate ligands. The thrombin binding aptamer (TBA) is a 15-base long oligodeoxynucleotide (5'-GGTTGGTGTGGTTGG-3') endowed with interesting anticoagulant properties. According to both X-ray and NMR spectroscopy investigations, TBA adopts a monomolecular antiparallel G-quadruplex structure, characterized by two stacked G-tetrads and three edge loops (two TT loops and one TGT loop, Figure) (2,3). Several studies have shown that G-tetrads are mostly responsible for the thermal stability of the aptamer, while loops are involved in the interaction with its target protein, namely thrombin, which is a serine protease playing a key role in the blood coagulation pathway (4). After its discovery, TBA has been subjected to a plethora of chemical modifications aimed at improving thermal stability, enhancing nucleases resistance and increasing anticoagulant activity (5). Besides the anticoagulant activity, just as other G-rich oligonucleotides, TBA has also shown antiproliferative properties (6). In this frame, the simultaneous anticoagulant activity of TBA represents a drawback in exploiting this additional biological property. In an effort to improve the anticoagulant activity or to preserve the antiproliferative properties by quenching the anticoagulant



ones, we have prepared some TBA derivatives exhibiting appropriate site-specific replacement of the residues in the loops with a dibenzyl linker or commercially available thymine analogues, such as 2'-deoxyuridine (**U**), 5-bromo-2'-deoxyuridine (**B**) and 5-hydroxymethyl-2'-deoxyuridine (**H**). All the new quadruplex-forming TBA based sequences were studied for their structural (CD, CD melting, NMR) and biological (PT and MTT assays) properties in comparison with the parent aptamer. The whole of data open up the possibility to modulate the TBA properties by using simple tiny modifications concerning specific positions.

References

1. F. Radom, P. M. Jurek, M. P. Mazurek, J. Otlewski, F. Jeleń, Aptamers: Molecules of great potential, *Biotechnol. Adv.* 31 (2013) 1260-1274.
2. R.F. Macaya, P. Schultze, F.W. Smith, J.A. Roe, J. Feigon, Thrombin-binding DNA aptamer forms a unimolecular quadruplex structure in solution, *Proc. Natl. Acad. Sci. U.S.A.* 90 (1993) 3745-3749.
3. J.A. Kelly, J. Feigon, T.O. Yeates, Reconciliation of the X-ray and NMR Structures of the Thrombin-Binding Aptamer d(GGTTGGTGTGGTTGG), *J. Mol. Biol.* 256 (1996) 417-422.
4. Russo Krauss, I., Merlino, A., Giancola, C., Randazzo, A., Mazzarella, L. and Sica, F. (2011) Thrombin-aptamer recognition: a revealed ambiguity. *Nucleic Acids Res.*, 39(17), 7858-7867.
5. A. Avino, C. Fabrega, M. Tintore, R. Eritja, Thrombin binding aptamer, more than a simple aptamer: chemically modified derivatives and biomedical applications, *Curr. Pharm. Des.*, 18 (2012) 2036-47.
6. V. Đapić, V. Abdomerović, R. Marrington, J. Peberdy, A. Rodger, J.O. Trent, P.J. Bates, Biophysical and biological properties of quadruplex oligodeoxyribonucleotides, *Nucleic Acids Res.* 31 (2003) 2097-2107.

The greening of protection/deprotection strategies in peptide synthesis.

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The presence of functional groups in a wide range of biologically active compounds makes their protection and deprotection an important and frequently mandatory exercise in synthetic organic chemistry.¹ In particular, protection and deprotection of the α -amino functionality of amino acids is one of the most important issues in peptide synthesis. Therefore, introduction as well as removal must be done in mild conditions that do not affect the remaining protecting groups or even the peptide chain.²

Although there are hundreds of protective groups that can be introduced and removed by a variety of methods, new and milder strategies continue to be developed for many of the existing protective groups; nevertheless, most of them have their own particular drawbacks.

The selection of mild reaction conditions for the use of protective groups is a crucial seek of the contemporary synthetic chemistry.

The use of ionic liquids (ILs) and deep eutectic solvents (DES) in organic synthesis has received great attention due to their unusual properties as nonconventional solvents.³

Recently, we explored the applicability of these green solvents as reaction media, for the selective introduction and removal of various protecting groups⁴⁻⁶ and for the synthesis of potential biologically active compounds.



References: 1. P. G. M. Wuts and T. W. Green, *Greene's Protective Groups in Organic Synthesis*, John Wiley and Sons, Hoboken, NJ, 4th edn, **2007**. 2. E. Wuensch, Houben-Weyl, *Methods of Organic Chemistry*, ed., E. Muller, O. Bayer, H. Meerwin and K. Ziegler, George Thieme, Stuttgart, New York, 4th edn, **1974**, vol. 15/1, p. 46. 3. P. Wasserscheid and T. Welton, *Ionic Liquids in Synthesis*, Wiley-VCH, **2004**. 4. M. Oliverio, P. Costanzo, R. Paonessa, M. Nardi, A. Procopio, *RSC Adv.*, **2013**, 3, 2548-2552. 5. M. L. Di Gioia, A. Barattucci, P. Bonaccorsi, A. Leggio, L. Minuti, E. Romio, A. Temperini, C. Siciliano, *RSC Adv.*, **2014**, 4, 2678-2686. 6. M. L. Di Gioia, A. Gagliardi, A. Leggio, V. Leotta, E. Romio, A. Liguori *RSC Adv.*, **2015**, 5, 63407-63420. 7. M. Nardi, N. Herrera Cano, P. Costanzo, M. Oliverio, G. Sindona, A. Procopio *RSC Adv.*, **2015**, 5, 18751-18760

Design, synthesis of new heterocyclic compounds and their biological activity against MCF-7 cell line.

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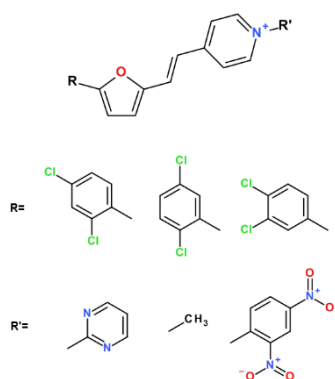
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In the last few years, a wide range of heterogeneous styrene systems were studied for the development of new chemical scaffolds for the design of a lead compound as new drug that could show potential antitumor activity towards MCF-7 cell line (breast cancer). The compounds previously synthesized and tested are highly conjugated structures where an electron-rich molecular portion (thiophenic, furanolic or pyrrolic) is separated from the ethylene spacer by a second low electron-poor molecular moiety (N-methylpyridinium, N-methyl-quinolinium or N, N-dimethyl-imidazolium).

In 2013, a database of 59 compounds, with antiproliferative activity towards the MCF-7 tumor cell line, has been generated (1) with the aim of carrying out QSAR studies and developing new drugs using Volsurf + software.(2)

Therefore, nine new diheteroaryl-ethylene systems (Scheme 1) have been designed, characterized by the presence of 5-phenyl-2-furanyl structures, such as electron-rich units, and a 4-pyridine salt with different substituents, as electron-poor units.

The designed compounds were projected into the Volsurf + model for prediction of their antitumor activity. The results obtained for the synthesized molecules suggest that all compounds should exhibit good anti-tumour activity against MCF-7 cells. We here reports the design, the synthesis, the biological evaluation and the study on their mechanism of action.



Scheme 1

References:

1. Fortuna Cosimo G., et al. "Modeling, design and synthesis of new heteroaryl ethylenes active against the MCF-7 breast cancer cell-line." *Molecular BioSystems* 9.10 (2013): 2426-2429.
2. The VolSurf+ Manual available at: <http://www.moldiscovery.com/docs/vsplus/>

Synthesis and application of bifunctional chelating agents based on AAZTA scaffold

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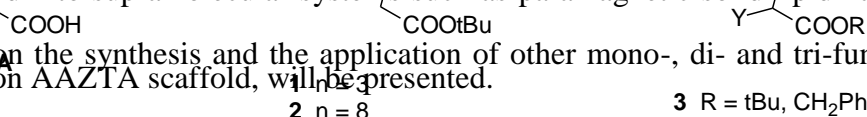
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AAZTA (6-amino-6-methylperhydro-1,4-diazepinetetraacetic acid) is an innovative ligand designed to strongly chelate gadolinium ion and providing in this way a stable MRI contrast agent with increased relaxivity due to the coordination of two water molecules (1). Moreover, AAZTA proved to be an efficient chelating agent for other metal and radiometal ions, such as ⁶⁸Ga and ⁴⁴Sc, widely employed in PET imaging (2).

Bifunctional chelating agents (BFCA) are molecules containing two different moieties: a metal chelating unit and a reactive functional group. One well known application of BFCA is their covalent conjugation to biomolecules (e.g. peptides, antibodies) in order to obtain new entities applicable in the fields of molecular imaging, diagnostic imaging (MRI, SPECT, PET), tumor therapy (3).

A reactive group can be easily introduced on the structure of AAZTA to give BFCA based on this scaffold. For example, compound 1 was conjugated to a RGD peptidomimetic and labeled with ⁶⁸Ga to target $\alpha_v\beta_3$ integrins (4), while compound 2 was coupled to a minigastrin derivative providing a new theranostic agent (5). In another example, compound 1 was conjugated to a set of fatty secondary amines or amino phospholipids to obtain lipophilic gadolinium complexes that were incorporated into supramolecular systems such as paramagnetic solid lipid nanoparticles (SLN) (6).

In this communication the synthesis and the application of other mono-, di- and tri-functionalized BFCA 3, based on AAZTA scaffold, will be presented.



References:

1. S. Aime, L. Calabi, C. Cavallotti, E. Gianolio, G. B. Giovenzana, P. Losi, A. Maiocchi, G. Palmisano, M. Sisti, *Inorg. Chem.*, **2004**, *43*, 7588-7590.
2. Z. Baranyai, F. Uggeri, G. B. Giovenzana, A. Bényei, E. Brücher, S. Aime, *Chem. Eur. J.*, **2009**, *15*, 1696-1705; Z. Baranyai, F. Uggeri, A. Maiocchi, G. B. Giovenzana, C. Cavallotti, A. Takács, I. Tóth, I. Bánai, A. Bényei, E. Brucher, S. Aime, *Eur. J. Inorg. Chem.*, **2013**, 147-162; G. Nagy, D. Szikra, G. Trencsényi, A. Fekete, I. Garai, A. M. Giani, R. Negri, N. Masciocchi, A. Maiocchi, F. Uggeri, I. Tóth, S. Aime, G. B. Giovenzana, Z. Baranyai, *Angew. Chem. Int. Ed.*, **2017**, *56*, 2118-2122.
3. L. Lattuada, A. Barge, G. Cravotto, G. B. Giovenzana, L. Tei, *Chem. Soc. Rev.* **2011**, *40*, 3019-3049; E. W. Price, C. Orvig, *Chem. Soc. Rev.* **2014**, *43*, 260-290.
4. L. Manzoni, L. Belvisi, D. Arosio, M. P. Bartolomeo, A. Bianchi, C. Brioschi, F. Buonsanti, C. Cabella, C. Casagrande, M. Civera, M. De Matteo, L. Fugazza, L. Lattuada, F. Maisano, L. Miragoli, C. Neira, M. Pilkington-Miksa, C. Scolastico, *ChemMedChem* **2012**, *7*, 1084-1093.
5. J. Pfister, D. Summer, C. Rangger, M. Petrik, E. von Guggenberg, P. Minazzi, G. B. Giovenzana, L. Aloj, C. Decristoforo, *EJNMMI Research* **2015**, 5:74.
6. G. A. Rolla, M. Botta, L. Tei, C. Cabella, S. Ghiani, C. Brioschi, A. Maiocchi, *Chem. Eur. J.*, **2013**, *19*, 11189-11193

QU-IBX and B3-IBX: safe IBX adducts for periodinane oxidation reactions

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Oxidation reactions of organic compounds are useful reactions widely employed in the pharmaceutical industry. In this field, in particular, mild and selective reagents are preferred. The well-known Dess-Martin periodinane (DMP) and its precursor 2-iodoxybenzoic acid, known as IBX, offer a plethora of chemo- and regio-selective reactions (1) but their use in industry is strongly limited by their hazardous explosive properties (2). Growing interest in industrial applications of both periodinane reagents in recent years has prompted research on safer solutions allowing the use of periodinanes even in large industrial scale synthesis. In this communication, two new oxidants QU-IBX (fig.1) and B3-IBX (fig.2), adducts of IBX with quinoline and nicotinamide (vitamin B3), respectively (3) will be presented. These adducts have been characterized by XRPD, NMR and DSC and revealed a considerable reduction of decomposition enthalpy to safer levels (table 1). Moreover both adducts show the same reactivity and selectivity of IBX and a series of oxidation reactions performed using both adducts will be presented to demonstrate their potential as a valid alternative to IBX on large scale synthesis.

Fig.1

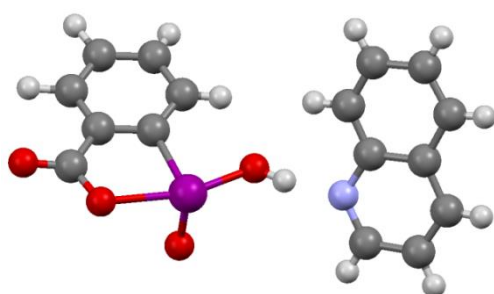


Fig.2

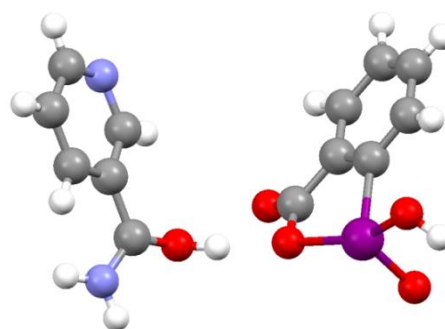


Table 1.

Compound	P.M. mol/kg	T onset °C	ΔH_{DEC} J/g
IBX	280,02	218,5	1164
DMP	424,15	136,0	829
QU-IBX	409,18	145,9	584
B3-IBX	402,15	134,9	724

References: 1. Duschek, A.; Kirsch, S.F. *Angew. Chem. Int. Ed.* **2011**, *50*, 1524-1552. 2. Plumb, J.B.; Harper, D.J. *Chem. and Eng. News* **1990**, *68*(29). 3. Mantegazza S., Razzetti G., Attolino E., Vladiskovic C., Stable adducts of 2-iodoxybenzoic acid WO2017037296.

Light-Activated Amine Detection via Innovative Diarylethene Probes

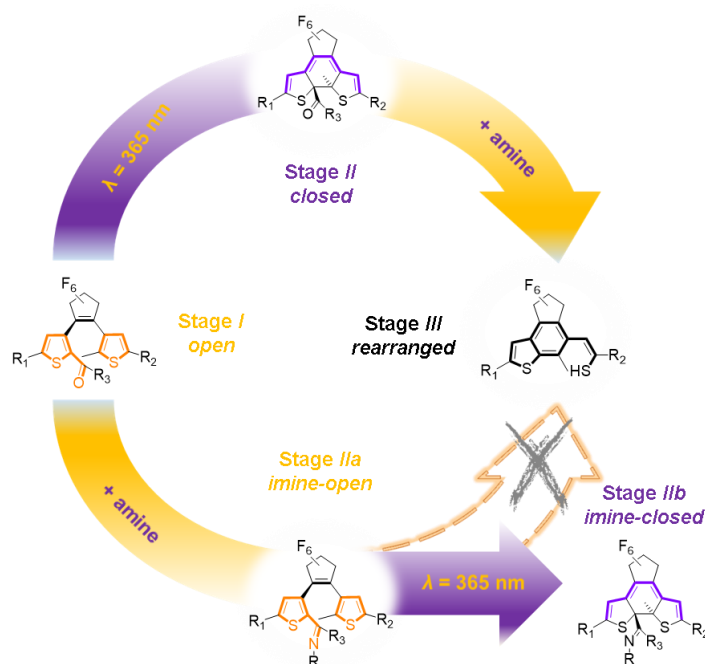
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Amino compounds, besides the role played in fundamental biological mechanisms (i.e. as neurotransmitters), could become toxic for living beings, beyond certain concentrations. Several biogenic amines (cadaverine, putrescine, spermidine, etc.) are products of bacteria thermal or enzymatic decarboxylation operated on aminoacids.(1) Thus, revelation of those amines could give indication concerning food quality or hygiene levels.(2)

In the literature, a variety of chromatographic, enzymatic and colorimetric methodologies are reported for the determination of amines concentrations,(3) however it is still missing a protocol combining inexpensive equipment and a single-component molecular probes.

Here we describe an accurate colorimetric assay based on diarylethenes (DAEs) for the rapid detection of a wide range of amines. The molecular sensors consist of carbonyl-substituted DAEs, which undergo an amine-induced decoloration reaction, selectively in the ring-closed isomer. Thus, these probes can be activated at the desired moment by light irradiation simply using a common UV lamp for laboratories, with a sensitivity that allows amine detection in concentrations up to 10^{-6} M in solution. In addition, the practical DAEs immobilization on paper allows for amine sensing on solid supports.



References:

1. Santos, M. H. S. *Int. J. Food. Microbiol.* **1996**, 29, 213-231
2. Bulushi, I. A., Poole, S., Deeth, H. C., Dykes, G. A. *Crit. Rev. Food. Sci.* **2009**, 49, 369-377
3. a) Latorre-Moratalla, M. L., Bosch-Fusté, J., Lavizzari, T. Bover-Cid, S., Veciana-Nogués, M. T., Vidal-Carou, M. C. *J. Chromatogr. A* **2009**, 1216, 7715-7720; b) Leonardo, S., Campàs, M. *Microchim. Acta* **2016**, 183, 1881-1890; c) Askim, J. R., Mahmoudi, M. Suslick, K. S. *Chem. Soc. Rev.* **2013**, 42, 8649-8682.

Acknowledgements:

The *European Commission* (via ITN “iSwitch”), the *Alexander von Humboldt Foundation* and the *German Research Foundation* (via SFB 658, project B8) are gratefully acknowledged.

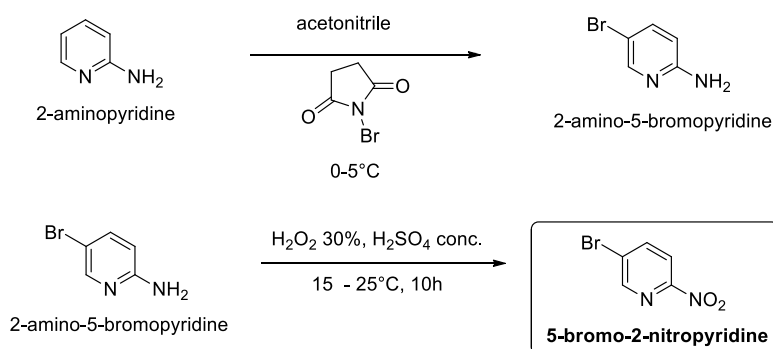
Handling Hydrogen Peroxide On Large Scale: Synthesis of 5-bromo-2-nitropyridine

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Organic chemistry oxidations are often times considered to be problematic, even more so when they have to be implemented on large scale. The very nature of the transformation in which fuel, oxidant and energy are present altogether makes it an interesting subject to be studied and very rewarding from the challenges it poses to the process safety community.

Herein we wish to presents our results on the safety assessment and process development of the synthesis of the 2-nitro-5-bromopyridine. The two steps synthetic procedure utilizes a NBS bromination of 2-aminopyridine leading to the 2-amino-5-bromopyridine intermediate followed by oxidation with a mixture of H₂O₂ 30% and H₂SO₄ 98% (also known as Caro's acid or Piranha mixture).



Process development and safety proceeded hand in hand towards the obtainment of a sound reproducible process which was applied on full scale within a short time frame.

The currently optimized oxidation procedure implies the addition of a sulfuric acid solution of 2-amino-5-bromopyridine onto a pre-mixed cooled solution of hydrogen peroxide in sulfuric acid (5.6:1 w/w) in a temperature range of 15-25 °C.

A rationale for the choice of reagents, temperatures and operation conditions will be described (1).

References: (1) Agosti, A.; Bertolini, G.; Lautz, C.; Glarner, T.; Deichtmann, W. *Org. Process Res. Dev.*, 2017, 21, 451-459

Zwitterionic Deep Eutectic Solvents as Effective Alternatives to Organic Solvents and to Ionic Liquids

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The search for novel organic liquids that could possess environmental advantages is a key factor in the green chemistry framework. The most studied and used liquids in this field are represented by Ionic Liquids (ILs). (1) These organic liquids showed many benefits such as non-volatility, high recycle capabilities and high yields and favourable reaction conditions in many organic reactions. Unfortunately, ILs show many disadvantages due to their toxicity and to their low biodegradability. Moreover, the synthesis of these liquids often requires many steps involving the use of other organic solvents. In the recent years, Deep Eutectic Solvents (DESs) are rapidly increasing their importance as relevant alternatives to organic solvents and to ILs. (2) These novel liquids possess the same advantages of ILs (non-volatility, recycling capabilities, high yields in many chemical reactions) but they showed low or absent toxicity. Moreover, the realization of a DES is performed by simply mixing at the proper molar ratio two solid compounds, preventing the use of other organic solvents and any synthetic step. A DES is formed, in fact, by mixing a hydrogen bond donor (HBD) molecule with a hydrogen bond acceptor (HBA) one. The applications of these mixtures are wide: solvents for synthetic chemistry, nanoparticle synthesis, use as dissolution and separation liquids, solvents for extraction from natural matrixes, solar cells components and so on. The most studied DESs in literature are mixtures of choline chloride as HBA molecule with different compounds as HBD (Urea, glycerol, carboxylic acids and so on). In order to avoid the presence of chloride that could provoke unwanted side reactions, we developed novel Deep Eutectic Solvents based on quaternary ammonium methanesulfonate salts (as HBA molecules) mixed with p-toluenesulfonic acid (as HBD). (3) These novel liquids have been used as dual solvent-catalyst for esterification of several carboxylic acids with different alcohols via Fischer reaction. The step forward on the realization of novel DESs was to avoid the presence of any counterion using zwitterionic molecules, both as HBA or HBD components in different classes. These novel classes of mixtures are formed by carboxybetaine, sulfobetaine and amine-N-oxide molecules. The DESs of carboxybetaine class were successfully used as solubilizing agents of aromatic amino acids (which are normally scarcely soluble in water) and for the extraction of oxyprenylated phenylpropanoids in olive, soy, peanuts, corn and sunflower oil. (4,5) The second class of zwitterionic DESs was developed by mixing differently structured sulfobetaine molecules with (1S)-(+)-10-Camphorsulfonic acid. (6) These liquids were studied as solvents/catalysts in C-C bond formation via Claisen-Schmidt reaction. (7) The advantages of the use of this DES in this probe reaction are represented by: the green properties of the media and its low toxicity; the absence of harmful acids to catalyze the aldol condensation because of the HBD molecule composing the DES mixture; the recycling and the re-use of the DES in subsequent reaction cycles; the mild conditions and the excellent conversions and yields observed. The last class of DESs presented in this work was realized with amine-N-oxide zwitterionic molecules as HBA molecules. (8) These mixtures showed an excellent low viscosity even at room temperature and an excellent capability of solubilization of differently structured polymers.

References: 1. Welton, T. Chem. Rev. 1999, 99.8, 2071-2084. 2. Paiva, A. et al. ACS Sustain. Chem. Eng. 2014, 2.5, 1063-1071. 3. De Santi, V. et al. Tetrahedron Lett. 2012, 53.38, 5151-5155. 4. Cardellini, F. et al. RSC Adv. 2014, 4.99, 55990-56002. 5. Ferrone, V. et al. Food Chem. (submitted, 2017). 6. Cardellini, F. et al. RSC Adv. 2015, 5.40, 31772-31786. 7. Tiecco, M. et al. RSC Adv., 2016, 6.49, 43740-43747. 8. Germani, R. et al. J. Mol. Liq. (submitted, 2017).

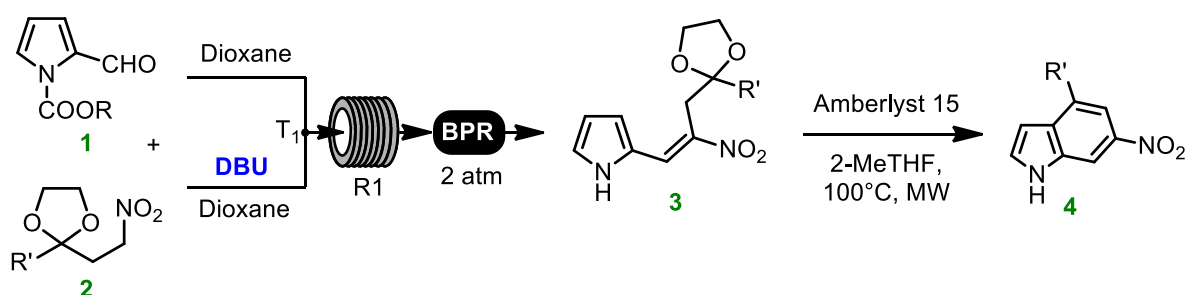
Innovative Two-Step Synthesis of Polysubstituted 6-NitroIndoles

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Heterocyclic compounds are those cyclic compounds in which one or more of the ring carbons are replaced by another atom. The non-carbon atoms in such rings are referred to as "heteroatoms." (1,2) Such bicyclic heterocyclic compounds containing pyrrole ring with benzene ring fused to α,β -position are known as Indoles.(3) The indole nucleus is an important element of many natural and synthetic molecules with significant biological activity, it is also a popular component of fragrances and the precursor to many pharmaceuticals.(4) Thus, the development of new and more friendly synthetic pathways, for the synthesis of this core structure, are of particular interest. In this contest, we settled a flow system-microwave two-step assisted process, for the synthesis of polysubstituted 6-nitroindoles (Scheme 1).



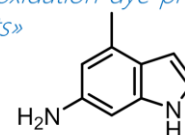
Scheme 1. Overall process to 6-nitroindoles

The importance of this class of indole derivatives is related to the synthesis of nucleosides starting from 6-nitroindole, which are of actual biological interest. This class of compounds is very important due to the fact that, indoles bearing nitro substituents on the benzenoid ring can be reduced to the corresponding aminoindoles which are precursors to other biologically active compounds.(5,6) Our method allows to overcome all the limitations of previous methodologies, such as low yield and regioselectivity.

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L'Oreal US5938792 «Process for dyeing keratinous fibers with aminoindoles and oxidation dye precursors at basic pH's and dyeing agents»

0,01-3,5% in hair dye



References: 1. L.D. Quin, J.A. Tyrell, *Fundamentals of Heterocyclic Chemistry: Importance in Nature and in the Synthesis of Pharmaceuticals*; John Wiley & Sons, Inc., **2010**; 170. 2. F. Sato, et al. *J. Am. Chem. Soc.*, **1997**, *119*, 6984–6990. 3. H. Sashida, et al. *Tetrahedron Letters*, **1999**, *40*, 5395–5398. 4. M. Małosza, et al. *Synthesis* **2002**, *15*, 2203–2206. 5. J. Jiang, G.W. Gribble, *Tetrahedron Letters* **2002**, *22*, 4115–4117. 6. C. Crey-Desbiolles, N. Berthet, M. Kotera, P. Dumy, *Nucleic Acids Res*, **2005**, *33*, 1532–1543.

NMR study of mixed micelles: zwitterionic – cationic surfactant systems

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Surfactant molecules in a solvent self-associate into various kinds of supramolecular assemblies such as micelles, vesicles, and liquid crystals and their mixture, especially those of nonionic and ionic surfactants are used in many practical applications, such as detergents, cosmetics, oil recovery, drug delivery systems, emulsified polymerization, coating technology, and mesostructured nanofilms (1). For these applications, the structural and solution properties of the mixed surfactant systems should be controlled effectively. Therefore, it is useful to understand how the molecular structures of surfactants in mixtures affect the solution properties, such as the size, shape, and surface charge density of the mixed micelles. For these reasons, structural properties of nonionic-ionic surfactant mixed micellar solutions have been investigated theoretically and experimentally (2). In the mixture of two or more different surfactants (nonionic and ionic), the complex aggregation behavior of the mixture of surfactants in solution is a result of a delicate balance of opposing forces, i.e., the steric hindrance among the polar head groups of the surfactant molecules and electrostatic repulsion energy between charges on the polar head of the ionic surfactant molecules (3). Therefore, the structural properties of the nonionic-ionic mixed micellar solutions should be studied as a function of the molar ratio to determine the effect of molecular interaction between the surfactants in a mixed micelle on its formation. Practically, this understanding can help in choosing relevant surfactant structures that will result in the desired properties. NMR spectroscopy is one of the most convenient methods for simultaneous monitoring of changes in aggregate morphologies of interaction between components. In this study, we investigated the formation in water of mixed micelle using zwitterionic and anionic surfactants employing multinuclear NMR to study the influence of intramicellar interaction and surfactant molecular shape on the properties of mixed micelles.

In our experiments, we kept the surfactant concentration well above their cmc values, so the observed chemical shifts are those of aggregated assemblies formed upon mixing of the surfactants.

Interestingly enough, NMR experiments suggest that under the chosen experimental conditions upon mixing of pure surfactants two different families of mixed aggregates are formed both larger than the original single component micelles. The fact that the different mixed micelles coexist unchanged many days after solution preparation, suggest that the system is under thermodynamic control.

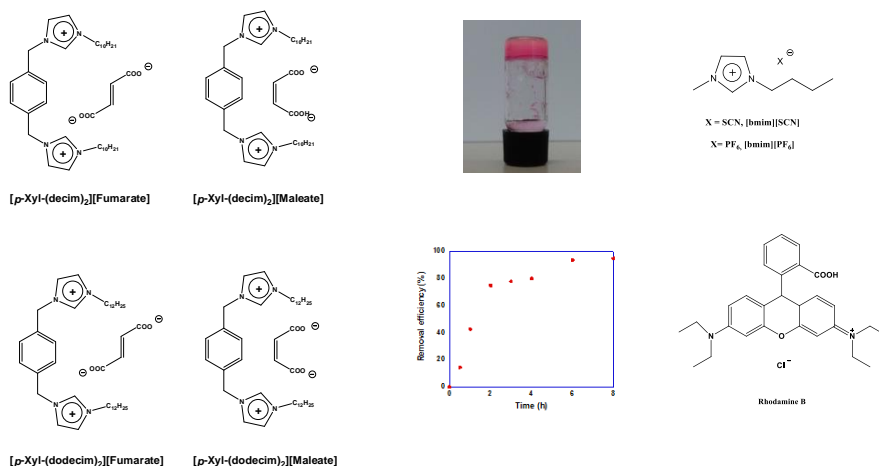
References: 1. Tadros T. A., *Applied Surfactants: Principles and Applications*; Wiley-VCH: Weinheim, **2005**. 2. Danov, K. D.; Kralchevsky, P. A.; Ananthapadmanabhan, K. P., *Adv. Colloid. Interfac.* **2014**, 206, 17-45. 3. Shiloach, A.; Blankshtein, D., *Langmuir* **1998**, 14, 7166-7182.

Diimidazolium-based supramolecular ionogels for dye removal from wastewaters

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Dyes are major pollutants of industrial wastewaters deriving mainly from the textile, paper and cosmetic sectors.(1) Many strategies exist to tackle this issue, among which adsorption. In this methodology, dye-polluted waters are treated with porous materials called sorbents. Recently supramolecular gels have emerged as a promising class of nanostructured materials for the remediation of wastewaters. Supramolecular gels are originated by the self assembly of small molecules (LMGWs) in solution.(2) A recent development in this field is represented by ionogels, in which LMGWs gel ionic liquids.(3) Using organic salts as gelators for ionic liquids gives rise to fully ionic gels. Studying ionogels obtained from diimidazolium salts, we found that they possess convenient properties such as unaltered or in some cases enhanced conductivity compared with the parent components.(4)



In the light of this, we have studied the ability of ionogels originated by diimidazolium salts to act as sorbents for the removal of dyes from water. We chose salts bearing isomeric dicarboxylate anions and differing for the alkyl chain length on the imidazolium cations. Ionogels were obtained in different imidazolium based ionic liquids and characterized in terms of thermal stability, rheological properties and gelation kinetics. Dye removal capability of the ionogels was studied using rhodamine B as a model cationic dye. In general, the gelation ability of the salts considered was mainly affected by the alkyl chain length while the anion exerted a minor effect. Moreover the gelation kinetics was mainly affected by the ionic liquid anion. Finally, a more articulate behavior was found for the rheological properties and the removal efficiency of Rhodamine B from water.

References:

- McMullan, G.; Meehan, C.; Conneely, A.; Kirby, N.; Robinson, T.; Nigam, P.; Banat, I.; Marchant, R.; Smyth, W. *Applied Microbiol. Biotechnol.* **2001**, *56*, 81.2. Hirst, A. R.; Escuder, B.; Miravet, J. F.; Smith, D. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 8002. 3. Marr, P. C.; Marr, A. C. *Green Chem.* **2016**, *18*, 105. 4. Rizzo, C.; D'Anna, F.; Noto, R.; Zhang, M.; Weiss, R. G. *Chem. Eur. J.* **2016**, *22*, 11269.

Assessment of drug-induced phospholipidosis risk based on distribution coefficient in brain polar lipids

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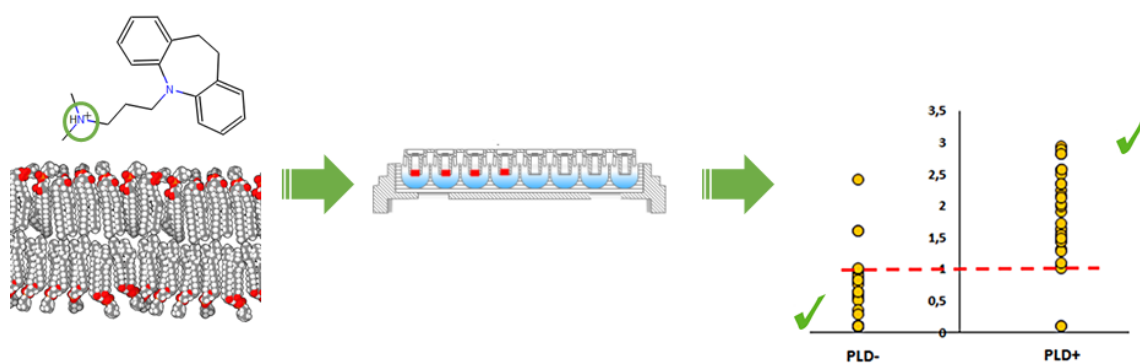
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In vitro safety assessment in early drug discovery represents an important step to detect potential safety-related liabilities. It reduces late stage attrition and allows candidate optimization.

Aside cell-based assays, high-throughput safety assessment screenings based on the correlation of physico-chemical properties of organic compounds with their biological effect have been successfully developed.(1) They include both *in silico* and experimental methods. In this study, we report on the use of the LogD_{BPL} assay (a recently published assay for the determination of drug distribution coefficients between an aqueous phase and porcine brain polar lipids extract) for phospholipidosis (PLD) risk evaluation.(2) From a mechanistic perspective, drugs inducing PLD are commonly cationic amphiphilic compounds containing an amino group protonated under physiological conditions. The combination of basic and lipophilic features in the chemical structure is responsible for the accumulation of these drugs into lysosomes due to acidic environment, inducing potential toxic outcomes.

Our study (3) showed that LogD_{BPL} is an efficient descriptor to assess PLD risk, especially when corrected using the pK_a value of compounds. A rule-based approach was developed, stating that PLD inducing drugs must possess: (i) LogD_{BPL} ≥ 1; (ii) at least an amine basic center with pK_{aMBC} > 7, and (iii) be mostly in their protonated state at pH = 5.

Comparisons with other physico-chemical parameters related to distribution, like effective permeability by PAMPA and LogD_{oct}, proved that LogD_{BPL} better correlates with PLD effect of drugs.



References: 1. Kerns, E. H. *J. Pharm. Sci.* 2001, 90, 1838-1858. 2. Belli, S.; Assmus, F.; Wagner, B.; Honer, M.; Fischer, H.; Schuler, F.; Alvarez-Sanchez, R. *Mol. Pharm.*, 2015, 12, 4529-4541. 3. Goracci, L.; Ceccarelli, M.; Wagner, B.; Alvarez-Sanchez, R.; Cruciani, G. *Chem. Res. Toxicol.* 2017, published ahead of print, doi: 10.1021/acs.chemrestox.6b00459.

Identification of new ErbB4 inhibitors by inverse virtual screening

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We have applied the inverse virtual screening protocol (1-5) to a small library of 19 synthetic compounds that showed a weak activity against the enzyme JMJD3. Our analysis suggested the enzyme ErbB4 as a new putative target of the investigated compounds. This macromolecule is a receptor tyrosine-protein kinase, member of the epidermal growth factor receptor subfamily and identified as potential target for cancer therapy. Experimental *in vitro* assays show that 5 compounds present inhibitory activity against ErbB4 in the low micromolar range. We have also investigated the binding of the identified lead compounds toward the highly structural related isoform ErbB2. The experimental evidences highlight a selectivity towards ErbB4. Moreover, one of the selected compounds shows antiproliferative activity against carcinoma (HCT) and breast (MCF7) cancer cells in low micromolar range.

1. Lauro, G.; Romano, A.; Riccio, R.; Bifulco, G. *Nat. Prod.* **2011**, *74*, 1401-1407. 2. Lauro, G.; Masullo, M.; Piacente, S.; Riccio, R.; Bifulco, G. *Med. Chem.* **2012**, *20*, 3596-3602. 3. Cheruku, P.; Plaza, A.; Lauro, G.; Keffer, J.; Lloyd, J. R.; Bifulco, G.; Bewley, C. A. *Med. Chem.* **2012**, *55*, 735-742. 4. Scrima, M.; Lauro, G.; Grimaldi, M.; Di Marino, S.; Tosco, A.; Picardi, P.; Gazzerro, P.; Riccio, R.; Novellino, E.; Bifulco, M.; Bifulco, G.; D'Ursi, A. M. *Med. Chem.* **2014**, *57*, 7798-7803. 5. Gong, J.; Sun, P.; Jiang, N.; Riccio, R.; Lauro, G.; Bifulco, G.; Li, T.-J.; Gerwick, W.; Zhang, W. *Lett.* **2014**, *16*, 2224-2227. 7. Settleman, J. *Cancer Cell* **2009**, *16*, 278-279.

Recent advances in the discovery of novel microsomal prostaglandin E₂ synthase-1 (mPGES-1) inhibitors

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Microsomal Prostaglandin E₂ synthase 1 (mPGES-1) catalyzes the conversion of prostaglandin H₂ (PGH₂) to prostaglandin E₂ (PGE₂). Its expression is increased in response to pro-inflammatory stimuli, and the involvement of this enzyme in different pathologic conditions, such as atherosclerosis and arthritis, prompts for the development of new and safer anti-inflammatory drugs (1,2). Recently, several clinical studies have also shown increased levels of mPGES-1 in various human cancers (e.g. colon, colorectal, stomach, pancreas, cervix, prostate cancer), thus encouraging the discovery of new mPGES-1 inhibitors as potential anticancer agents (3).

Thanks to the support of Associazione Italiana per la Ricerca sul Cancro (AIRC) (Investigator Grants IG_12777 and IG 17440, PI: Prof. Giuseppe Bifulco), we have developed a set of new mPGES-1 inhibitors featuring unprecedented chemical cores. The new inhibitors have been identified following two different computational approaches:

1. Structure-based drug design and optimization of new compounds obtainable by one-pot synthetic methods (4,5)
2. Lead and Fragment Virtual Screening (VS) from synthesizable and commercially available compounds (6,7)

The different compounds evaluated *in silico* were then selected for the subsequent phases of chemical synthesis and biological evaluation *in vitro*, identifying a set of new mPGES-1 inhibitors, all endowed with at least micromolar activity. The enhancements of the potency and of the pharmacokinetic properties of the identified compounds represent the next steps for disclosing new optimized mPGES-1 inhibitors prone to be tested in human cell lines, in inflammation and cancer animal models *in vivo*, and by small animal imaging.

References: 1. Claveau, D.; Sirinyan, M.; Guay, J.; Gordon, R.; Chan, C. C.; Bureau, Y.; Riendeau, D.; Mancini, J. A. *J. Immunol.* **2003**, *170*, 4738-4744. 2. Chang, H.-H.; Meuillet, E. *Future Med. Chem.* **2011**, *3*, 1909-1934. 3. Nakanishi, M.; Gokhale, V.; Meuillet, E. J.; Rosenberg, D. W. *Biochimie* **2010**, *92*, 660-664. 4. Lauro, G.; Strocchia, M.; Terracciano, S.; Bruno, I.; Fischer, K.; Pergola, C.; Werz, O.; Riccio, R.; Bifulco, G. *Eur. J. Med. Chem.* **2014**, *80*, 407-415. 5. Terracciano, S.; Lauro, G.; Strocchia, M.; Fisher, K.; Werz, O.; Riccio, R.; Bruno, I.; Bifulco, G. *ACS Med. Chem. Lett.* **2015**, *6*, 187-191. 6. Lauro, G.; Tortorella, P.; Bertamino, A.; Ostacolo, C.; Koeberle, A.; Fischer, K.; Bruno, I.; Terracciano, S.; Gomez-Monterrey, I. M.; Tauro, M.; Loiodice, F.; Novellino, E.; Riccio, R.; Werz, O.; Campiglia, P.; Bifulco, G. *ChemMedChem* **2016**, *11*, 612-619. 7. Lauro, G.; Manfra, M.; Pedatella, S.; Fischer, K.; Cantone, V.; Terracciano, S.; Bertamino, A.; Ostacolo, C.; Gomez-Monterrey, I. M.; De Nisco, M.; Riccio, R.; Novellino, E.; Werz, O.; Campiglia, P.; Bifulco, G. *Eur. J. Med. Chem.* **2017**, *125*, 278-287

Cytotoxic secondary metabolites from Mediterranean Fabaceae species display antiproliferative activity against colon cancer cell lines

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Several drugs currently in clinical use are of natural product origin. This success in drug discovery is due to their high chemical variability and their well-defined three-dimensional structure (1). In this work, the crude polar extracts from *Astragalus boeticus*, *Ononis diffusa* and *Trigonella corniculata* have been investigated for their cytotoxic activity against a panel of colon cancer cell lines, including those resistant to the conventional drugs. An NMR-based metabolomic approach was used to completely characterise the metabolic profiles of the plant extracts (3). In particular, an extensive 2D NMR analysis identified in the mixture the main secondary metabolites. In detail: *A. boeticus* extract contains flavonols and cycloartane triterpenes; *O. diffusa* has a very complex metabolome, especially for the aromatic component and, on the contrary, *T. corniculata* presents little variability in terms of secondary metabolites, showing a protodioscin derivative as unique main compound. Attempting to isolate in a short term the active principles from the crude extracts, a bioguided-fractionation has been performed using different chromatographic techniques. Moreover, the combinatorial use of NMR (mainly DQF-COSY, COSY, TOCSY, HSQC, H2BC, HSQCTOCSY, HMBC, CIGAR-HMBC and NOESY experiments) and TAMDEM HR-MS, elucidated the structures of the isolated molecules. As a result, five cycloastragenols were isolated from *A. boeticus* and, despite their common basic skeleton, only one among them exerts the antiproliferative properties. In the same way, oxylipin compounds, differently capable of inhibiting the cellular growth, have been separated from *O. diffusa*. These findings revealed a clear relationship between the structure and the related function of the compounds under investigation, permitting the understanding of the chemical groups essential for the biological activity. Finally, a protodioscin glycoside has been easily isolated from *T. corniculata*, confirming that this is the unique molecule responsible for the cytotoxicity of the extract. In conclusion, the above-mentioned results encouraged further experiments in order to figure out the molecular mechanism of cell death induced by the cytotoxic secondary metabolites.

References

- (1) T. Troiani, E. Martinelli, S. Napolitano, D. Vitagliano, L. P. Ciuffreda, S. Costantino, F. Morgillo, A. Capasso, V. Sforza, A. Nappi, R. De Palma, E. D'Aiuto, L. Berrino, R. Bianco, F. Ciardiello, **2013**. Increased TGF- α as a Mechanism of Acquired Resistance to the Anti-EGFR Inhibitor Cetuximab through EGFR–MET Interaction and Activation of MET Signaling in Colon Cancer Cells. *Clin Cancer Res.* 19(24):6751-6765
- (2) I. Paterson, E.A. Anderson, **2005**. The Renaissance of Natural Product as Drug Candidates. *Science.* 310: 451-453
- (3) H.K. Kim, Y.H. Choi, R. Verpoorte, **2010**. NMR-based metabolomic analysis of plants. *Nat. Protoc.* 5: 536-549

Synthesis of new peptide-drug conjugates for targeted cancer diagnosis and therapy

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Treatment with chemotherapeutics is associated with severe side effects because of the lacking selectivity of anticancers towards cancer cells. The development of a selective treatment of cancer cells could allow a significant reduction of the drug dosage with a consequent reduction of side effects in patients. Neurotensin (NT) is an almost ubiquitous peptide hormone whose type 1 receptors (NTR1) are overexpressed by certain type of tumors. Thus NT could be used as targeting peptide for the development of a peptide-base targeting therapy. To overcome the typical low *in-vivo* stability of natural peptide, the Multiple Antigen Peptide (MAP) form of neurotensin was synthesized. The tetrabranching form (NT4) ensure both an enhanced resistance to proteases and peptidases(1) and a polyvalent interaction with membrane cell receptors. Through *in-vitro* and *in-vivo* tests using fluorophore-MAP-NT conjugate the targeting activity of the tetrabranching peptide was demonstrated. (2). On the base of these results, the development of drug-MAP-NT conjugate could represent a suitable tool for a selective anticancer therapy. Among anticancer drugs, taxanes, highly effective chemotherapeutic drugs against proliferating cancer, showed serious side effects because of their high toxicity and hydrophobicity. So, during my PhD, we focused the attention on the development of paclitaxel-MAP-NT conjugates, bearing one or more drug unit. The proper reversible functionalization of the cytotoxic molecule, the nature of the better linker between the drug and the MAP-NT moiety and the suitable reaction for assembling the conjugate, along with the pharmacological properties of such conjugates (Figure 1) will be the topics of this communication.

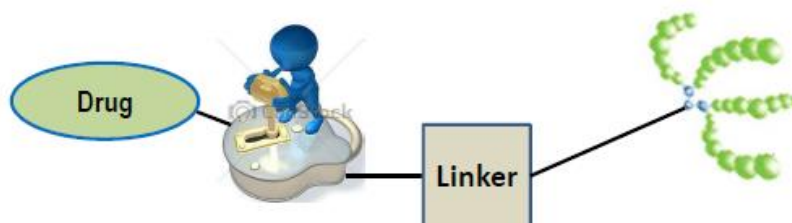


Figure 1 – MAP-NT-drug conjugates

References:

1. Bracci, L.; Falciani, C.; Lelli, B.; Lozzi, L.; Runci, Y.; Pini, A.; De Montis, M. G.; Tagliamonte, A.; Neri, P.; *J. Biol. Chem.* **2003**, 278, 46590-46595.
2. Brunetti, J., Falciani, C., Lelli, B., Minervini, A., Ravenni, N., Depau, L., Siena, G., Tenori, E., Menichetti, S., Pini, A., Carini, M., Bracci, L. *BioMed. Res. Int.*, **2015**, Article ID 173507.

Synthesis and Biological Evaluation of Some Pyrimidin-2,4-diones as Novel Non-Nucleoside Reverse Transcriptase Inhibitors

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Modified pyrimidines constitute the backbone of many antiretroviral agents acting as non nucleoside reverse transcriptase inhibitors (NNRTIs) (1, 2). 1-[(Hydroxyethoxy)methyl]-6-(phenyl-sulfanyl)thymine (HEPT; **1**) and its analogue (TNK-651; **2**) 2-alkoxy-6-benzyl-3,4-dihydro-4-oxopyrimidine (DABO; **3**), diaryl-pyrimidines (DAPYs; **4**) and their derivatives (Fig. 1) are all families of potent NNRTIs that, through binding at the allosteric, non-nucleoside binding pocket (NNIBP) of RT, prevent the conformational transition needed for the formation of a productive polymerase–RNA complex.

In this context, the synthesis and biological activity of a new class of 3-pyrimidinyl isoxazolidines **5**, as HEPT analogues, has been reported (3). Tested in vitro for their biological activity, compounds **5** showed a nearly complete inhibition of AMV RT and HIV RT in the nanomolar range, with weak cytotoxicities towards human cells.

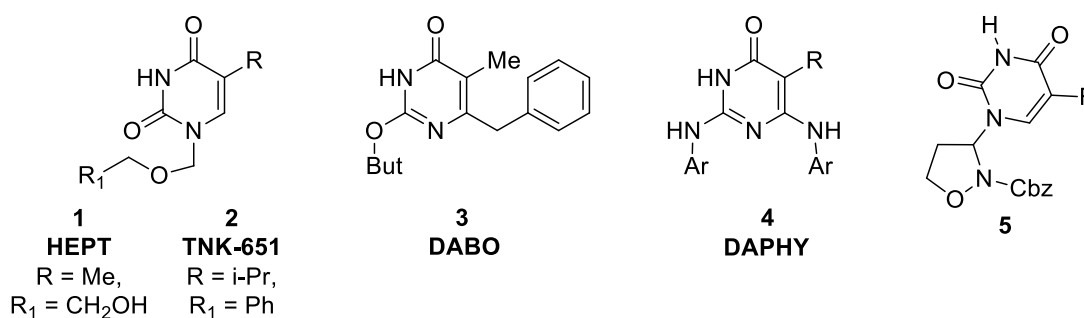


Figure 1.

We report here the design, synthesis and biological evaluation of a series of compounds amenable to derivatives **5**, where structural elaborations have been performed towards inhibiting different targets of HIV-1. The replacement of the substituent at C-5 with an ethereal unit gave compounds **6** which showed an improved inhibitory activity towards HIV-1. Removal of the isoxazolidine ring led to subtypes **7** and **8** which selectively inhibited the RNase H function of RT. The redesign of N-1 and C-5 moieties afforded compounds **9** which inhibit drug-resistant HIV-1 mutants (Fig. 2).

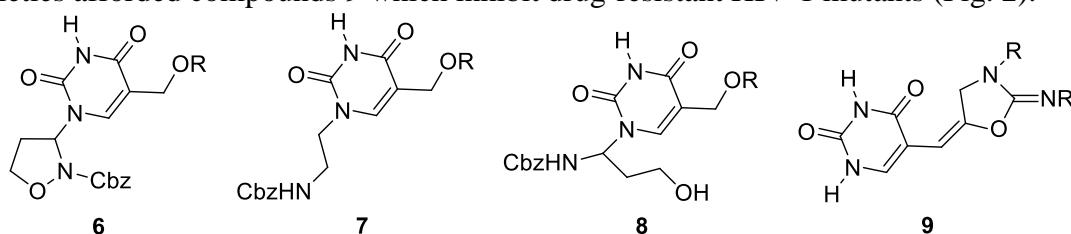


Figure 2.

References: 1. A. Moss, C. Felton, S. Nanzicu, *Frontiers in HIV Research*, G. D. Morse, S. Nanzicu Eds, **2015** vol 1, 44-61. 2. G. Romeo, U. Chiacchio, A. Corsaro, P. Merino, *Chem. Rev.* **2010**, *110*, 3337–3370. 3. R. Romeo, S. V. Giofrè, B. Macchi, A. Mastino, P. Merino, G. Romeo, U. Chiacchio. *ChemMedChem*, **2012**, *7*, 565–569

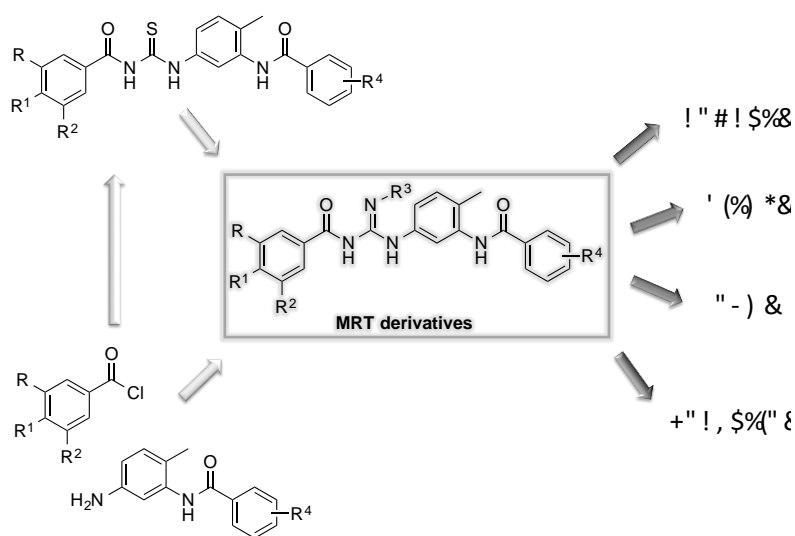
Synthesis and decoration of small molecules targeting the Hedgehog Signaling Pathway

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The Hedgehog (HH) pathway is well recognized to be critical for embryonic development and adult tissue maintenance and repair as well as for cancer onset and progression. In addition, recent studies have highlighted HH pathway as a good therapeutic target in different viral and bacterial infections. Acylguanidine and acylurea derivatives recently developed by our group emerged as interesting SMO inhibitors (1,2). A new synthetic approach has been developed to get a more efficient and scalable preparation of the compounds and to access a family of diversely decorated derivatives. Amongst these products we found some structures active in various human cancer cell lines such as chronic myeloid leukemia, medulloblastoma, and melanoma (3, 4), as well as against several virus (5); MRT derivatives modulate alkaptonuria (AKU) a rare disease involving cartilage degradation, thus demonstrating a possible role of HH pathway in this pathology (6).



Using a virtual screening approach a new family of compounds active as Gli inhibitors has also been recently developed (7) and the synthesis of a small library of derivatives with interesting anticancer activity is reported.

References: 1. Solinas, A. *et al J. Med. Chem.* **2012**, *55*, 1559. 2. Hoch, L. *et al FASEBJ* **2015**, *29*, 1817. 3. Chiarenza, A. *et al PLOS ONE* **2016**, *11*, e0149919. 4. Santini, R.; Stecca, B.; Petricci, E.; Manetti, F. *unpublished results*. 5. Diurantel, D.; Petricci, E.; Manetti, F. *unpublished results*. 6. Gambassi, S. *et al. J Cell Physiol* **2016**; 9999, 1–9. 7. EP17166194.5

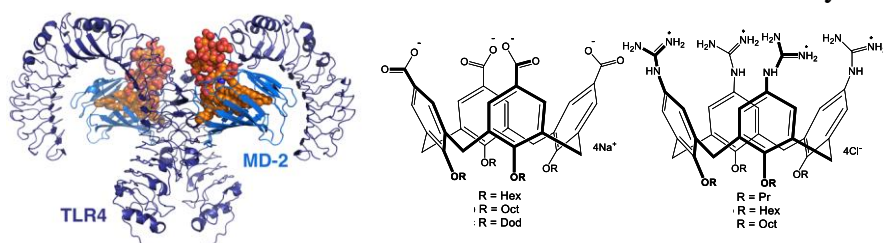
Amphiphilic Guanidinocalixarenes Inhibit Lipopolysaccharide- and Lectin-stimulated Toll-like Receptor 4 Signaling

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Toll-like Receptors (TLRs) are receptors that recognize pathogen-associated molecular patterns. Among TLRs, TLR4 in particular is the sensor of Gram-negative bacteria endotoxins lipopolysaccharide (LPS) and lipooligosaccharide (LOS) (1). TLR4 is mainly expressed on monocytes, dendritic cells and macrophages. LPS binds sequentially to lipid binding protein (LBP), cluster of differentiation 14 (CD14), and to myeloid differentiation factor 2 (MD-2) (2) that non-covalently associates with TLR4 promoting the formation of the activated receptor multimer (TLR4/MD-2.LPS)₂ (Figure, left) on the plasma membrane (3). While the role of TLR4 as LPS sensor is fundamental for initiating inflammatory and immune responses, excessive and deregulated TLR4 activation leads to acute sepsis and septic shock, associated to high lethality and for which no specific pharmacological treatment is available (4,5). TLR4 can also be activated by endogenous factors called damage-associated molecular patterns (DAMPs), derived from damaged, necrotic, or infected tissues. DAMPs-activated TLR4 signaling is implicated in a large array of pathologies including atherosclerosis (6), rheumatoid arthritis (7), neuroinflammations, neuropathic pain (8) and neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) (9).

To block abnormal TLR4 signaling we proposed and synthesized a series of facial amphiphilic ligands based on a calix[4]arene scaffold, all characterized by the presence of charged heads on a rim and lipophilic tails on the other (some examples in Figure). Preliminary molecular modeling studies evidenced the possibility for these compounds to bind inside the binding pocket of CD14 and MD2. Subsequent biological tests on cells showed that some of them are strong inhibitors of TLR-4 activation even in absence of LPS. This means that their activity is due to their interaction directly



with TLR-4 or its dimer with MD-2 or with one of the receptors involved in the activation pathway, rather than to the simple binding to LPS (10).

References: 1. Poltorak, A.; He, X.; Smirnova, I.; Liu, M.; Van Huffel, C.; Du, X.; Birdwell, D.; Alejos, E.; Silva, M.; Galanos, C.; Freudenberg, M.; Ricciardi-Castagnoli, P.; Layton, B.; Beutler, B. *Science* **1998**, *282*, 2085-2088. 2. Gioannini, T.; Teghanemt, A.; Zhang, D.; Coussens, N.; Dockstader, W.; Ramaswamy, S.; Weiss, J. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 4186-4191. 3. Park, B.; Song, D.; Kim, H.; Choi, B.; Lee, H.; Lee, J. *Nature* **2009**, *458*, 1191-1195. 4. Gogos, C. A.; Drosou, E.; Bassaris, H. P.; Skoutelis, A. *J. Infect. Dis.* **2000**, *181*, 176-180. 5. Brunialti, M.; Martins, P.; Barbosa de Carvalho, H.; Machado, F.; Barbosa, L.; Salomao, R. *Shock* **2006**, *25*, 351-357. 6. Erridge, C. J. *Innate Immun.* **2009**, *1*, 340-349. 7. Abdollahi-Roodsaz, S.; Joosten, L. A.; Roelofs, M. F.; Radstake, T. R.; Matera, G.; Popa, C.; van der Meer, J. W.; Netea, M. G.; van den Berg, W. B. *Arthritis Rheum.* **2007**, *56*, 2957-2967. 8. Cao, L.; Tanga, F. Y.; Deleo, J. A. *Neuroscience* **2009**, *158*, 896-903. 9. Casula, M.; Iyer, A. M.; Spliet, W. G.; Anink, J. J.; Steentjes, K.; Sta, M.; Troost, D.; Aronica, E. *Neuroscience* **2011**, *179*, 233-243. 10. Sestito, S. E.; Facchini, F. A.; Morbioli, I.; Billod, J.-M.; Martin-Santamaria, S.; Casnati, A.; Sansone, F.; Peri, F. *J. Med. Chem.* *accepted*.

Synthesis and stereochemical properties of axially chiral benzo[1,2-*b*:4,3-*b'*]dithiophene derivatives

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Thiophene-containing fused aromatic compounds represent an interesting class of π -conjugated systems in functional organic materials (1). Among them, benzo[1,2-*b*:4,3-*b'*]dithiophene (**BDT**) and its derivatives are widely studied, especially as units in mono and polydisperse oligomers in the field of the materials science (2), and as π -spacers in push-pull organic chromophores for photovoltaic applications (3). Moreover, **BDT** is a key intermediate for the synthesis of inherently chiral helical systems such as tetrathia[7]helicenes (4). For all these reasons, **BDT** can be identified as a key starting molecule that, through a judicious functionalization of the α -positions of the thiophene rings, can allow access to more complex and interesting systems. Exploiting the experience acquired in our laboratories on the synthesis and functionalization of **BDT** derivatives (5,6), we have studied a novel and simple synthetic route to prepare bis(benzo[1,2-*b*:4,3-*b'*]dithiophene) systems **2**, through Pd-catalyzed cross coupling reactions, starting from bromides **1** (Figure 1).

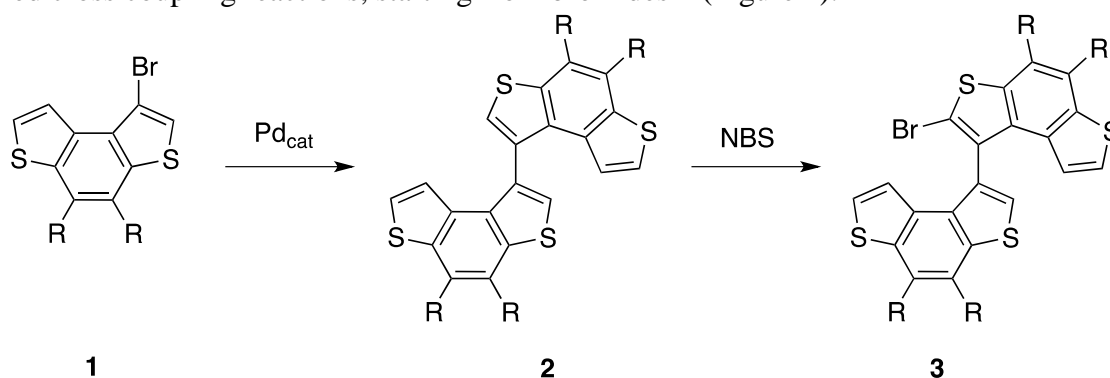


Figure 1

This strategy provides a convenient route to an interesting class of chiral atropisomeric heterobiaryl derivatives with C_2 -symmetry, which can be selectively functionalized into bromides **3**. The chiroptical properties of compounds **2** and **3** have been fully elucidated by experimental and theoretical studies. Bromides **3** are expected to have potential applications in asymmetric reactions, including the enantioselective synthesis of tetrathiahelicene derivatives.

References: 1. Rieger, R.; Beckmann, D.; Mavrinskiy, A.; Kastler, M.; Müllen, K. *Chem. Mater.* **2010**, *22*, 5314. 2. Nishide, Y.; Osuga, H.; Saito, M.; Aiba, T.; Inagaki, Y.; Doge, Y.; Tanaka, K. *J. Org. Chem.* **2007**, *72*, 9141. 3. Longhi, E.; Bossi, A.; Di Carlo, G.; Maiorana, S.; De Angelis, F.; Salvatori, P.; Petrozza, A.; Binda, M.; Roiati, V.; Mussini, P. R.; Baldoli, C.; Licandro, E. *Eur. J. Org. Chem.* **2013**, *84*. 4. Licandro, E.; Rigamonti, C.; Ticozzelli, M. T.; Monteforte, M.; Baldoli, C.; Giannini, C.; Maiorana, S. *Synthesis* **2006**, 3670. 5. Cauteruccio, S.; Dova, D.; Graiff, C.; Carrara, C.; Doulcet, J.; Stephenson, G. R.; Licandro, E. *New J. Chem.* **2014**, *38*, 2241. 6. Stephenson, G. R.; Cauteruccio, S.; Doulcet, J. *Synlett* **2014**, 701.

Bioinspired organocatalysis of C-C bond-forming reactions

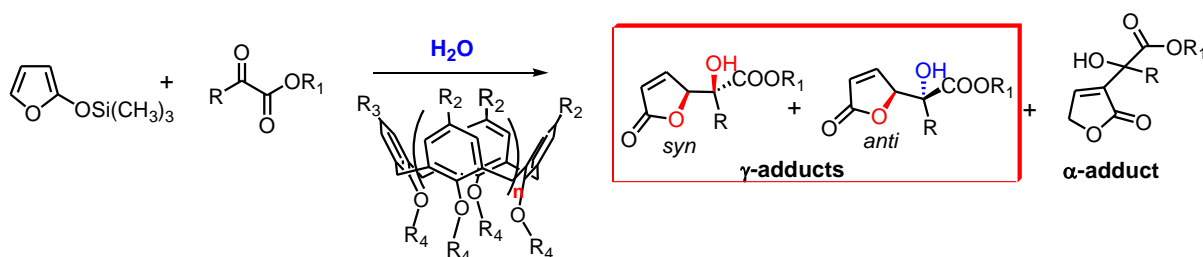
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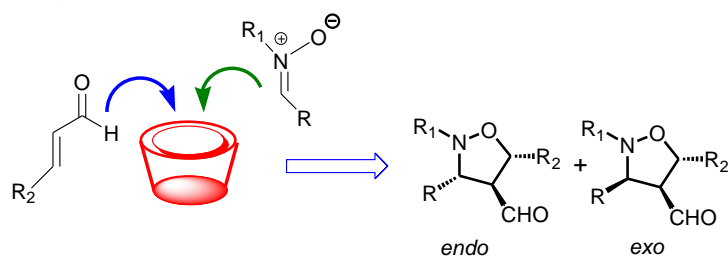
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Over the last few decades, there has been a particular attention to the development of new and efficient synthetic strategies inspired to mimic the performance, selectivity and specificity in biological processes. (1,2) In this context, the replacement of organic solvents with more environmentally benign water and the design of "artificial" enzymes with the desirable features of natural ones but without their intrinsic drawbacks such as poor substrate versatility and ease of denaturation, represent promising fields. (3,4) We report here our recent studies on these two issues based on the use of calixarene derivatives. In fact, their hydrophobic character combined with their recognition abilities make them valid organocatalysts for the vinylogous Mukaiyama aldol reaction under "on-water" conditions (5,6) and provide a confined reaction environment to efficiently conduct 1,3-dipolar cycloaddition of nitrones to α,β -unsaturated aldehydes.(7)

Calixarenes as organocatalysts under "on-water" conditions



Catalysis inside nanocavities



1. J. G. Hernandez, E. Juaristi *Chem. Comm.* **2012**, 48, 5396-5409
2. L. Marchetti, M. Levine *ACS Catal.* **2011**, 1, 1090-1118
3. R. N. Butler, A. G. Coyne *Chem. Rev.* **2010**, 110, 6302-6337
4. M. B. Gawande, V. D. B. Bonifácio, R. Luque, P. S. Branco, R. S. Varma *Chem. Soc. Rev.* **2013**, 12, 5522-5551
5. M. De Rosa, P. La Manna, A. Soriente, C. Gaeta, C. Talotta, P. Neri, *RSC Adv.* **2016**, 6, 91846-91851.
6. M. De Rosa, P. La Manna, A. Soriente, C. Gaeta, C. Talotta, N. Hickey, S. Geremia, P. Neri *Chem. Eur. J.* **2017**, DOI: 10.1002/chem.201701247.
7. G. Floresta, C. Talotta, C. Gaeta, M. De Rosa, U. Chiacchio, P. Neri, A. Rescifina, *J. Org. Chem.* **2017**, DOI: 10.1021/acs.joc.7b00227

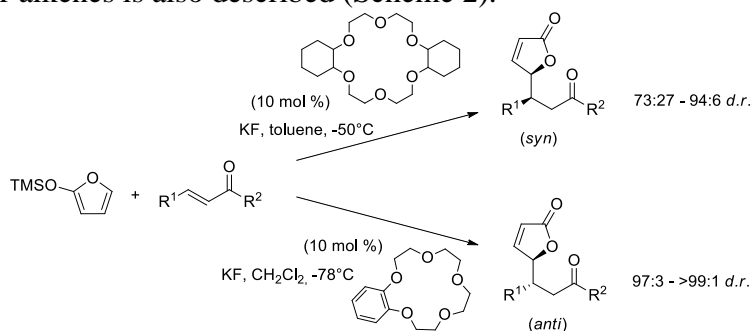
Highly diastereoselective synthesis of γ -butenolides and phthalides by Michael addition catalyzed by crown ethers

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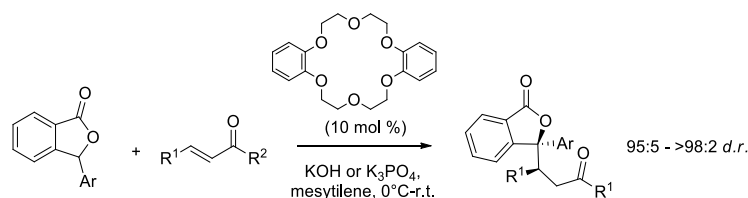
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γ -Butenolides (1) and phthalides (2) are structural motifs found in numerous natural products and pharmaceutically useful analogues displaying a wide range of biological activities. In addition, their frameworks proved to be useful chiral building blocks for the synthesis of diverse bioactive natural compounds. Much effort has thus been devoted to the stereocontrolled construction of these lactones. An attractive strategy for the stereoselective introduction of a substituent in the C-3 position of the γ -lactone framework is the Michael addition to appropriate electron-poor alkenes. The vinylogous Michael addition of 2(5*H*)-furanones or 2-silyloxyfurans to α,β -unsaturated ketones reported to date often employ expensive chiral catalysts and usually favor the *anti* products (3). On the other hand the stereoselective Michael addition of phthalides has been scarcely investigated and limited to activated phthalide-3-carboxylic esters (4,5).

In this communication we report crown ethers as efficient achiral and off-the-shelf catalysts for the diastereoselective Michael addition of γ -butenolides and 3-aryl-phthalides to α,β -unsaturated ketones. In particular, we have developed an unprecedented switchable diastereoselective vinylogous Mukaiyama-Michael reaction of 2-trimethylsilyloxyfuran with α,β -unsaturated ketones, that enables the synthesis of both *syn* or *anti* adduct depending on the crown ether's cavity size and the solvent employed (Scheme 1). The first highly diastereoselective Michael addition of 3-aryl-phthalides to diverse electron-poor alkenes is also described (Scheme 2).



Scheme 1



Scheme 2

References: 1. Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem. Int. Ed.* **2009**, *48*, 9426-9451. Salamone, M.; Bietti, M. *Acc. Chem. Res.* **2015**, *48*, 2895-2903. 2. Lin, G.; Chan, S. S.-K.; Chung, H.-S.; Li, L. S. In *Studies in Natural Products Chemistry: Bioactive Natural Products*, Vol. 32 (Part L); Atta-ur-Rahman, Ed.; Elsevier, Amsterdam, 2005; pp. 611-669. 3. Jusseau, X.; Chabaud, L.; Guillou, C. *Tetrahedron* **2014**, *70*, 2595-2615. 4. Luo, J.; Jiang, C.; Wang, H.; Xu, L.-W.; Lu, Y. *Tetrahedron* **2013**, *54*, 5261-5265. 5. Luo, J.; Wang, H.; Zhong, F.; Kwiatkowski, J.; Xu, L.-W.; Lu, Y. **2013**, *59*, 5775-5777.

Design of a new chiral nanosupported catalyst for asymmetric reactions

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Asymmetric catalysis is nowadays considered one of the strongest tools to obtain enantiopure products: starting from prochiral molecules, it enables to synthesize optical active compounds with the help of small amount of the appropriate chiral catalyst. The opportunity to recover and reuse the catalyst, most of the times valuable molecules, has led to the adoption of new techniques belonging to material chemistry. In the last years, the growing study of nanostructured materials has given birth to a variety of new applications in many fields, among which catalysis. New chiral nanosystems has been developed, combining advantages of both homogeneous and heterogeneous catalysis: nanoparticles' dispersibility in organic solvents makes their catalytic activity close to that of their homogeneous counterparts; at the same time, they are easily separated from the reaction mixture resulting in an economical and environmental benefit (1).

Recently, we were involved in the design and synthesis of new chiral nanosystems characterized by a β -amino alcohol fragment as catalytic site, a recurrent motif in many chiral catalysts (2), (Fig 1-A). Before immobilizing the catalyst, it was necessary to optimize the structure of the chiral ligand by proving it in the enantioselective addition of diethylzinc to aldehydes, often chosen as reaction test. After an extensive fine tuning process ligand **1** was found to be an excellent chiral catalyst in the selected reaction (yield 88-98%, *ee*=90-98%, Fig 1-B), and a good one in the asymmetric version of another organic reaction, the nitroaldol or Henry reaction, source of nitroalcohols, a synthetically interesting class of compounds (Fig 1-C)

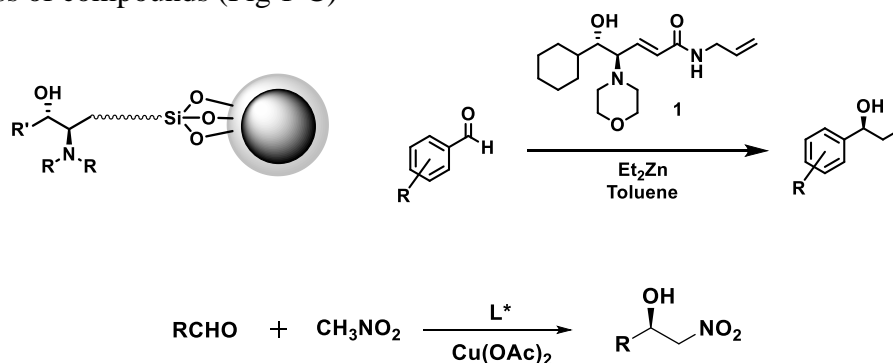


Fig 1

In parallel, we are focusing on the optimization of the immobilization conditions and on the choice of the best solid support (Fig 2). These new β -amino alcohol nanosupported chiral catalysts will finally be tested in the same reaction previously optimized in the homogeneous phase.

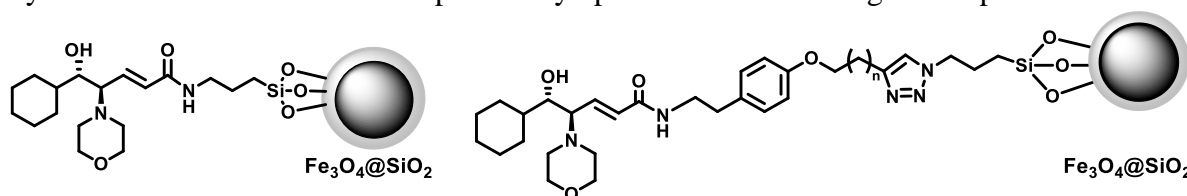


Fig 2

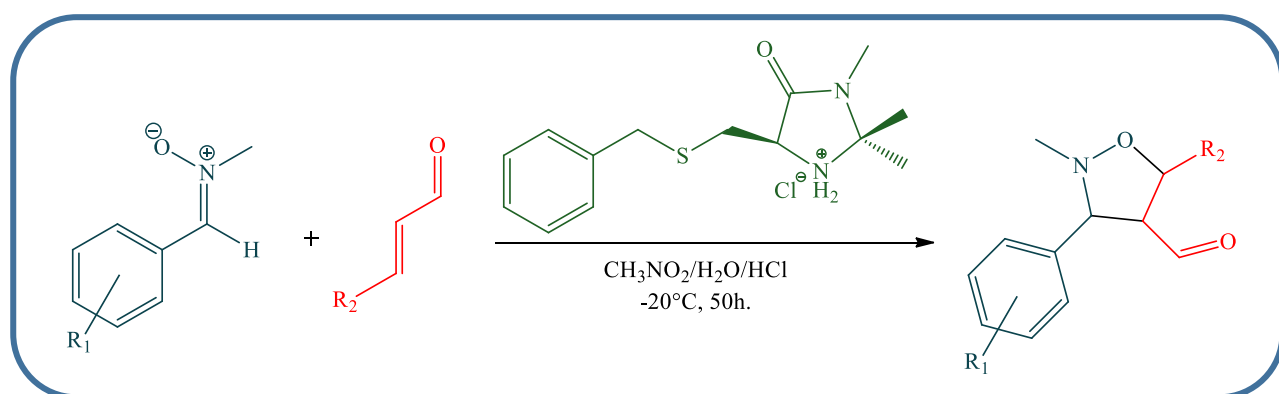
References: 1. Rossi LM, Costa NJS, Silva FP, Wojcieszak R. *Green Chem.*, **2014**, *16*, 2906-2933. 2. Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* 1996, *96*, 835-875.

Asymmetric 1,3-dipolar cycloadditions catalyzed by a new imidazolidinone organocatalyst

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Organocatalysis exploits the small organic molecules to increase the speed of the reactions (1). Catalysis is divided into non covalent and covalent. The covalent catalysis mediated by iminium ion has been used in various applications. Pollak decarboxylation (2) was the first example of asymmetric catalysis and was performed using the L-Proline (3). According to this model, it was later developed a new type of the enantioselective imidazolidinone catalysts (4). In this work, we designed and synthesized a new type of asymmetric imidazolidinone organocatalyst, (5S)-2,2,3-trimethyl-5-thiobenzyl-4-imidazolidinone [A]. This latter, after characterization, was initially tested on Diels-Alder reaction in which it has been possible to observe excellent catalytic efficiency at low load percentages (5).



Scheme 1

In this work our research group will describe the results about 1,3-Dipolar Cycloaddition Reactions using various substituted nitrones as 1,3-dipoles and α,β -unsaturated aldehydes as dipolarophiles (Scheme 1). The reaction yields and diastereomeric excesses are very high and excellent enantiomeric ratios of the reaction products have been observed in presence of the catalyst A.

References:

1. P. I. Dalko, *Enantioselective Organocatalysis*, 2007, Ed. WILEY-VCH.
2. K. J. Pedersen, *J. Phys. Chem.*, 1934, 38, 599.
3. Woodward et al., *J. Am. Chem. Soc.*, 1981, 103, 3210.
4. R. Naef, D. Seebach, *Helv. Chim. Acta*, 1985, 68, 135.
5. A. De Nino, L. Maiuolo, P. Merino, M. Nardi, A. Procopio, D. Roca-López, B. Russo, V. Algieri, *ChemCatChem*, 2015, 7, 830-835.

A new highly efficient strategy to prepare racemic *Anatabine*

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Among 4000 different compounds isolated and identified in *Nicotiana tabacum* plants, *Anatabine* represents the most abundant of minor alkaloids (1), found with an intermediate enantiomeric ratio.

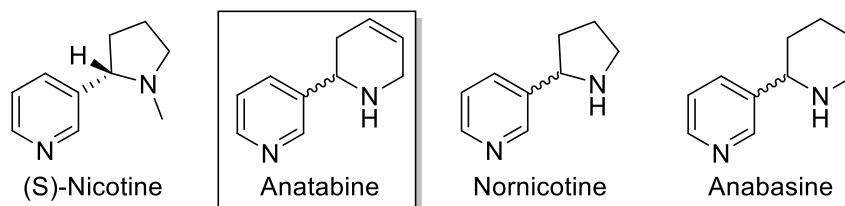
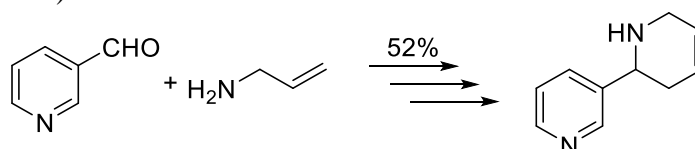


Fig.1 Nicotine and structurally related alkaloids found in fresh leaves of *Nicotiana tabacum* plants.

In particular *Anatabine* possesses several important pharmacological properties such as *anti-inflammatory* activity (2); it also suppresses amyloid beta production (3), and reduces autoimmune thyroiditis (4). Furthermore, it has been demonstrated that *Anatabine* decreases nicotine self-administration, suggesting its possible role as agonist medication for treatment of nicotine addiction (5).

As a consequence, many methodologies for its synthesis have been developed, however they present important limitations such as low over-all yields (6), use of harsh conditions (7) or toxic agents (8). In order to overcome these drawbacks, herein we present a novel synthetic strategy to prepare racemic *Anatabine* within few steps, in good overall yield, starting from low-cost commercially available building blocks (Scheme 1).



Scheme 1.

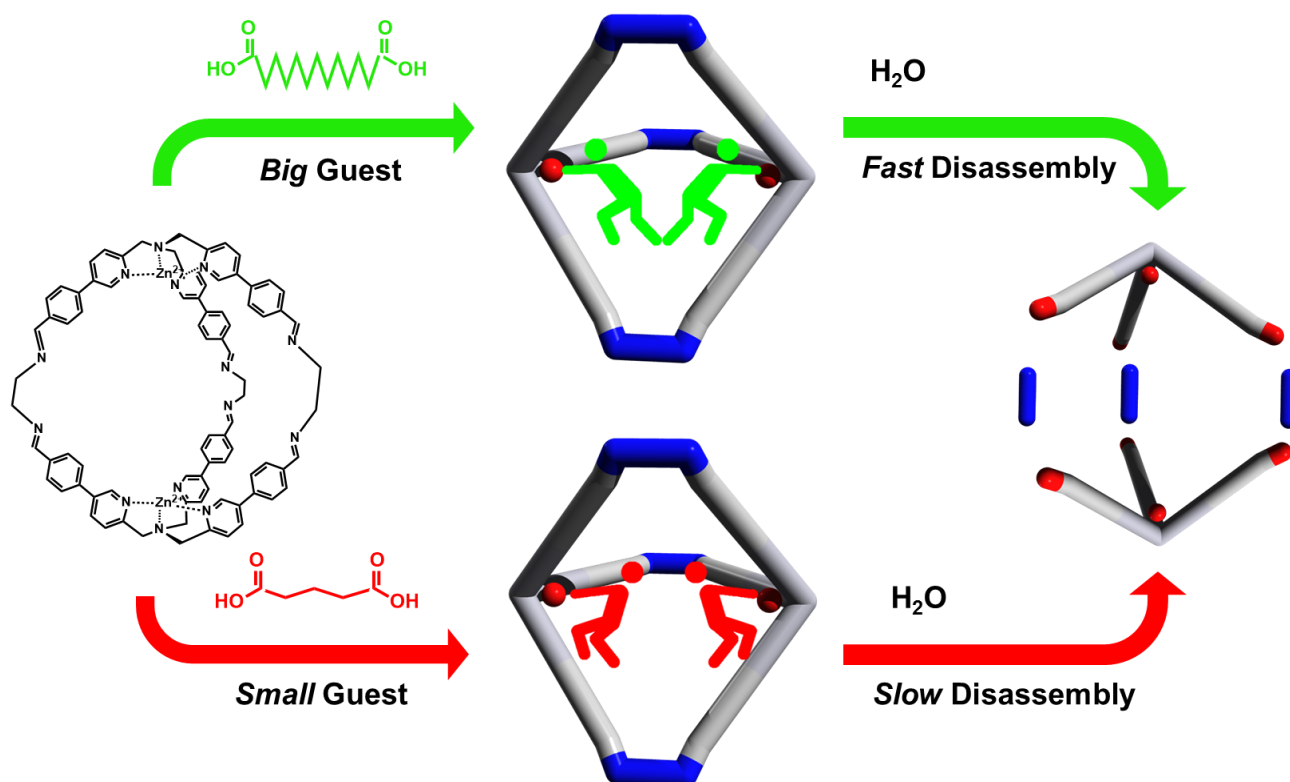
References: 1. Rouchaud, A.; Kem, W. R. *J. Heterocyclic Chem.*, **2010**, *47*, 569-581. 2. Paris, D.; Beaulieu-Abdelahad, D.; Abdullah, L.; Bachmeier, C.; Ait-Ghezala, G.; Reed, J.; Verma, M.; Crawford, F.; Mullan, M. *Eur. J. Pharmacol.* **2013**, *698* (1-3), 145-153. 3. Paris, D.; Beaulieu-Abdelahad, D.; Bachmeier, C.; Reed, J.; Ait-Ghezala, G.; Bishop, A.; Chao, J.; Mathura, V.; Crawford, F.; Mullan, M. *Eur. J. Pharmacol.* **2011**, *670* (2-3), 384-391. 4. Caturegli, P.; De Remigis, A.; Ferlito, M.; Landek-Salgado, M.A.; Iwama, S.; Tzou, S.C. *Endocrinology* **2012**, *153* (9), 4580-4587. 5. Mello, N. K.; Fivel, P. A.; Kohut, S. J.; Caine, S. Barak. *Exp. and Clin. Psychopharm.* **2014**, *22* (1), 1-8. 6. Saloranta, T.; Leno, R. *Tetrahedron Lett.* **2011**, *52*, 4619-4621. 7. Felbin, F.-X.; Girard, S.; Vo-Thanh, G.; Robins, R. J.; Villieras, J.; Lebreton, J. *J. Org. Chem.*, **2001**, *66*, 6305-6312. 8. Balasubramanian, T.; Hassner, A. *Tetrahedron: Asymmetry* **1998**, *9* (13), 2201-2205.

Molecular Events within Confined Spaces

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Self-assembly of small molecules in complex architectures is becoming the leading strategy for the formation of novel functional systems and materials. Among the different bond-formation synthetic strategies, imine condensation chemistry combined with coordination chemistry has been extensively used to obtain a large variety of molecular architectures ranging from supramolecular cages to topological structures. In the recent years we have been interested in the self-assembly of tris(2-pyridylmethyl)amine derived structures.(1) In this communication we report about a novel supramolecular cage built from the self-assembly of tris(2-pyridylmethyl)amine zinc complexes through imine condensation chemistry. The cage recognition properties over a variety of structurally related guests, together with the kinetic study of the template assembly and disassembly, have been investigated in detail. This knowledge has been used to selectively modulate the rate of both assembly and disassembly processes. In particular, a novel disassembly method induced by strain release of the guest has been developed.(2)



References:

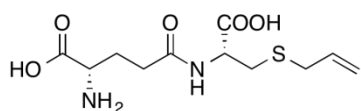
1. F.A. Scaramuzzo, G. Licini, C. Zonta *Chem. Eur. J.* **2013**, *19*, 16809. E. Badetti, K. Wurst, G. Licini, C. Zonta *Chem. Eur. J.* **2016**, *22*, 6515. R. Berardozzi, E. Badetti, N.A. Carmo dos Santos, K. Wurst, G. Licini, G. Pescitelli, C. Zonta, L. Di Bari *Chem. Commun.* **2016**, *52*, 8428. F. A. Scaramuzzo, E. Badetti, G. Licini, C. Zonta *Eur. J. Org. Chem.* **2017**, 1438
2. C. Bravin, E. Badetti, F.A. Scaramuzzo, G. Licini and C. Zonta *J. Am. Chem. Soc.* **2017**, *139*, 6456–6460.

Synthetic application of bacterial γ -glutamyltransferases (GGTs)

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γ -Glutamyl dipeptides are compounds characterized by an amide bond involving the amino group of one amino acid and the γ -carboxyl group of a glutamic acid residues. They show interesting properties with respect to their parent amino acids. For example, the bitterness of aromatic and branched-chain amino acids used in oral dietary supplements is alleviated or even abolished upon γ -glutamylation, as does the unpleasant smell of seleno amino acids, the source of the micronutrient selenium.



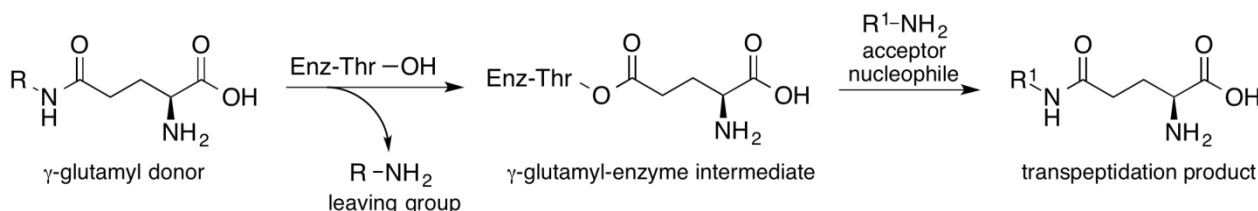
γ -L-glutamyl-S-allyl-L-cysteine
naturally occurring flavor enhancer found in garlic

γ -Glutamyl derivatives of *S*-substituted cysteines are naturally occurring flavor enhancers found in garlic and onion.¹

Although their possible applications render the γ -glutamyl derivatives economically interesting compounds, their supply remains a problem. Isolation from natural sources, if any, is laborious and low-yielding, as their content may vary with cultivation and storage.² Chemical synthesis is not economical,

due to the need of protection/deprotection steps. A viable alternative could then rely on an enzymatic approach taking advantage by the use of a γ -glutamyltransferase.

γ -Glutamyltransferases (GGTs, EC 2.3.2.2) are widespread, conserved enzymes found in bacteria, plants and animals.³ They catalyze the transfer of a γ -glutamyl moiety from a donor compound, usually glutathione, to an acceptor amino acid through a γ -glutamyl-enzyme intermediate involving a catalytically active threonine residue.



As a first approach, a commercially available, crude γ -glutamyltransferase of animal origin was used in our laboratories for the synthesis of some naturally occurring derivatives found in garlic.⁴ Then, our research group turned attention to bacterial enzymes, especially from GRAS (*Generally Referred as Safe*) microorganisms. The GGT from *B. subtilis* seemed to be well suited for our purposes and a detailed study of this enzyme was since then undertaken.⁵

Recent findings obtained about the enzymatic activity of *B. subtilis* GGT and related to the peculiar architecture of its active site will be presented, in relation to its application as a biocatalyst for the synthesis of γ -glutamyl derivatives of economical interest.

This work is supported by Fondazione Cariplo (TailGluTran Project, 2016-0741)

References: 1. Y. Ueda, M. Sakaguchi, K. Hirayama, R. Miyajima, and A. Kimizuka *Agric. Biol. Chem.* **1990**, *54*, 1639; 2. M. Ichikawa, N. Ide and K. Ono *J. Agric. Food Chem.* **2006**, *54*, 4849-4854; 3. I. Castellano and A. Merlino, *Cell. Mol. Life Sci.* **2012**, *69*, 3381-3394; 4. G. Speranza and C. F. Morelli *J. Mol. Catal. B: Enzym.* **2012**, *84*, 65-71; 5. C. F. Morelli, C. Calvio, M. Biagiotti, and G. Speranza *FEBS J.* **2014**, *281*, 232-245.

Functionalized triazolylidenes as versatile mesoionic carbenes: metal complexes for catalysis and luminescent materials

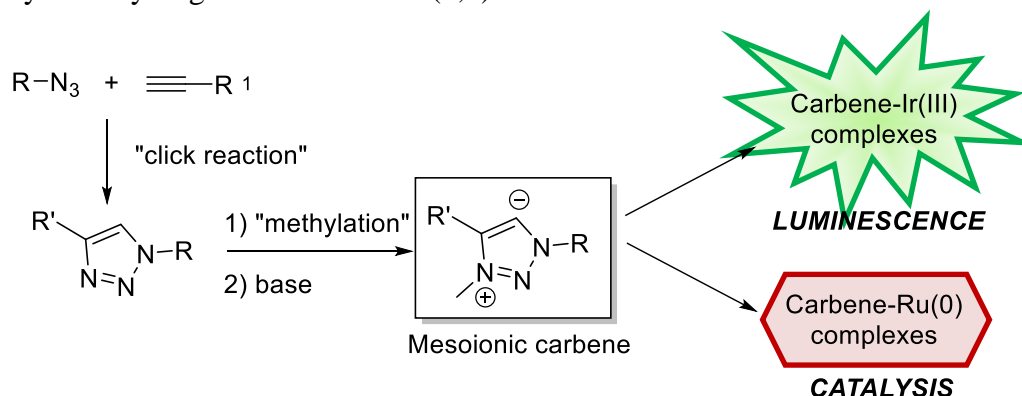
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1,2,3-Triazol-5-ylidene derivatives have recently emerged as a new class of so-called mesoionic carbenes,(1) and have found a wide range of applications as ligands in metal complexes.(2) The success of this class of ligands is based on a combination of favorable features, as a result of their strong donor character and the easy preparation of the triazole precursors through the regioselective copper(I) catalyzed 'click' cycloaddition of alkynes with azides (CuAAC).(3) Subsequent *N*-alkylation and deprotonation of the readily obtained 1,2,3-triazoles afford the desired mesoionic carbene ligands.(4)

The presence of a heteroatom in a suitable position of a substituent of the triazolylidene can lead to a bis-chelating ligand or to a ligand carrying an activating functionality.

We exploited such triazolylidene mesoionic carbenes to obtain a wide set of both positive and neutral Ir(III)-complexes,(5,6) with good luminescent performances, and neutral Ru(0)-complexes, used as active catalysts in hydrogenation reactions.(6,7)



References: 1. a) Mathew, P.; Neels, A.; Albrecht, M. *J. Am. Chem. Soc.* **2008**, *130*, 13534–13535. b) Guisado-Barrios, G.; Bouffard, J.; Donnadieu, B.; Bertrand, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 4759–4762. 2. a) Donnelly, K. F.; Petronilho, A.; Albrecht, M. *Chem. Commun.* **2013**, *49*, 1145–1159. b) Aizpurua, J. M.; Fratila, R. M.; Monasterio, Z.; Pérez-Esnaola, N.; Andreieff, E.; Irastorza, A.; Sagartzazu-Aizpurua, M. *New J. Chem.* **2014**, *38*, 474–480, and cited references. 3. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599. 4. Crabtree, R. H. *Coord. Chem. Rev.* **2013**, *257*, 755–766 and cited references. 5. A. Baschieri, F. Monti, E. Matteucci, A. Mazzanti, A. Barbieri, N. Armaroli, L. Sambri, *Inorg. Chem.*, **2016**, *55*, 7912–7919. 6. Unpublished results. 7. C. Cesari, A. Cingolani, C. Parise, S. Zacchini, V. Zanotti, M.C. Cassani, R. Mazzoni, *RSC Adv.*, **2015**, *5*, 94707.

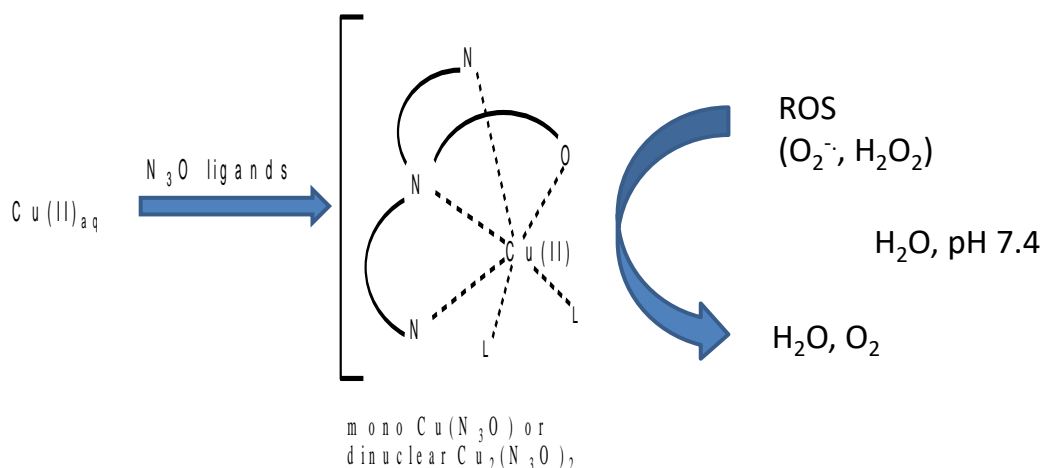
Copper complexes with biomimetic antioxidant activity

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The anomalous production of reactive oxygen species (ROS), generated as by-products of normal cellular metabolism, is responsible for an enhanced oxidative stress, which is ultimately associated with several disorders, chronic diseases and ageing. A major defense strategy of living systems against the ROS is represented by the antioxidant enzymes (1). These primarily belong to the superoxide dismutase (SOD) family, whose task is the disproportionation of $O_2^{\cdot-}$ into O_2 and H_2O_2 . This latter oxidant is then detoxified by catalase (CAT) enzymes upon conversion into O_2 and H_2O . The active sites of the antioxidant enzymes contain metal ions as Cu(II) and Mn(III), coordinated by a set of N and O donor atoms. Despite the large availability of metal complexes showing a similar coordination environment, the efficient mimicking of the enzymatic redox activity still represents a challenging goal (2,3).

In this communication, the use of tetradentate N_3O tripodal ligands, for the preparation of antioxidant synthetic enzymes, will be presented. In particular, mononuclear and dinuclear copper complexes have been prepared and tested under physiological-like conditions, in order to assess their structure-dependent catalytic behavior towards SOD-like and CAT-like reactions, showing in some cases an interesting dual activity.



Moreover, since free Cu(II) ions may also be responsible for an enhanced ROS production, the ligands have been tested to scavenge these ions from an aqueous solution, in order to convert their harmful reactivity into a benign antioxidant activity, while the peroxidase-like reactivity of the resulting complexes has been evaluated in the presence of different substrates. The speciation and the stability of the complexes will be also discussed.

1. K. Jomova, M. Valko *Toxicology*, **2011**, 283, 65-87.
2. A. Squarcina, A. Sorarù, F. Rigodanza, M. Carraro, G. Brancatelli, T. Carofiglio, S. Geremia, V. Larosa, T. Morosinotto, M. Bonchio *ACS Catal.*, **2017**, 7, 1971–1976.
3. G. Britovsek, M. Grau, F. Rigodanza, A. J P White, A. Sorarù, M. Carraro, M. Bonchio *Chem. Commun.*, **2014**, 50, 4607-4609.

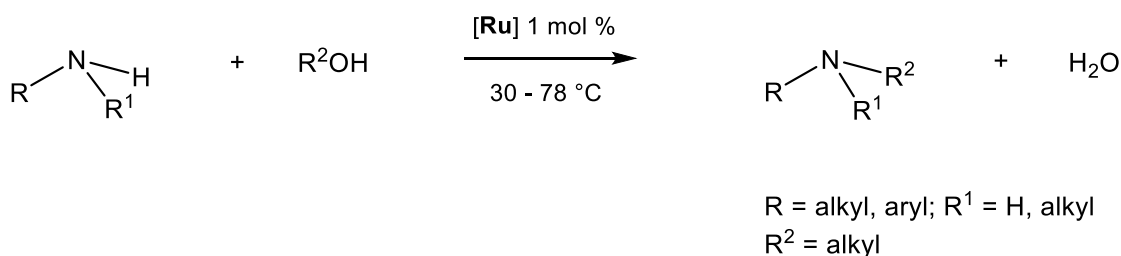
Mild *N*-Alkylation of Amines with Alcohols Catalyzed by Acetate Ruthenium Complexes

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The formation of C-N bonds for the preparation of amines compounds is a reaction of high relevance for the synthesis of bulk and fine chemicals (1). The preparation of several drug molecules involves *N*-substitution transformations that are usually performed by reaction of amines with alkylating agents or via reductive amination. In this context, the catalytic *N*-alkylation of amines using environmentally friendly alcohols as alkylating reagents and affording water as only byproduct, is an attractive atom-economic way for the C-N bond formation (2,3).

We report here the straightforward synthesis of the carboxylate ruthenium complexes of formula Ru(OAc)₂(diphosphane)(CO)_n (n = 0, 1). These compounds are efficient catalysts for the *N*-alkylation of amines using primary alcohols under mild reaction conditions, with an alcohol / amine molar ratio of 10-100. Evidence has been provided that in catalysis a monohydride species is formed through an equilibrium reaction.



References:

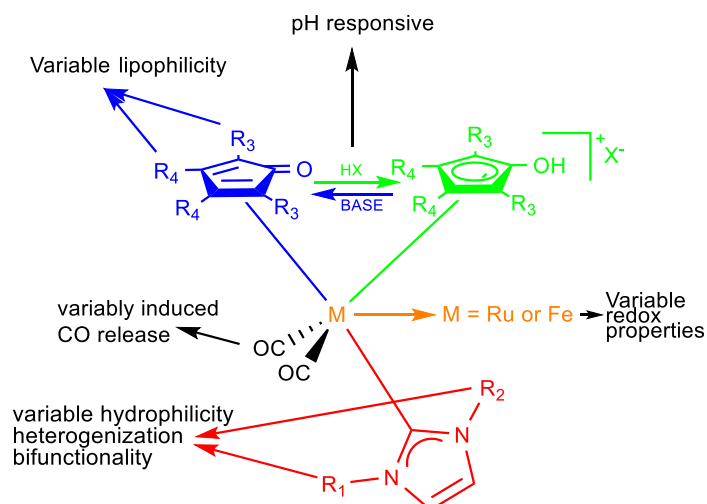
1. J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337.
2. X. Ma, C. Su, Q. Xu, *Top. Curr. Chem. (Z)* **2016**, *374*, 27.
3. J. Leonard, A. J. Blacker, S. P. Marsden, M. F. Jones, K. R. Mulholland, R. Newton, *Org. Process Res. Dev.* **2015**, *19*, 1400.

The power of ligand combination in redox active ruthenium and iron complexes.

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In recent years, cyclopentadienone complexes have drawn attention due to their air-water stability, availability from cheap starting materials, and unique catalytic features arising from the presence of a non-innocent ligand.(1) In the meantime N-heterocyclic carbenes increased their ubiquity as ancillary ligands in catalysis and other fields due to their great potential for both easy synthesis and functionalization.(2) Our recent research interest has been thus devoted to the development of novel ruthenium and iron based complexes combining carbonyls, cyclopentadienones and variously functionalized N-heterocyclic carbenes.(3) These complexes can be rapidly protonated on cyclopentadienone by strong acid (e.g. HOTf) giving rise, in the case of ruthenium, to active precursors for bifunctional hydrogenation and dehydrogenation catalysis.(4)



The straightforward synthetic method allowed the design of complexes containing hydroxyl, amino and pyridine functionalized NHC directed to the improvement of their catalytic activity, to the development of supported materials and to the preparation of water-soluble complexes. Herein, we report on the chemistry of the ruthenium complexes as bifunctional catalysts in hydrogenation and dehydrogenation with particular emphasis on the peculiar role that a basic nitrogen on the lateral chain of NHC can play on the mechanism investigated by *in situ* IR and DFT calculations. Joy and pain of the shift to earth abundant iron congeners will be then described. Finally the potential of these ligand-metal combinations in biphasic catalysis, bio-derived substrate transformations, electrochemistry and bio-inorganic chemistry will be also outlined.

References: 1. A. Quintard and J. Rodriguez *Angew. Chem. Int. Ed.* 53 (2014), 4044. 2. Hopkinson, M.N., Richter, C., Schedler, M. and Glorius, F., *Nature* 510 (2014) 485. 3. [Ru] C. Cesari, S. Conti, S. Zacchini, V. Zanotti, M. C. Cassani and R. Mazzoni, *Dalton Trans.*, 2014, 43, 17240. [Fe] A. Cingolani, C. Cesari, S. Zacchini, V. Zanotti, M.C. Cassani and R. Mazzoni *Dalton Trans.*, 44 (2015), 19063; 4. Cesari, C., Mazzoni, R., Muller-Bunz, H. and Albrecht, M., *J. Organomet. Chem.* 793 (2015) 256; Cesari, C., Cingolani, A., Parise, C., Zacchini, S., Zanotti, V., Cassani, M.C. and Mazzoni, R., *RSC Adv.* 5 (2015) 94707.

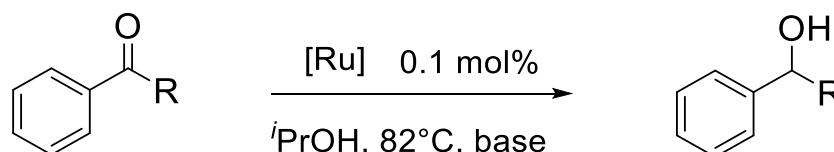
Synthesis of New Carbonyl Diphosphane Ruthenium Complexes for Catalytic C-H Bond Activation Reactions

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Homogeneous catalysis plays a key role in development of new chemo- and enantio-selective syntheses that point to efficiency and low environmental impact. For this purpose, great concern has been devoted to processes that employ non-toxic reagents / solvents and that can be carried out under mild reaction conditions, using low quantities of catalysts. As regards the reduction of carbonyl compounds, ketones and aldehydes are generally converted to alcohols with strongly reducing agents, namely NaBH₄ and LiAlH₄⁽¹⁾. In addition, dihydrogen at high pressure (HY) has been widely used with ruthenium based catalysts⁽²⁾. Milder reaction conditions associated with low risks can be achieved via transfer hydrogenation (TH) using 2-propanol catalyzed by efficient ruthenium catalysts⁽³⁾.

We report here a straightforward procedure for the preparation of a class of ruthenium carbonyl compounds RuX₂(PP)(CO)_n (X = Cl, OCOCH₃, OCOCF₃) (n = 0 - 2) bearing aryl and alkyl diphosphane ligands. Ruthenium hydride complexes are formed by reaction with H₂ via dihydrogen splitting or with hydrogen donor molecules. These derivatives easily react with nitrogen ligands affording efficient catalytic species for the hydrogenation and transfer hydrogenation of carbonyl compounds and other hydrogen borrowing reactions.



References:

1. J. Magano, J. R. Dunetz, *Org. Process Res. Dev.* **2012**, *16*, 1156
2. M. Yoshimura, S. Tanaka, M. Kitamura, *Tetrahedron Lett.* **2014**, *55*, 3635
3. D. Wang, D. Astruc, *Chem. Rev.* **2015**, *115*, 6621.

Oceans of data for informed decisions in chemistry. The shortest path from the question to insight

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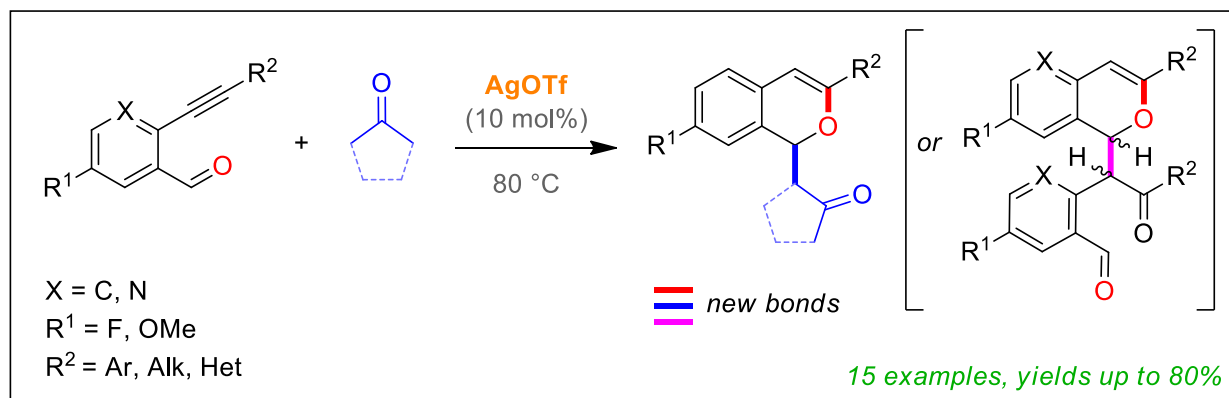
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Domino Addition/Cycloisomerization Reactions of 2-Alkynyl-Arylaldehydes: Silver Catalyzed Synthesis of 1,3-Dicarbo-Substituted-Isochromenes

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One of the most efficient methods for the construction of 1-substituted isochromenes (and related heteroaryl compounds) is the metal catalyzed regioselective domino cycloisomerization/nucleophilic addition reaction of a 2-alkynyl(hetero)arylaldehyde in the presence of a suitable nucleophile.¹ The reaction with oxygen nucleophiles is the probably the most studied one. Several metal catalyst have been used, and our group recently gave a contribution in the field of silver catalyzed² synthesis of 1-alkoxyisochromenes.³ Conversely, the reaction with carbon nucleophiles, and in particular with enolizable carbonyl compounds, is relatively less investigated.⁴ We report here our recent results regarding the silver catalyzed synthesis of 1,3-dicarbo-substituted isochromene derivatives starting from 2-alkynyl(hetero)arylaldehydes and enolizable carbonyl compounds.⁵ The reaction proceeded in a cascade fashion under mild reaction conditions with absolute regioselectivity and moderate-to-good yields. In some cases, the reaction produced unexpected diastereoisomeric couple of homodimeric products. The divergent formation of the 1-acylisochromenes and the alternative homodimeric products has been tentatively explained by some experiments and two conceivable competitive paths have been proposed.



References: (1) a. Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198. b. Wang, H.; Kuang, Y.; Wu, J. *Asian J. Org. Chem.* **2012**, *1*, 302–312. (2) Fang, G.; Bi, X. *Chem. Soc. Rev.* **2015**, *44*, 8124–8173. (3) Dell'Acqua, M.; Castano, B.; Cecchini, C.; Pedrazzini, T.; Pirovano, V.; Rossi, E.; Caselli, A.; Abbiati, G. *J. Org. Chem.* **2014**, *79*, 3494–3505. (4) a. Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.*, **2004**, *126*, 7458–7459. b. Sakthivel, K.; Srinivasan, K. *Org. Biomol. Chem.* **2014**, *12*, 269–277. c. Manojveer, S.; Balamurugan, R. *Eur. J. Org. Chem.* **2015**, 4254–4260. d. Fan, X.-W.; Cheng, Y. *Org. Biomol. Chem.* **2012**, *10*, 9079–9084. (5) Dell'Acqua, M.; Pirovano, V.; Peroni, S.; Tseberlidis, G.; Nava, D.; Rossi, E.; Abbiati G. *Eur. J. Org. Chem.* **2017**, 1425–1433.

Silylcarbocyclisation-desilylation reactions of *N*-tosyl-2-ethynylaniline: a new protocol for the synthesis of 2-hydroxyindoline derivatives

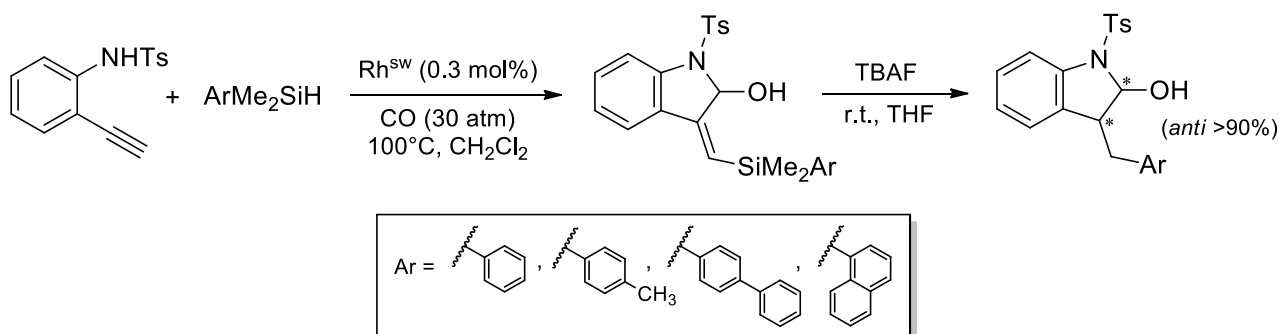
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2-Hydroxyindolines are useful building blocks for the preparation of pharmaceutical and biologically active compounds. (1) However, to the best of our knowledge only few synthetic procedures have been developed; most of them are based on the reduction of corresponding lactams or on cyclisation processes of variously substituted anilines. (2)

We found that β -lactams and β -lactones can be easily obtained from propargyl amides and propargyl alcohols by means of rhodium-catalysed silylcarbocyclisation reactions with dimethylarylsilanes; subsequent treatment with TBAF promotes a desilylation step, consisting in a 1,2-migration of aryl group from the silyl moiety to the adjacent carbon atom. (3) Very recently, we extended our silylcarbocyclisation-desilylation protocol to the preparation of various 4-(arylmethyl)isochroman-3-ones starting from 2-ethynylbenzyl alcohol and arylsilanes with different steric properties. (4)

Here we report that silylcarbocyclisations of *N*-tosyl-2-ethynylaniline with dimethylarylsilanes, carried out with catalytic $\text{Rh}^+[(\text{C}_7\text{H}_8)(\text{BPh}_4)]^-$ (Rh^{sw} , 0.3 mol%) under CO pressure (30 atm) at 100°C, generate (*Z*)-1-tosyl-3-((dimethylarylsilyl)methylene)indolin-2-ols with good yields (51-68%). These compounds can be submitted to a facile TBAF-promoted desilylation step with migration of the aryl group, affording the corresponding *N*-tosyl-3-(methylaryl)indolin-2-ols quantitatively and with very high diastereoselectivity (*anti* > 90%).



References: 1. M. Somei, F. Yamada, T. Kurauchi, Y. Nagahama, M. Hasegawa, K. Yamada, S. Teranishi, H. Sato, C. Kaneko, *Chem. Pharm. Bull.* **2001**, *49*, 87-96. 2. a) A. Arizpe, F. J. Sayago, A. I. Jiménez, M. Ordóñez, C. Catiuela, *Eur. J. Org. Chem.* **2011**, 3074-3081; b) K. Samizu, K. Ogasawara, *Heterocycles* **1995**, *41*, 1627-1629; c) J. V. N. Vara Prasad, *Org. Lett.* **2000**, *2*, 1069-1072. 3. a) L. A. Aronica, G. Valentini, A. M. Caporusso, P. Salvadori, *Tetrahedron* **2007**, *63*, 6843-6854; b) L. A. Aronica, C. Mazzoni, A. M. Caporusso, *Tetrahedron* **2010**, *66*, 265-273; c) L. A. Aronica, A. M. Caporusso, C. Evangelisti, M. Botavina, G. Alberto, G. Martra, *J. Organomet. Chem.* **2012**, *700*, 20-28. 4. G. Albano, M. Morelli, L. A. Aronica, *Eur. J. Org. Chem.* **2017**, *In press*, DOI: 10.1002/ejoc.201700455.

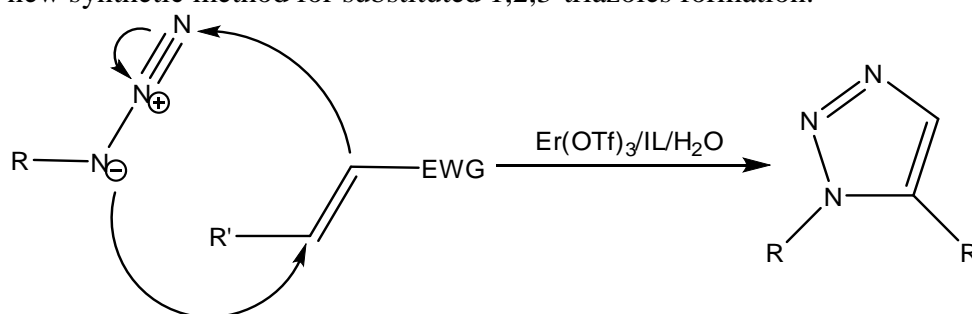
Er(OTf)₃ in ionic liquid catalyzed [3 + 2] cycloaddition of azides with electron-deficient dipolarophile: regioselective synthesis of substituted 1,2,3-triazoles.

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The 1,2,3-triazole nucleus represents a significant class of biologically active nitrogen compounds that exhibit a number of important biological properties, such as antibacterial, anticancer, antiviral, and antituberculosis.¹ Moreover, 1,2,3-triazoles have found industrial applications as dyes, agrochemicals, corrosion inhibitors, and photostabilizers. Therefore, the building up of a 1,2,3-triazole moiety invokes ever growing synthetic efforts.

Recently, the system Er(OTf)₃/IL/H₂O used to catalyze Diels Alder reactions has emerged as a versatile tool for developing syntheses due to their numerous advantages, namely, their relatively high efficiency, water compatibility, mild reaction conditions, and eco-friendly catalytic reactions.² Herein, we report that substituted 1,2,3-triazoles can be obtained by [3 + 2] cycloaddition of azides with electron-deficient dipolarophiles catalyzed by the Er(OTf)₃/IL/H₂O system (Scheme 1), thereby providing a new synthetic method for substituted 1,2,3-triazoles formation.



Scheme 1

To the best of our knowledge, this is the first time that system Er(OTf)₃/IL/H₂O has been described for [3 + 2] cycloadditions of alkyl azide with electron-deficient dipolarophiles. In addition the IL containing the catalyst can be readily separated from the reaction products and recovered in excellent purity for direct reuse.

References:

1. Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013**, 113, 4905.
2. A. De Nino, A. Garofalo, L. Maiuolo, A. Procopio, B. Russo, O. Bortolini *Appl. Catal. A* **2010**, 372, 124–1293.

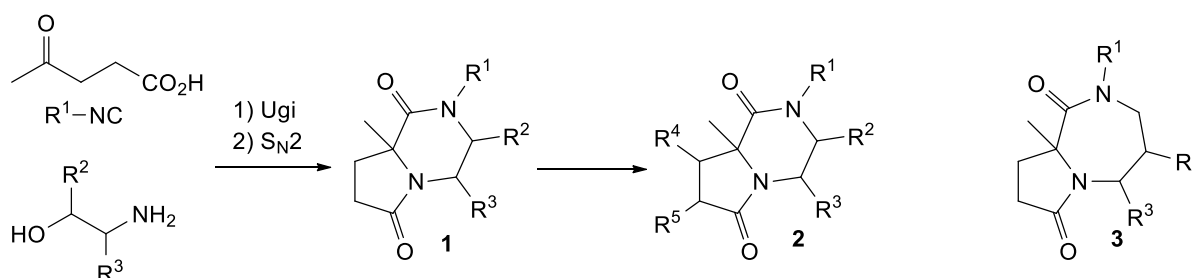
Synthesis of bio-based heterocycles from levulinic acid using the Ugi multicomponent reaction

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Levulinic acid is one of the most important biomass derived fine chemicals. It is in the US Department of Energy (DOE) list of the 12 most important building blocks that can be derived from sugars (1). Production of levulinic acid on large scale is already a well assessed methodology. Its prize is, at the moment, about 1 \$ / Kg, but it is expected to go further down, starting from waste sugar sources. Thus, the main problem now is not how to get it, but how to find new applications of it, i.e. through conversion it into high added-value compounds. Several use of levulinic acid, especially in the polymer field, are thus under study (2). However, transformations into nitrogen derivatives, especially heterocycles has not been explored very much so far, with the exception of the synthesis of δ -aminolevulinic acid (DALA), used in photodynamic therapies. Isocyanide-based MCRs can be a perfect tool to access levulinic derived heterocycles. IMCRs and levulinic acid are old friends. Actually Passerini used levulinic acid in his reaction as early as in 1923 (3) and, more recently, Ugi reactions of levulinic acid, leading to pyroglutamic acid amides, have been reported by various groups (4-7).

However, we thought that there was still ample room for further development in this area. Our plan was to combine the Ugi reaction with an intramolecular substitution reaction (8), affording, in just 2 steps, very interesting bicyclic structures like **1** or **3**. They incorporate classical "privileged structures", such as pyroglutamic acid (9), ketopiperazine and diazepanone. Towards this goal we started from levulinic acid and 1,2-aminoalcohols or 1,3-aminoalcohols and developed a very efficient (in terms of yields and operational simplicity) protocol. Further diversity inputs have been introduced into compounds **1** by enolate alkylation or dehydrogenation-Michael sequences. Starting from chiral enantiopure aminoalcohols, enantiopure **1-3** could be obtained, and the diastereoselectivity in the Ugi reaction will be discussed.



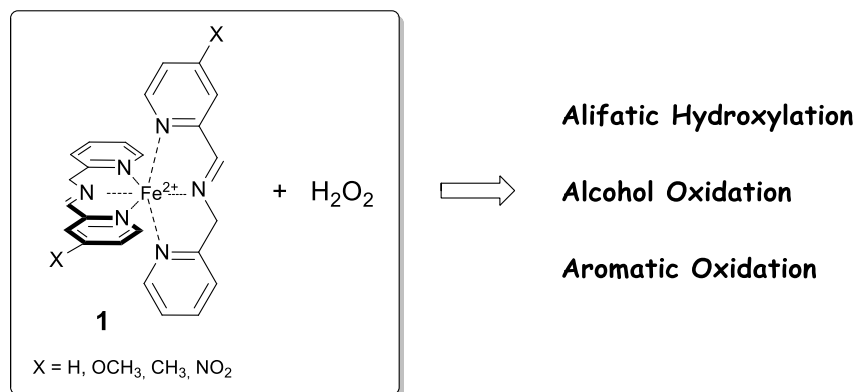
1. Isikgor, F. H.; Becer, C. R. *Polym. Chem.* **2015**, *6*, 4497-4559.
2. Hartweg, M.; Becer, C. R. *Green Chem.* **2016**, *18*, 3272-3277.
3. Passerini, M. *Gazz. Chim. Ital.* **1923**, *53*, 331-332.
4. Harriman, G. C. B. *Tetrahedron Lett.* **1997**, *38*, 5591-5594.
5. Wang, W.; Herdtweck, E.; Domling, A. *Chem. Commun.* **2010**, *46*, 770-772.
6. Hulme, C.; Ma, L.; Cherrier, M. P.; Romano, J. J.; Morton, G.; Duquenne, C.; Salvino, J.; Labaudiniere, R. *Tetrahedron Lett.* **2000**, *41*, 1883-1887.
7. Hanusch-Kompa, C.; Ugi, I. *Tetrahedron Lett.* **1998**, *39*, 2725-2728.
8. Banfi, L.; Riva, R.; Basso, A. *Synlett* **2010**, 23-41.
9. Stefanucci, A.; Novellino, E.; Costante, R.; Mollica, A. *Heterocycles* **2014**, *89*, 1801-1825.

Oxidation of Hydrocarbons and Alcohols with H₂O₂ Catalyzed by Nonheme Imine Based Iron Complexes

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Nonheme iron complexes represent a class of powerful and versatile catalysts that are able to efficiently catalyze selective oxidations of organic compounds using environmentally benign hydrogen peroxide as the terminal oxidant. In order to avoid expensive and complex nonheme ligand structures, we have synthesized and fully characterized simple nonheme iron complexes with imine-based ligands (1) assembled in one pot from cheap and commercially available reagents (2-aminopicoline and 4-substituted-2-picolyl aldehydes). (1, 2)



The oxidation of hydrocarbons indicates that these complexes exhibit high turnover numbers in aliphatic C-H hydroxylation, comparable to the most efficient nonheme iron catalysts prepared so far. Good yields of carbonyl products were obtained in the oxidation of aliphatic alcohols, while the preferential oxidation of the aromatic ring was observed in the oxidation of benzylic alcohols (3). In line with these results, the imine iron catalyst was also very efficient and selective in the oxidation of the aryl ring in alkylaromatic compounds. A series of mechanistic studies provided evidence that oxidations are metal based. Activation of the complex likely involves an initial oxidation to the ferric state followed by a ligand arm dissociation that enables the H₂O₂ binding and activation.

References: 1. Olivo, G.; Arancio, G.; Mandolini, L.; Lanzalunga, O.; Di Stefano, S. *Catal. Sci. Technol.* 2014, 4, 2900-2903. 2. Olivo, G.; Nardi, M.; Vidal, D.; Barbieri, A.; Lapi, A.; Gomez, L.; Lanzalunga, O.; Costas, M.; Di Stefano, S. *Inorg. Chem.* 2015, 54, 10141-10152. 3. G. Olivo, S. Giosia, A. Barbieri, O. Lanzalunga, S. Di Stefano, *Org & Biomol. Chem.* 2016, 14, 10630.

Structural characterisation of Peripolin, a new 3-hydroxy-3-methylglutaryl flavonoid glycoside from bergamot juice

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In 2009 two 3-hydroxy-3-methylglutaryl flavonoid glycosides (HMG-flavonoids), Melitidin and Brutieridin, were isolated and characterized from bergamot fruit (1). Experimental and theoretical research studies report that HMG-flavonoids possess an inhibitory effect on HMGR, the key-step enzyme in the biosynthesis of cholesterol (2,3,4). In the present work, a new 3-hydroxy-3-methylglutaryl flavonoid glycoside was isolated and identified as HMG conjugate of neoeriodictin (eriodictiol 7-(2''- α -rhamnosyl-6''-(3'''-hydroxy-3'''-methylglutaryl)- β -glucoside) by mass spectrometry and NMR experiments (Fig. 1). Structural characterization by NMR spectra showed that two diastereomeric forms of molecules exist, as with many flavanones in citrus fruits (5).

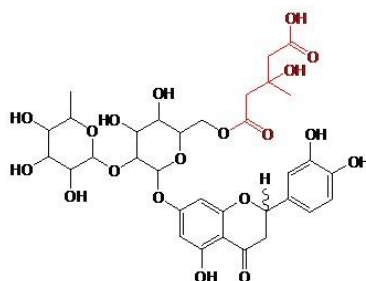


Fig. 3 Structure of Peripolin

Several analytical experiments were performed to assess the structure of new compound. Isolated flavonoid was evaluated by accurate tandem mass spectrometry experiments using a quadrupole time of flight instrument equipped by an electrospray source (ESI-QqTof). Moreover, basic and enzymatic hydrolysis reactions were performed on the pure sample, in order to obtain information on the ester moieties and aglycone.

The negative HRESI-MS provided the elemental composition $C_{33}H_{39}O_{19}^-$. ESI-MS/MS experiments were performed in both positive and negative ion mode and provided several diagnostic fragment ions.

1H -NMR and 2D-NMR experiments confirm the structure of the new HMG-flavonoid glycoside and showed the presence of a mixture of diastereoisomers in bergamot juice.

References:

1. Di Donna, L., De Luca, G., Mazzotti, F., Napoli, A., Salerno, R., Taverna, D., et al. (2009). *Journal of Natural Products*, 72(7), 1352–1354.
2. Di Donna, L., Dolce, V., & Sindona, G. (2008). Patent Nr. CS2008A00019.
3. Leopoldini, M., Malaj, N., Toscano, M., Sindona, G., & Russo, N. (2010). *Journal of Agricultural and Food Chemistry* 58, 10768–10773
4. Di Donna, L., Iacopetta, D., Cappello, A. R., Gallucci, G., Martello, E., Fiorillo, M., Dolce, V., Sindona, G. (2014). *Journal of Functional Food* 558–568
5. Maltese, F., Erkelens, C., van der Kooy, F., Hae Choi, Y., Verpoorte, R. (2009). *Food Chemistry* 116, 575–579

The dual role of Ionic Liquids in Gold Nanoparticles Drug Delivery-Systems

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Gold nanoparticles (AuNPs) are attractive scaffolds for the preparation of organic-inorganic hybrids through the stable interaction between the gold surface and different classes of functional groups. AuNPs are used to carry and release drugs, as biological sensors or for imaging.¹ Ionic liquids (ILs) is the term for low-melting salts obtained by the combination of a large variety of organic cations and anions.² Recently, ILs were used in nanotechnology for the preparation of metal nanoparticles by electrostatic interactions.³

In this work, we propose a drug delivery-system consisting of AuNPs capped with an ionic liquid, which bears a bioactive portion. First, we studied simple long-chain ILs, and evaluated the stability of the AuNPs by varying the cationic portion and the length of the alkyl chains. (**Figure 1**)

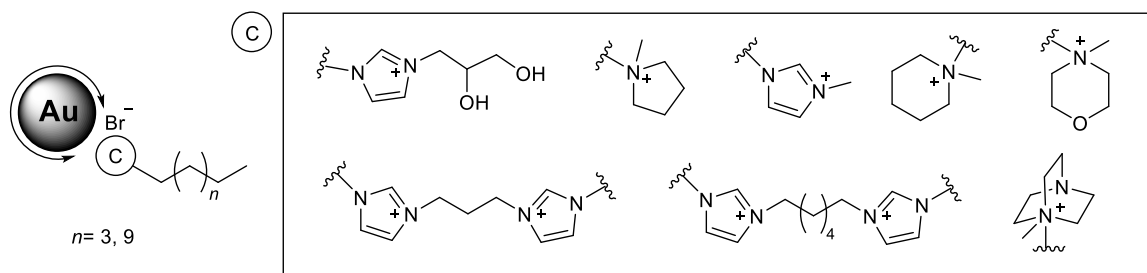


Figure 1

These AuNPs have been synthesized in water through a simple one-pot procedure.⁴ Based on the results obtained from this preliminary study, ILs decorated with a bioactive portion were synthesized and used to obtain AuNPs. In particular, we chose a monosaccharide tail considering the role played by sugars in a plethora of biological events. (**Figure 2**)

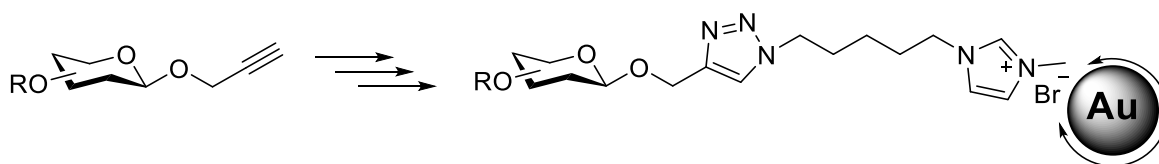


Figure 2

Generally, AuNPs were characterized by Ultraviolet-Visible spectroscopy (UV/Vis), Transmission Electron Microscopy (TEM) and Nuclear Magnetic Resonance (NMR).

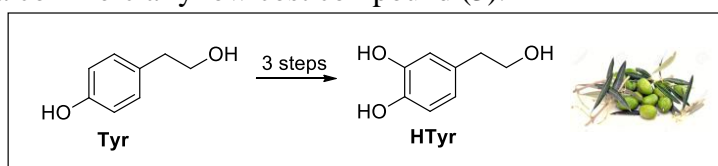
References: 1) Daniel, M.-C.; Astruc, D. *Chem. Rev.* **2004**, *104*, 293.; 2) Chiappe, C.; Pieraccini, D. *Journal of Physical Organic Chemistry* **2005**, *18*, 275.; 3) Safavi, A.; Zeinali, S. *Colloids and Surfaces A: Physicochemical and Engineering Aspects* **2010**, *362*, 121.; 4) Faraday, M. *Philosophical Transactions of the Royal Society of London* **1857**, *147*, 145.

Hydroxytyrosol-controlled release from poly(vinyl) alcohol (PVA) combined with nanostructured starch

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Hydroxytyrosol (HTyr) is a phenolic antioxidant present in the olive oil and olive oil by-products (1,2) available in our laboratories on a large scale and in high purity by a selective and efficient IBX-oxidation of tyrosol, a commercially low cost compound (3).



The potentiality of using this molecule for both food and non-food applications could be increased projecting and developing novel materials that permit a controlled release to prolong the antioxidant effect over the time. In this light, on the basis of our previous results (4,5), we included HTyr into poly(vinyl) alcohol (PVA) combined with nanostructured starch. Among polymers to be used as matrix, we selected PVA, a biodegradable, biocompatible and non-toxic polymer characterized by high polarity and strong solubility in water with good optical, physical and thermo-mechanical properties. At the same time, for the production of nanomaterials, our attention has been turned on starch, a natural, renewable and biodegradable polymer consisting of amylose, a linear macromolecule composed by α -1,4-D-glucopyranose chains and amylopectin, a highly branched macromolecule with α -1,4-D-glucopyranose and α -1,6-D-glucopyranose chains. The ratio of these two components is generally related to the botanic origin of starch, which is also responsible for the shape, size and crystalline organization of the corresponding granules (6). In particular, our starting materials were starch extracted from the bread wheat variety Cadenza (WT, amylose content 33%) and a derived-high amylose line (HA, amylose content 75%). For each type of starch, we prepared nanocrystals (NC_{WT}, NC_{HA}) and nanoparticles (NP_{WT}, NP_{HA}) by acid hydrolysis and high power ultrasound irradiation. Then, we developed novel ternary films, namely PVA/NC_{WT}/HTyr, PVA/NC_{HA}/HTyr, PVA/NP_{WT}/HTyr and PVA/NP_{HA}/HTyr, that we characterized in terms of morphological, thermal and optical properties. Finally, we tested these formulations for antioxidant food packaging applications. In this light, overall and specific migration tests were performed using a hydrophilic food simulant according to the current European legislation in order to evaluate the kinetic of release of HTyr from each film. Experimental data showed that HTyr was released in a controlled manner from all ternary films and the released HTyr still retained a strong antioxidant activity. The release profiles demonstrated the key role of the different types of nanostructured starch in the novel formulations in promoting a controlled release of HTyr.

References: 1. Romani, A.; Pinelli, P.; F. Ieri, Bernini, R. *Sustainability* **2016**, *8*, 1002-1012. 2. Bernini, R.; Merendino, N.; A. Romani, F. Velotti. *Curr. Med. Chem.* **2013**, *20*, 655-670. 3. Bernini, R.; Mincione, E.; Barontini, M.; Crisante, F. *J. Agr. Food Chem.* **2008**, *56*, 8897-8904. 4. Fortunati, E.; Luzi, F.; Dugo, L.; Fanali, C.; Tripodo, G.; Santi, L.; Kenny, J. M.; Torre, L.; Bernini, R. *Polym. Int.* **2016**, *65*, 872-882. 5. Fortunati, E.; Luzi, F.; Fanali, C.; Dugo, L.; Belluomo, M. G.; Torre, L.; Kenny, J. M.; Santi, L.; Bernini, R. *J. Renew. Mat.* **2017**, *5*, 81-95. 6. Angellier, H.; Choinsard, L.; Molina-Boisseau, S.; Ozil, P.; Dufresne, A. *Biomacromol.* **2004**, *5*, 1545-1551.

Phytochemical analysis of *Daphne sericea* Vahl. from Majella National Park

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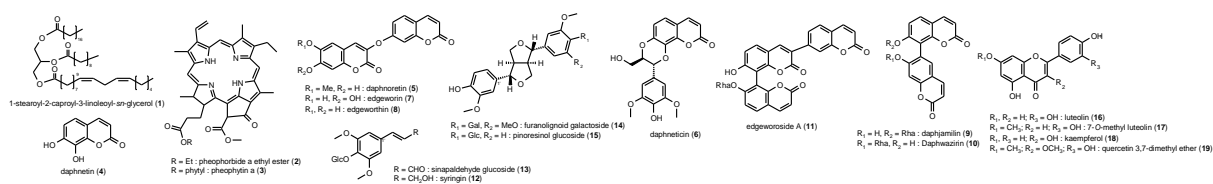
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The genus *Daphne* (Thymelaeaceae family) comprise about 95 species worldwide distributed and several of these have been largely used in traditional medicines to treat several illnesses. The Italian territory account on about 10 species of this genus and *Daphne sericea* Vahl. (1,2) is one of these. It grows mainly in the Thyrrhenian coast and in several sites with a spot distribution in the Appennines (3). The studied sample was collected in the territory of Majella National Park which represent a hot spot for biodiversity in central Italy with the presence of several endemic and rare species. Because the presence of a wide variety of biological activities in species of the *Daphne* genus much attention has been paid to their phytochemistry, but for what concern the species *sericea*, in literature is present only one study which reported on the isolation of a few flavonoid related to luteolin (4).

The phytochemical analysis of the ethanolic extract obtained from the aerial parts of *D. sericea* led to the isolation of nineteen compounds belonging to different classes of natural products. Among these the coumarins resulted the main components with the presence of two monomeric coumarins, five bis-coumarins as aglycones or in glycosidic form and one trimeric coumarin glycoside, followed by four flavonoids, two glycosidic furoflignans, two glucosidic phenylpropanoids, two cyclic tetrapyrrole derivatives of chlorine family and an unsaturated trygliceride.

The majority of these compounds were recognized for the first time during this study from *D. sericea* and have a chemosystematic relevance since they have been isolated from other species and subspecies of this genus (5,6). Among the identified compounds, in addition to the chemosystematic markers, have been also recognized several components which resulted to be new constituents also for the genus.

For what concern the bioactivities all these constituents are responsible of interesting biological effects, which range from the antioxidant one to the key enzyme inhibition and the anticancer ones (6), making so *D. sericea* a precious source of bioactive molecules.



References: 1. Pignatti S (1982) Flora d'Italia. Edagricole: Bologna, vol 2 pag. 454. 2. Conti F., Abbate G., Alessandrini A., Blasi C (2005). An annotated checklist of the Italian vascular flora, Palombi Editore, Roma. 3. Di Pietro R, (2001). Aspetti cenologici e distributivi di *Daphne sericea* Vahl nel Lazio. Fitosociologia 38(2): 45-61. 4. Ulubelen A, Bucker R, Mabry TJ, (1982) Flavone 5-O-glucosides from *Daphne sericea*. Phytochemistry, 21(3): 801-803. 5. Venditti A, Sanna C, Lorenzetti LM, Ballero M, Bianco A, (2017) New coumarinyl ethers in *Daphne oleoides* Schreb. collected from Sardinia Island. Chem Biodiv, (in press, available online). DOI: 10.1002/cbdv.201700072. 6. Xu W-C, Shen J-G, Jiang J-Q (2011) Phytochemical and biological studies of the plants from the genus *Daphne*. Chem Biodiv 8, 1215–1233.

Phytochemical comparison among three *Sideritis* taxa from Central Italy

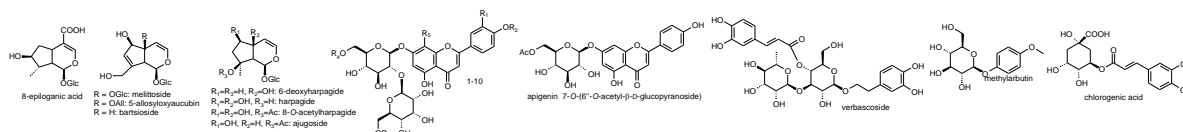
Alessandro Venditti^a, Claudio Frezza^b, Mauro Serafini^b, Sebastiano Foddai^b, Marcello Nicoletti^b,
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The genus *Sideritis* is one of the most important genera in the Lamioideae subfamily of Lamiaceae. The Italian Flora comprises five taxa belonging to this genus (1), i.e. *S. hirsuta* L., *S. hyssopifolia* L. subsp. *hyssopifolia*, *S. italica* (Mill.) Greuter & Burdet, *S. montana* L. subsp. *montana* and *S. romana* L. subsp. *romana*, among which *S. italica* is considered as an endemism. Locally known as "Stregonia", plants of the *Sideritis* genus are often used in infusion as tonics, carminatives, diuretics and digestives and for this reason are known as "mountain teas"(2).

In this study we reported on the phytochemical comparison of the secondary metabolites patterns in three species (*S. romana*, *S. italica* and *S. montana*) with particular attention to the chemosystematic markers of Lamiales (iridoids, acetylated flavonoids containing allose and glycosidic phenylpropanoids) to verify their implication in the taxonomy of these species.

The presence of iridoids was confirmed in all the three species with the presence of harpagide, 8-*O*-acetylharpagide, 6-deoxyharpagide, 5-alloxyloxyaucubin, monomelittoside, ajugoside, 8-epiloganic acid and bartsioside. Yet, they resulted to be not homogeneously distributed and each species showed a characteristic composition (3,4,5). The phenylpropanoid verbascoside was detected only in *S. italica*, while the acetylated flavonoids containing allose (six different derivatives) were identified in all the species and, also for these metabolites, each species revealed a characteristic composition, with only one compound shared with the others. Other secondary metabolites, belonging to different classes of natural products, were also recognized, namely chlorogenic acid and methylarbutin in *S. montana*, siderol in *S. italica*; phytol and a series of acetylated glycosidic flavonoids related to apigenin and luteolin in *S. romana*. The presence of these constituents, with specific distribution, represents an additional marker of differentiation between the three *Sideritis* species. Moreover, the different metabolic profiles exhibited by these three *Sideritis* species is consistent with the current classification, morphologically-based, of the different sections of the genus.



References: 1. Conti F., Abbate G., Alessandrini A., Blasi C (2005). An annotated checklist of the Italian vascular flora, Palombi Editore, Roma. 2. Özcan M., Chalchat J. C., Akgül A. (2001). Food Chem., 75, 459. 3. Venditti A, Bianco A, Maggi F, Nicoletti M. (2013). Polar constituents composition of endemic *Sideritis italica* (MILL.) GREUTER et BURTER from Central Italy. Nat Prod Res. 27(15):1408-12. 4. Venditti A, Bianco A, Frezza C, Serafini M, Giacomello G, Giuliani C, Bramucci M, Quassinti L, Lupidi G, Lucarini D, Papa F, Maggi F. (2016). Secondary Metabolites, Glandular Trichomes and Biological Activity of *Sideritis montana* L. subsp. *montana* from Central Italy. Chem Biodivers. 13(10):1380-1390. 5. Venditti A., Frezza C., Guarcini L., Foddai S., Serafini M., Bianco A. (2016). Phytochemical Study of a Species with Ethnopharmacological Interest: *Sideritis romana* L. European Journal of Medicinal Plants, 12(3): 1-9. DOI: 0.9734/EJMP/2016/23809.

Ethno-pharmacological value and phytochemical variability of *Galeopsis ladanum* subsp. *angustifolia* (Ehrh. ex Hoffm.) Gaudin

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Galeopsis ladanum subsp. *angustifolia* (Ehrh. ex Hoffm.) Gaudin (Lamiaceae) is a Mediterranean small annual herbaceous plant. It is spread all along the national territory with the only exceptions of Apulia, Calabria and Sardinia whereas its presence is uncertain in Sicily (1). *Galeopsis* species are well known to possess important pharmacological properties i.e. anti-oxidant, anti-inflammatory, astringent, anti-anemic, expectorant, remineralizing and diuretic (1,2,3).

In this work we report a re-investigation of the secondary metabolites obtained from a sample of *G. angustifolia* collected in Civita di Oricola (Abruzzo region) at 600 m a.s.l. The aims were to compare its phytochemical pattern with that observed in a different sample collected in Latium region at 1800 m a.s.l. (4) and to evaluate the obtained results from the first sample under the ethno-pharmacological point of view, too.

Both of these scopes were achieved by analyzing the ethanolic extract of the aerial parts by means of Chromatographic and Spectroscopic techniques (NMR and MS).

Eight compounds were evidenced: verbascoside [1], 7-[[2-*O*-(6-*O*-acetyl- β -D-allopyranosyl)- β -D-glucopyranosyl]oxy]-2-(4-hydroxy-phenyl)-5,8-dihydroxy-4*H*-1-benzopyran-4-one [2], 7-[[2-*O*-(6-*O*-acetyl- β -D-allopyranosyl)- β -D-glucopyranosyl]oxy]-2-(4-methoxy-phenyl)-5,8-dihydroxy-4*H*-1-benzopyran-4-one [3], 7-[[2-*O*-[(6-*O*-acetyl- β -D-allopyranosyl)- β -D-glucopyranosyl]oxy]-2-(3-hydroxy-4-methoxy-phenyl)-5,8-dihydroxy-4*H*-1-benzopyran-4-one [4], harpagide [5], 8-*O*-acetyl-harpagide [6], chlorogenic acid [7] and quinic acid [8].

The marker compounds (iridoids [5-6] and acetylated-allosyl-flavonoids [2-4]) were reconfirmed. Indeed, several qualitative differences were evidenced and compounds [7] and [8] resulted to be new constituents of this species. The presence of these compounds suggests the hypothesis to use this species for ethno-pharmacological purposes. In fact, all of them are known to exert pharmacological activities: verbascoside as antimicrobial and anti-inflammatory (5); the three flavones as anti-oxidant and neuro-protector (6); the two iridoids as anti-tumour, anti-bacterial and anti-inflammatory (5); chlorogenic acid as cicatrizing agent (7); quinic acid as anti-oxidant and anti-inflammatory (8).

Nevertheless further and deeper studies should be made in order to better understand how they all interact with each other and participate to the phytocomplex action of this plant.

References: 1. Pignatti S (1982) Flora d'Italia. Edagricole: Bologna, vol 2 pag. 454. 2. Matkowski A, Tasarz P, Szypuła E (2008) Antioxidant activity of herb extracts from five medicinal plants from Lamiaceae, subfamily Lamioideae. J Med Pl Res, 2(11): 321-330. 3. Mazza F (2000) Itinerari alla scoperta delle erbe officinali del Monte Amiata. Stampa: Siena, Italy. 4. Venditti A, Serrilli AM, Bianco A (2013) A new flavonoid and other polar compounds from *Galeopsis angustifolia* Ehrh. ex Hoffm. Nat Prod Res, 27(4-5): 412-416. 5. Frezza C, Venditti A, Di Cecco M, Ciaschetti G, Serafini M, Bianco A (2017) Iridoids and phenylethanoid glycosides from the aerial parts of *Ajuga tenorei*, an endemic Italian species, Nat Prod Res, 31(2): 218-223. 6. Uriate-Pueyo I, Calvo MI (2010) Structure-activity relationships of acetylated flavone glycosides from *Galeopsis ladanum* L. (Lamiaceae). Food Chem. 120: 679-683. 7. Chen W, Liou S, Tzeng T, Lee S, Liu, I (2013) Effect of topical application of chlorogenic acid on excision wound healing in rats. Planta Med, 79: 616-621. 8. Pero RW, Lund H, Leanderson T (2009) Antioxidant metabolism induced by quinic acid. Increased urinary excretion of tryptophan and nicotinamide. Phytother Res, 23(3): 335-346.

N-Heterocyclic Carbenes functionalized polystyrene monolithic microreactors for continuous flow stereoselective umpolung catalysis

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In a previous study, our research group developed a novel synthetic route for the immobilization of racemic thiazolium salts on monolithic polystyrene and silica with the aim to investigate heterogeneous umpolung catalysis in flow-mode.(1)

As a logical extension of that study, we reasoned about the utilization of polystyrene monolithic columns functionalized with chiral N-Heterocyclic Carbenes (NHCs) in stereoselective umpolung continuous-flow processes.

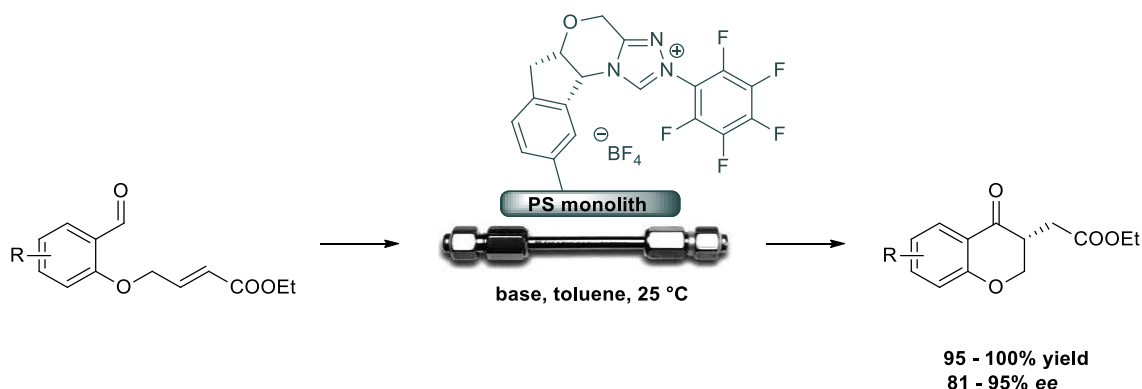
Triazolium salt pre-catalysts have been chosen for the scope due to their well-documented activity in a wide variety of stereoselective umpolung transformations.(2)

After some experimentation, a covalent immobilization strategy of the Rovis triazolium pre-catalyst was optimized on polystyrene and the catalyst activity and recyclability were first tested under batch conditions. The stereoselective intramolecular Stetter reaction leading to optically active chromanones was chosen as the benchmark, detecting excellent results in terms of yield (>95%) and stereoselectivity (*e.e.*: 81-95%).

Subsequently, the continuous flow process was investigated by fabricating the corresponding monolithic microreactors (pressure-resistant stainless-steel columns) and evaluating the catalyst effectiveness during the time.

Importantly, it has been demonstrated by a brief substrate scope study that the polymeric matrix and the continuous-flow regime synergistically contribute to preserve the activity of the carbene catalysts over time, thus hindering its deactivation process.

To the best of our knowledge, our study represents the first example of heterogeneous NHC-catalyzed stereoselective process under continuous-flow conditions.



(1) Bortolini, O.; Cavazzini, A.; Dambruoso, P.; Giovannini, P.P.; Cacioli, L.; Massi, A.; Pacifico, S.; Ragno, D. *Green Chem.* **2013**, *15*, 2981-2992.

(2) Flanagan, D.M.; Romanov-Michailidis, F.; White, N.A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307-9378.

Disperse dyes modification by Pd-catalyzed cross coupling reactions

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Disperse dyes are the most commonly used dyes in tinctorial processes. These dyes possess a very low solubility in water, therefore the use of surfactants is necessary to ensure a good dispersion in aqueous medium. These additives determine a substantial increase in tinctorial costs and their removal from dyeing wastewaters represents a challenge. To enhance the water solubility of disperse dyes, Bianchini and al.¹ developed the naturalization process, consisting in the conjugation of the chromophore to a 6'-piperazinyl-lactose unit through an amide bond. In this work, the previously synthesized 1-amino-2-bromo-4-hydroxy-anthracen-9,10-dione carboxylic acid derivative (C.I. Disperse Violet 17 carboxylic acid derivative **1**) was used as substrate in Pd-catalyzed cross coupling reactions (Fig. 1).

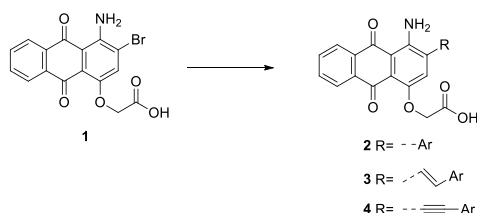


Figure 4

Different aryl derivatives were used to explore the reactivity in Suzuki, Heck and Sonogashira reactions, to extend the conjugation of the anthraquinone unit and to evaluate the changes in the absorption spectrum. The naturalization process was tested on one derivative for each of the three reactions and their dyeing potential was evaluated (Fig. 2). Only for Suzuki derivative the desired water soluble compound was obtained. The desired Heck derivative (compound **12**) was completely insoluble, while for the Sonogashira process the deprotection step gave a mixture of water soluble compounds including the desired one (compound **12**) and a product derived from HCl addition to the alkyne. Moreover, tinctorial proprieties of compound **11** are under study.

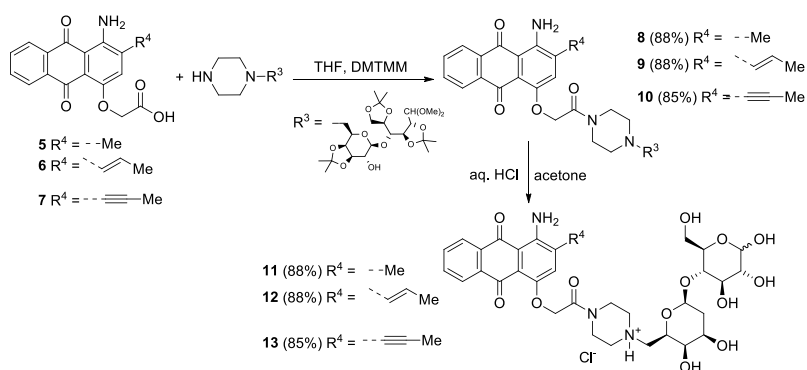


Figure 5

References: 1. Patent WO 2014177528 A1, 2014

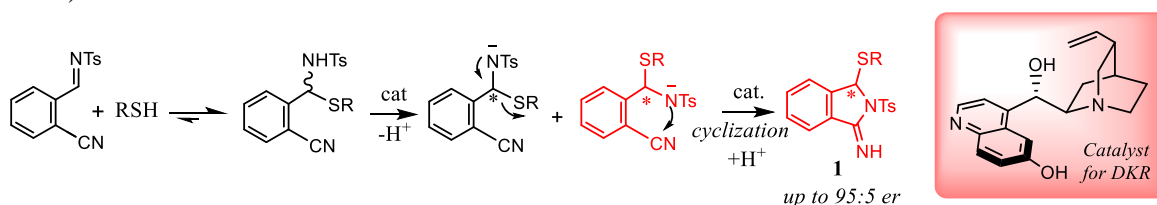
Novel chiral N,S-acetal cyclic structures as templates for functional, stereochemical and appendage diversity

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The attainment of functionally diverse small-molecule collections based on heterocyclic structures lies at the heart of the drug discovery process, thus representing an attractive challenge for the organic chemistry community (1). An efficient way to approach this target is the design of small libraries through the functional, stereochemical and appendage diversifications of suitable “molecular platforms”.

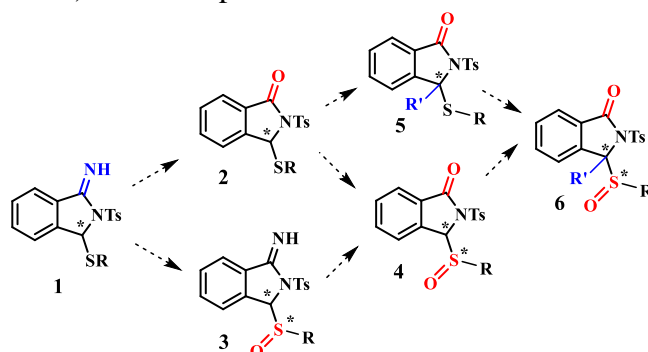
As a part of our research program based on the asymmetric construction and functionalization of isoindolinonic architectures and related compounds (2) we have recently realized the asymmetric synthesis of a new class of multi-heteroatomic cyclic compounds **1** containing the N,S-acetal functionality by one-pot reaction of thiols and 2-cyano-N-tosylbenzylideneimine using catalysts derived from cinchona alkaloid series. As showed in scheme 1, title compounds are effectively achieved *via* an highly stereoselective heterocyclization driven by a dynamic kinetic resolution (DKR).



Scheme 1. Proposed pathway for DKR

With this innovative methodology in hand, and in view of the presence of the tertiary stereogenic center, different functional groups and reactive sites, we decided to investigate the possibility to achieve molecular diversity through additional reactions on the compounds **1**.

In particular, in this communication, we will focus on the second reactivity of the title compounds aimed at obtaining enantioenriched isoindolinone-derived N(acyl),S-acetals **2** and chiral sulfoxides **3** and **4** paying attention to the configurational stability of the synthesized derivatives and, where appropriate, to the diastereoselectivity of the processes. Appendage diversity (aimed to the attainment of the products **5** and **6**) at the 3rd position of the isoindolinonic core will be also considered (Scheme 2).



Scheme 2. Examples of functional, stereochemical and appendage diversity of the heterocyclic core **1**

References: 1. W. R.J.D. Galloway, A. I. Llobet, D. R. Spring, *Nature Communications*, 1: 80 (2010), 1–13. 2. P. Antico, V. Capaccio, A. Di Mola, A. Massa, L. Palombi, *Adv. Synth. Catal.*, **354** (2012).

Synthesis and characterization of benzo[1,2-*b*:4,3-*b'*]dithiophene-based organosilicon compounds

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Silicon-containing polymers, having a regular alternating arrangement of silanylenes and π -electron systems in a polymer backbone, are of great interest as photoresists, semiconducting materials, and precursors of silicon carbide (1). On the other hand, much attention has been paid to thiophene-based heteroaromatic compounds due to their important photoelectric properties, and their use as charge transport materials in broad range of applications including OFETs, OLEDs and Solar Cells (2). Thiophene units bridged by silylene σ -linkages, including both small molecules and polymers, have been therefore studied extensively, because of their stability, in many optoelectronic applications (3). In this context only simple thiophene rings have been studied, hence living plenty of space for further structural engineering including the use of polyconjugated thiophene-based systems. For several years our group has been working on synthesis and functionalization of benzo[1,2-*b*:4,3-*b'*]dithiophene (BDT, Figure 1) derivatives (4,5), which are an interesting class of π -conjugated systems in functional organic materials (6), and are key intermediates for the synthesis of inherently chiral thiahelicenes (7).

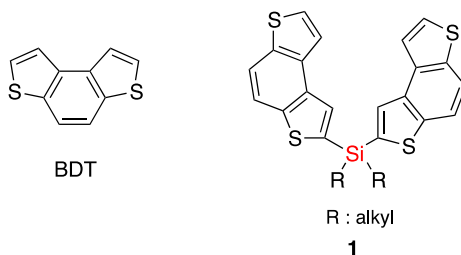


Figure 1.

In this communication we will report our new field of investigation where we have focused on the development of π -conjugated BDT units bridged by silylene σ -linkages of general formula **1**, as key intermediate to prepare active molecular or polymeric photoelectronic systems. We will discuss the synthesis of structures **1** along with the study of the optical, chemical and electrochemical properties.

References: 1. Moreau, C.; Serein-Spirau, F.; Biran, C.; Bordeau, M.; Gerval, P. *Organometallics* **1998**, *17*, 2797, and references therein. 2. See for example: Fong, H. H.; Pozdin, V. A.; Amassian, A.; Malliaras, G. G.; Smilgies, D.-M.; He, M.; Gasper, S.; Zhang, F.; Sorensen, M. *J. Am. Chem. Soc.* **2008**, *130*, 13202. 3. Ohshita, J.; Kunai, A. *Acta Polym.* **1998**, *49*, 379. 4. Cauteruccio, S.; Dova, D.; Graiff, C.; Carrara, C.; Doulet, J.; Stephenson, G. R.; Licandro, E. *New J. Chem.* **2014**, *38*, 2241. 5. Stephenson, G. R.; Cauteruccio, S.; Doulet, J. *Synlett* **2014**, 701. 6. Longhi, E.; Bossi, A.; Di Carlo, G.; Maiorana, S.; De Angelis, F.; Salvatori, P.; Petrozza, A.; Binda, M.; Roiati, V.; Mussini, P. R.; Baldoli, C.; Licandro, E. *Eur. J. Org. Chem.* **2013**, *84*. 7. Licandro, E.; Rigamonti, C.; Ticozzelli, M. T.; Monteforte, M.; Baldoli, C.; Giannini, C.; Maiorana, S. *Synthesis* **2006**, 3670

Synthesis and structural studies towards palmitoyl ethanolamide analogues

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Palmitoylethanolamide (PEA) is an endogenous fatty acid ethanolamide (FAE); FAEs are widely distributed in the central nervous system (CNS), the immune system, and the peripheral tissues of mammals, and have been shown to alleviate pain and inflammation, regulate motility and appetite, and produce anticancer, anxiolytic, and neuroprotective efficacies (1).

However, despite being a NAE such as anandamide (AEA) or oleamide (OA), PEA doesn't exhibit its affinity for the cannabinoid receptors CB1 and CB2 and cannot strictly be considered an endocannabinoid: the most robust evidence instead is for an action of PEA upon the nuclear receptor peroxisome proliferator-activated receptor alpha (PPAR- α) which is an ubiquitous transcription factor activated by various endogenous fatty acid derivatives.

PPARs are regulators of gene networks, controlling pain and inflammation.

PEA's actions are modulated mainly by its hydrolysis by two enzymes, fatty acid amide hydrolase (FAAH) and N-acylethanolamine-hydrolysing acid amidase (NAAA).

These enzymes are also responsible for other acylethanolamines hydrolysis and their sequestration, in case of PEA's pharmacological treatment, leads to an increase of other NAE's levels, strengthening their analgesic action through different molecular mechanisms including the stimulation of cannabinoid receptor CB1, with associated undesirable side effects (2,3,4).

We propose here the synthesis of potential PPAR ligands and a preliminary computational study, based on the receptor structure, towards a library of metabolically stable PEA's analogues with potential affinity toward PPAR- α .

References

1. Tuo, W., Leleu-Chavain, N., Spencer, J., Sansook, S., Millet, R., Chavatte, P. *J. Med. Chem.* **2017**, *60*, 4-46.
2. Re, G., Barbero, R., Miolo, A., & Di Marzo, V. *The Veterinary Journal*, **2007**, *173*(1), 21-30
3. Costa, B., Comelli, F., Bettoni, I., Colleoni, M., & Giagnoni, G. *Pain*, **2008**, *139*(3), 541-550
3. Panlilio, L. V., Thorndike, E. B., Nikas, S. P., Alapafuja, S. O., Bandiera, T., Cravatt, B. F., . & Justinova, Z. *Psychopharmacology*, **2016**, *233*(10), 1879-1888.

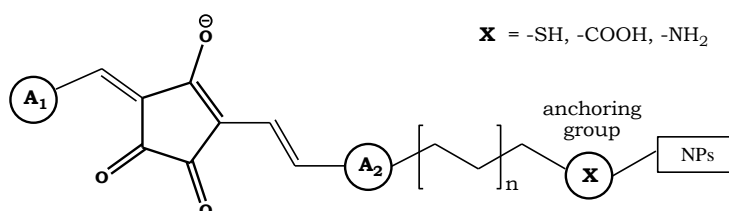
Synthesis and Investigation of Croconates as Smart Organic Coating for Nobel Metals Nanoparticles

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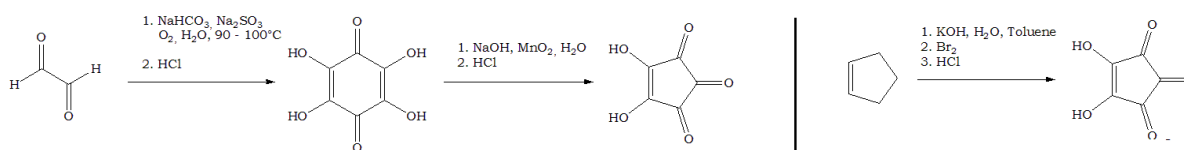
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Croconic acid is a cyclic organic molecule, belonging to a particular family of compounds called oxo-carbon acids. This molecule properly functionalized exhibit an absorption in NIR region and this property can be exploited in the design of NIR-harvesting 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.



The difficulty is to detect a synthetic pathway for the synthesis of the croconic acid and here two strategies are proposed (Scheme 1), as reported in literature ^(1, 2). Gold nanorods are synthesized with a *Seed-Mediated Growth* method ⁽³⁾.



Scheme 1

References: 1. Fatiadi, A.; Isbell, H.; Sager, W. *Journal of Research of the national Bureau of Standards- A. Physics and Chemistry*. **1962**, 67A. 153-162. 2. FUJI PHOTO FILM CO., LTD. - Patent: EP1707552 A1, **2006**. 3. Nikoobakht, B; El-Sayed, M.A. *Chem. Mater.* **2002**, 15, 1957-1962.

Flow chemistry as enabling technology for controlling the reactivity of fluorocarbenoids

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Fluorinated compounds have attracted a great deal of interest by scientists involved in many field of science and technology.⁽¹⁾ However, despite their importance, the selective introduction of monofluoromethyl groups (-CH₂F) into a small organic molecules is still a challenging task. Unlike the extensive use of other halocarbenoids in organic synthesis,⁽²⁾ fluorocarbenoids are still considered the "beast" in carbenoid chemistry due to their chemical instability that severely limited its use in synthetic process.⁽³⁾ In this communication, we report how we tried to face this challenge by employing flow microreactor technology. Fluorocarbenoids could be effectively generated and trapped with electrophiles providing a new successfully application of flash chemistry in short-lived intermediate reactions. Mechanistic insights and applications will be presented.⁽⁴⁾

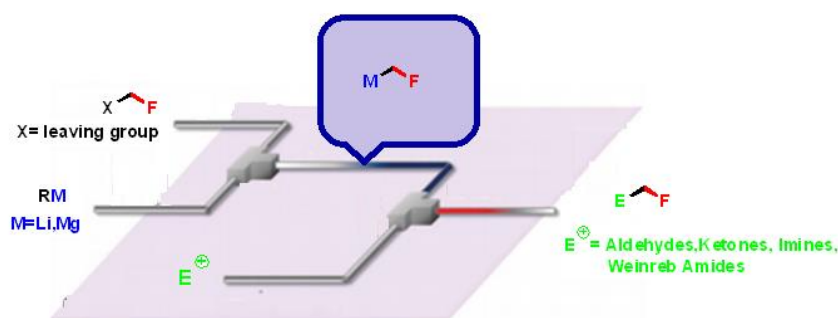


Figure 1. Strategies for the generation and trapping of highly reactive fluorocarbenoids.

References:

1. W. K. Hagmann, *J. Med. Chem.* 2008, 51, 4359.
2. a) V. Pace, A. Pelosi, D. Antermite, O. Rosati, M. Curini, W. Holzer, *Chem. Commun.* 2016, 52, 2639; b) V. Pace, L. Castoldi, A., D. Mamuye, T. Langer, W. Holzer, *Adv. Synth. Catal.* 2016, 358, 172; c) L. Degennaro, F. Fanelli, A. Giovine, R. Luisi, *Adv. Synth. Catal.* 2015, 357, 21.
3. S. Molitor, K-S. Feichtner, V. H. Gessner, *Chem. Eur. J* 2016, 22, 1.
4. F. Fanelli, G. Parisi, L. Degennaro, R. Luisi *Beilstein J. Org. Chem.* 2017, 13, 520.

TiCl₄-promoted Friedel-Crafts alkylations of arenes with alcohols

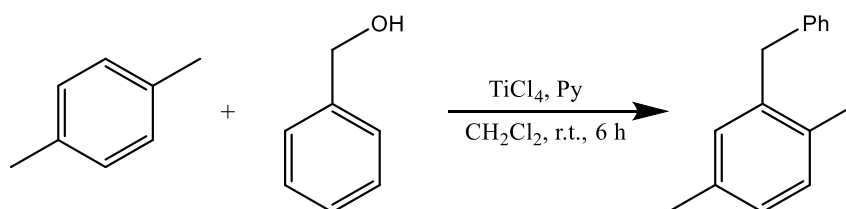
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Alkylations of arenes are usually performed using alkyl halides and Lewis or Bronsted acids as catalysts. Complex and difficult to prepare catalysts are required when alcohols are used as the source of the electrophilic reactants needed to effect the initial step of the aromatic substitution. (1)

Since titanium tetrachloride (TiCl₄) shows a great affinity for the oxygen atom (2) we chose it as suitable reagent to generate the specific electrophiles required for the Friedel-Crafts alkylation of aromatic substrates.

In a typical reaction, *p*-xylene (1 mmol) was treated, at room temperature, with benzyl alcohol (1 mmol) and pyridine (1 mmol) in the presence of non-catalytic TiCl₄ (4 mmol) using dichloromethane (CH₂Cl₂) as solvent. After 6 hours reacting 2-benzyl-1,4-dimethylbenzene was recovered as unique mono-alkylated reaction product in 65 % yield. (Scheme 1)

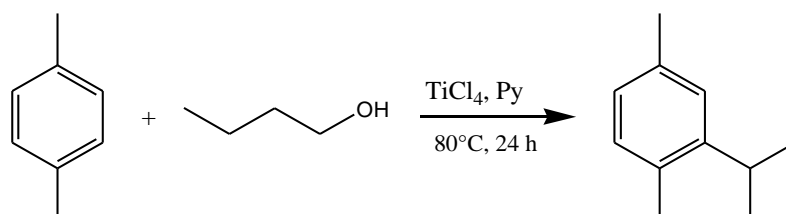


Scheme 1

The reaction was then extended to activated and slightly deactivated aromatic systems providing mostly mono-alkylated products.

The alkylation mediated by TiCl₄ was also applied to other alkyl alcohols; in these cases the reaction proceeded at higher temperature and with longer reaction times. In particular *p*-xylene (1 mmol) was treated, at 80 °C, with 1-butanol (1 mmol) and pyridine (1 mmol) in the presence of TiCl₄ used also as solvent. The reaction was allowed to proceed for 24 hours, after which 1-sec-butyl-2,5-dimethylbenzene was obtained in 94% yield. (Scheme 2)

The obtaining of this product indicates the formation of a carbocation intermediate that rearranges into the more stable secondary carbocation.



Scheme 2

In all cases, small amounts of polyalkylation products are present.

1. Ch. Ramesh Kumar, K.T. Venkateswara Rao, P.S. Sai Prasad, N. Lingaiah; *Journal of Molecular Catalysis A: Chemical* **2011**; 337:17–24.
2. A. Leggio, E. L. Belsito, S. Gallo and A. Liguori; *Tetrahedron Letters*, **2017**; 58:1512-1514.

Synthesis and Characterization of DBF-based organic electrochromic materials

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Electrochromism is the reversible change in optical properties that can occur when a material is electrochemically oxidized (loss of electron(s)) or reduced (gain of electron(s)), and it is of great academic and commercial interest. Even if, traditionally, materials have been considered as being electrochromic when they displayed distinct visible colour changes, the working definition of electrochromism has now been extended to include devices for modulation of radiation in the near infrared, thermal infrared and MW regions, so “colour” can now mean a response by detectors at these wavelengths, and not just by the human eye (1,2).

Among the electrochromic materials is used to find mainly oxides of transition metals (W, V, Mo, Nb, Ti, Ni, Co and Ir), and conjugated polymers, but also organic molecules start to have a particular relevance. Among the organic molecules that present electrochromism in the NIR, the most interesting are the mixed valence (MV) compounds which are generally constituted by a conjugated core covalently linked to the arylamine groups.

We have designed and synthesized new organic compounds, **T1-T2** and **H1-H2** with the dibenzofulvene (DBF)-thiophene π -conjugated bridging unit and, respectively, two and four diarylamine redox centres (Fig.1). These four molecules not only differ in the number of diarylamine units but also for their anchoring positions: **T1** and **H1** are substituted in the 2,7- positions of the DBF instead **T2** and **H2** in the 3,6- (3).

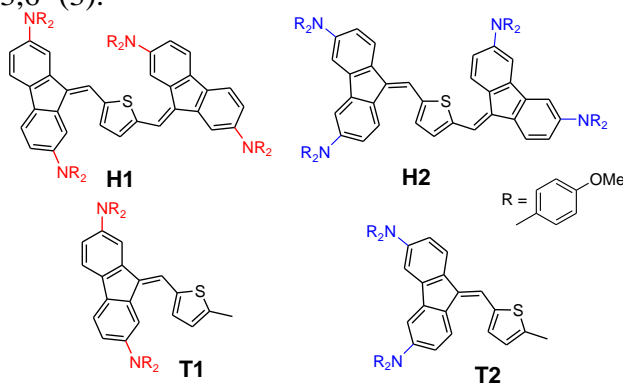


Fig.1 Chemical structures of 2,7- and 3,6- MVs compound.

In these systems we exploited their NIR absorption capability and the electronic coupling highlighting the importance of connection through the central bridge and the importance of amine substituents in the right position on the bridge.

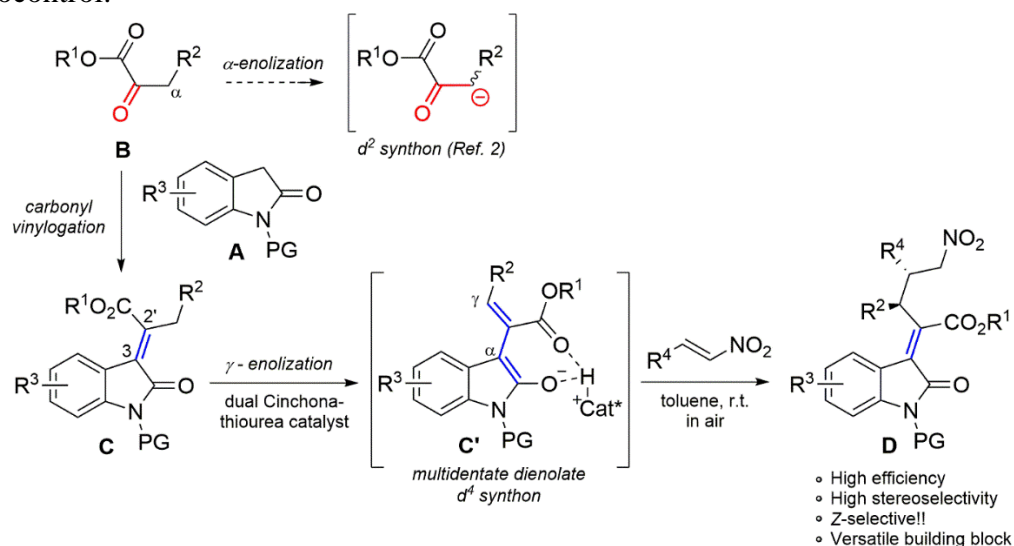
1. Rauh, R.D. (1999) Electrochromic window: an overview. *Electrochim. Acta*, **44(18)**, 3165-3176.
2. Rowley, N.M. and Mortimer R.J. (2002) New electrochromic materials, *Science Progress*, **85(3)**, 243-262.
3. Beneduci, A., Corrente, G.A., Fabiano, E., Maltese, V., Cospito, S., Ciccarella, G., Chidichimo, G., Gigli, G., Capodilupo, A.L. Submitted.

3-(Alkoxy carbonyl-2-Alkyliden)-2-Oxindoles: a new, enabling progeny of multidentate, vinylogous carbon nucleophiles for the direct, enantioselective, vinylogous Michael addition to nitroolefins

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2-Oxindole and 2-ketoester moieties play important roles in Nature: the former is the core scaffold of a wide range of relevant biological and pharmaceutical molecules,⁽¹⁾ while the latter appears in most crucial steps of biochemical processes as either donor or acceptor.⁽²⁾ In particular, due to their high degree of functionalization, α -enolizable 2-ketoesters have raised a wide interest in the field of organic synthesis, and in recent years, their role as valuable d^2 -synthons has been reconsidered and exploited.⁽²⁾ In this context, we envisioned that merging the 2-oxindole scaffold **A** with an enolizable 2-ketoester **B** in the form of 3-(alkoxy carbonyl-2-alkyliden)-2-oxindoles of type **C**, would result in a vinylogous variant of **B** that retains its pro-nucleophilic character but with peculiar additional features. In fact, the C- γ enolization of **C** by a suitable catalyst would generate a multidentate dienolate **C'** embedding an exocyclic, captodative acrylate moiety, whose electronic nature and reactivity (d^4 vs a^3) is intriguing. Capitalizing on our ongoing researches on the pro-nucleophilic behavior of enolizable alkylidene heterocyclic systems,⁽³⁾ we unveiled the d^4 -reactivity pattern of **C'** in a direct, vinylogous, and enantioselective Michael addition to nitroolefins orchestrated by a chiral, bifunctional cinchona-thiourea catalyst. This reaction provided various almost enantiopure nitroalkylidene oxindoles **D** in excellent yields, complete γ -site regioselectivity, and unprecedented Z-diaStereocontrol.⁽⁴⁾



References: 1. Millemaggi, A.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2010**, 4527. 2. (a) Raimondi, W.; Bonne, D.; Rodriguez, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 40. (b) Raimondi, W.; Bonne, D.; Rodriguez, J. *Chem. Commun.*, **2012**, 48, 676. 3. (a) Curti, C.; Rassu, G.; Zambrano, V.; Pinna, L.; Pelosi, G.; Sartori, A.; Battistini, L.; Zanardi, F.; Casiraghi, G. *Angew. Chem. Int. Ed.* **2012**, *51*, 6200. (b) Rassu, G.; Zambrano, V.; Pinna, L.; Curti, C.; Battistini, L.; Sartori, A.; Pelosi, G.; Zanardi, F.; Casiraghi, G. *Adv. Synth. Catal.* **2013**, *355*, 1881. (c) For a recent comprehensive review, see: Battistini, L.; Curti, C.; Rassu, G.; Sartori, A.; Zanardi, F. *Synthesis* **2017** DOI: 10.1055/s-0036-1589487. 5. Curti, C., et al. *manuscript in preparation*.

New “AIE” luminogens based on π -conjugated imidazolium salts

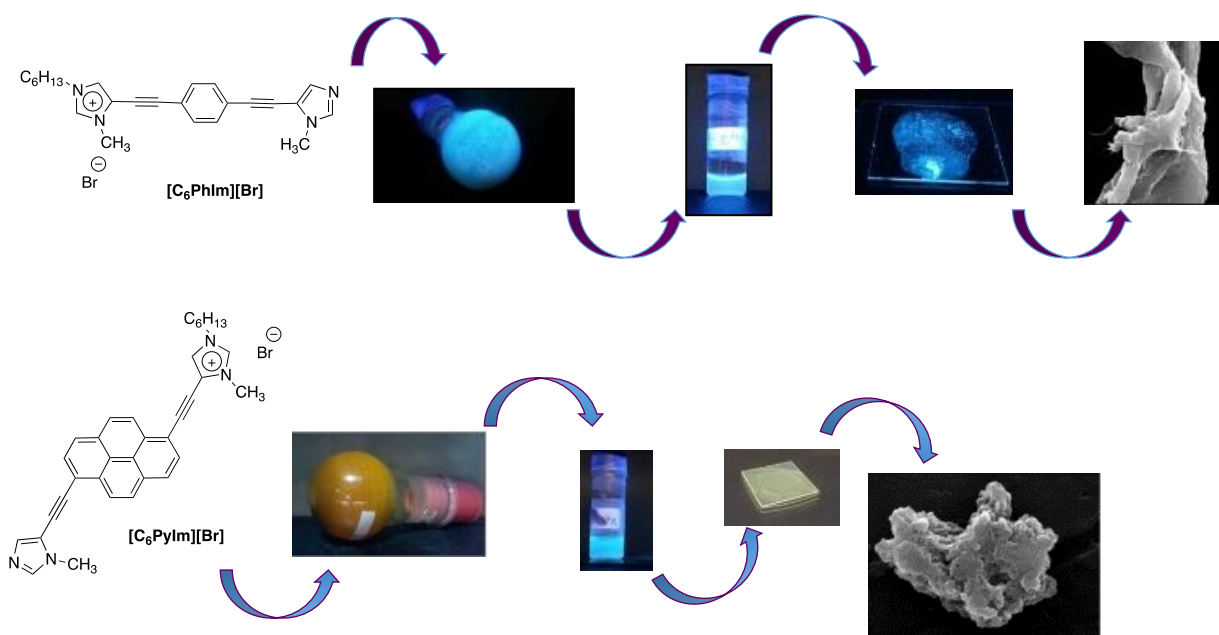
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In the last few years a growing interest has been detected towards the obtainment of organic materials able to behave as luminogenic materials. These should exhibit excellent solid state fluorescence and they generally find applications in the preparation of organic photoelectric devices (1). In this context, a key role is played by the so-called “Aggregation Induced Emission luminogens”, *i. e.* organic compounds able to give a significant increase in the emission intensity as a consequence of an aggregation process.

Bearing in mind above information, and in the framework of our interest in studying properties and applications of fluorescent organic salts (2), we synthesized two push-pull imidazolium based systems differing in the nature of central spacer (1,4-diethynylphenyl or 1,6-diethynylpyrenyl). They were analyzed for their intramolecular charge transfer and self-assembly ability.



Results obtained using a combined approach of different techniques (DSC, TGA, CV, UV-vis and fluorescence spectroscopy, SEM) show that our organic salts behave as push-pull systems. Furthermore, they give self-assembly processes with “AIE” phenomena. Properties of organic salts as well as the ones of aggregates they are able to form, both in solution and solid state, are significantly affected by the nature of the central spacer.

References

- (1) (a) Farinola, G. M.; Ragni, R. *Chem. Soc. Rev.* **2011**, *40*, 3467. (b) Lo, S.-C.; Burn, P. L. *Chem. Rev.* **2007**, *107*, 1097. (c) Roncali, J.; Leriche, P.; Cravino, A. *Adv. Mater.* **2007**, *19*, 2045. (d) Shen, J. Y.; Lee, C. Y.; Huang, T.-H.; Lin, J. T.; Tao, Y.-T.; Chien, C.-H.; Tsai, C. *J. Mater. Chem.* **2005**, *15*, 2455.
- (2) (a) D’Anna, F.; Noto, R. *Eur. J. Org. Chem.* **2014**, 4201. (b) D’Anna, F.; Marullo, S.; Lazzara, G.; Vitale, P.; Noto, R. *Chem. Eur. J.* **2015**, *21*, 14780. (c) Vitale, P.; D’Anna, F.; Ferrante, F.; Rizzo, C.; Noto, R. *Phys. Chem. Chem. Phys.* **2015**, *17*, 26903. (d) Billeci, F.; D’Anna, F.; Marullo, S.; Noto, R. *RSC Adv.* **2016**, *6*, 59502.

Synthesis and biological evaluation of new heteroaryl amides active toward HIV Protease

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Great efforts have been done to the discovery of new drugs for the treatment of human immunodeficiency virus (HIV) infection. The knowledge of the structure of HIV protease and its substrate allowed to prepare specific HIV protease inhibitors. (1)(2) The concept of targeting the protein backbone in structure-based drug design prompted us to prepare new non-peptidic templates, (3) which can maximize interactions in the HIV-protease active site. Herein, a new synthetic strategy is proposed to obtain heteroaryl structures active toward HIV protease in few steps and high yield, from commercially available optically active epoxides. Different substitution patterns are introduced onto a given isopropanol-sulfonamide *core*, switching the central *core*, with the presence of either H or benzyl group, and the type of heteroarene connected to the *core* through a carboxamide functionality (figure 1). *In vitro* inhibition activity will be evaluated by FRET methodology. Preliminary assays showed a general beneficial effect of carboxamide moiety, the IC₅₀ values ranging between 1 and 15 nM. (4) Docking analysis allowed to identify the favorable situation of benzofuryl derivatives in terms of number of interactions in the active site by extensive hydrogen bonding and hydrophobic interactions.

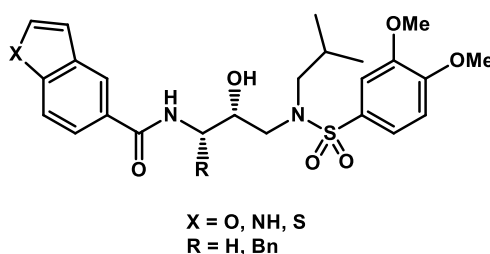


Figure 4

References: 1. Wensing, A. M. J.; Van Maarseveen, N. M.; Nijhuis, M. *Antiviral Res.* **2010**, *85*, 59-74. 2. Ghosh, A. K.; Chapsal, B. D.; Weber, I. T.; Mitsuya, H. *Acc. Chem. Res.* **2008**, *41*, 78. 3. Bonini, C.; Chiummiento, L.; Di Blasio, N.; Funicello, M.; Lupattelli, P.; Tramutola, F.; Berti, F.; Ostric, A.; Miertus, S.; Frece, V.; Kong, D.-X. *Bioorg. Med. Chem.* **2014**, *22*, 4792. 4. Armentano, F.; Bisaccia, F.; Chiummiento, L.; Funicello, M.; Lupattelli, P.; Miglionico, R.; Tramutola, F.; Berti, F. *manuscript in preparation*.

Pd nanoparticles obtained by pulsed laser ablation in liquid and applied to catalyzed ligand-free Suzuki reaction

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Nowadays nanoparticle catalysis is one of the most studied catalytic system because of their large surface area to volume ratio, their easy synthesis under mild condition and the possibility of catalyst recovery in order to replace costly metallic catalytic systems. Since palladium catalyzed cross-coupling reactions seems to be the most widely used method for generation of C-C bonds (1), it was studied a method to obtain palladium nanoparticle without use of toxic and costly solvents and reagents. Pulsed laser ablation in liquid can be considered as an efficient technique to produce metallic nanoparticles and nanostructures by one-step synthesis under benign condition.(2, 3) During the interaction of an intense laser pulse with a solid submerged in liquid, the formation of a plasma confined in a cavitation bubble can be observed. Inside the bubble, the rapid quenching of the high temperature plasma gets to the formation of polycrystalline NPs.(4) In this study well dispersed and quite spherical palladium nanoparticles were produced by pulsed laser ablation in liquid and they were used as catalyst in Suzuki cross-coupling reaction. Moreover, in order to compare the efficiency of the catalytic system, palladium nanoparticles were synthesized by direct reactions between ascorbic acid and a palladium salt, previously used in the Suzuki reaction.(5) The size and morphology of the obtained nanoparticles have been obtained by TEM and XRD techniques. Such prepared nanoparticles have been applied as catalyst for the formation of new C-C bond between methyl(*E*)-4-bromocrotonate and several aryl and heteroarylboronic acid. The reaction was carried out according to a protocol showing ligand-free palladium-catalyzed Suzuki cross-coupling and the better conditions using palladium nanoparticles were investigated to allow good yields of products.(6) Moreover, the obtained catalysts were reused for different cycles of reaction without lost of activity.

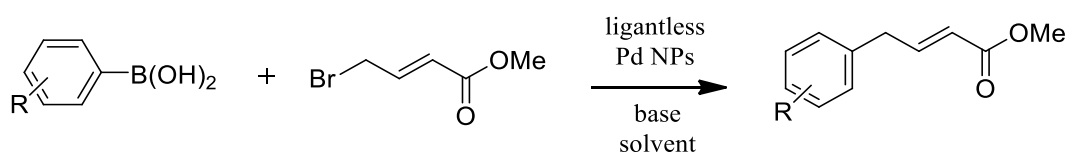


Figure 5

References: 1. A. Fihri, M. Bouhrara, B. Nekoueishahraki, J.M. Basset, Chem. Soc. Rev. 40 (2011) 5181-5203. 2. D. Zhang, B. Gökce, S. Barcikowski, Chem. Rev. 117 (2017) 3990-4103. 3. M. I. Mendivil, B. Krishnan, G.A. Castillo, S. Shaji, Appl. Surface Science. 348 (2015) 45-53. 4. A. De Bonis, M. Sansone, L. D'Alessio, A. Galasso, A. Santagata, R. Teghil, J. Phys. D: Appl. Phys. 46 (2013) 445301(9pp). 5. A. Zhang, M. Liu, M. Liu, Y. Xiao, Z. Li, J. Chen, Y. Sun, J. Zhao, S. Fang, D. Jia, F. Li, J. Mater. Chem. A, 2 (2014) 1369-1374. 6. L. Chiummiento, M. Funicello, P. Lupattelli, F. Tramutola Org. Lett. 14 (2012) 3928-3931.

Homo and hetero-nuclear 2D NMR techniques as useful tool for identification of cytotoxic compounds from complex extracts of *Urtica dioica*

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Nature have been a source of medicinal products for millennia with many useful drugs developed from plants. The natural product continued to play a highly significant role in drug discovery alone and/or as lead compounds (1).

Most of chemotherapeutic agents for cancer treatment are molecules isolated from natural sources. In the search for new anticancer agents from plants (2), *Urtica dioica* has been investigated.

Since ancient times *U. dioica* has been used in alternative medicine, but, only recently, different pharmacological properties of this plant extract, including those of an antioxidant, antimicrobial, antiulcer and antiproliferative, have been documented. In particular, the effects of an aqueous extract of *U. dioica* against the MCF-7 (3), prostate cancer tissues (4) and HeLa cells (5) have been reported. Pursuing the assessment of the pharmacological properties of *Urtica dioica*, in the current work the evaluation of antiproliferative activities on panel of different NSCLC (non-small cell lung cancer) cell lines has been assayed. The active extracts have been investigated in order to identify the metabolites responsible for the activities. Extensive 2D-NMR investigations (HSQC, TOCSY, CIGAR-HMBC, H2BC, HSQC-TOCSY) allowed to identify different compounds belonging tethahydrofuranc lignans, flavonol glycosides, oxilipins classes as principal constituent of active extracts. In particular, these data suggested the presence of a ω -3 hydroxyl fatty acid derivatives as well as fatty acid derivative with cumulated double bond as constituent of polar and medium-polar extracts .

References:

1. Newman DJ and Cragg GM. J Nat Prod 2012, 75: 311-315.
2. Pacifico S, Scognamiglio M, D'Abrosca B, Piccolella S, Tsfantakis N, Gallicchio M, Ricci A, Fiorentino A. J Nat Prod 2010, 73: 1973-1978.
3. Fattahi S, Ardekani AM, Zabihi E, Abedian Z, Mostafazadeh A, Pourbagher R, Akhavan-Niaki H. Asian Pac J Cancer Prev 2013, 14: 5317-5323.
4. Durak I, Biri H, Devrim E, Sözen S, Avcı A. Cancer Biol Ther 2004, 3: 855-857.
5. Asgarpanah J. and Mohajerani R. J Med Plants Res 2012; 6: 5714-5719.

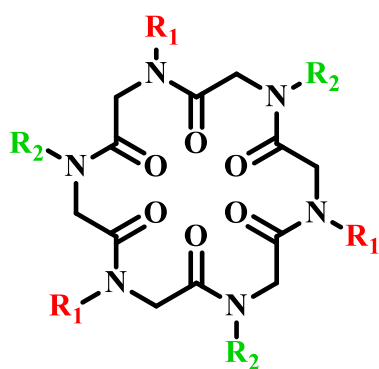
Cyclic hexameric cyclopeptoids as mimics of enniatins and beauvericin mycotoxins

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Cyclic peptoids, oligomers of *N*-alkyl glycines, (1) have recently emerged as important examples of peptidomimetics for their interesting complexing properties and innate ability to permeate biological barriers. (2)

In the present work, we demonstrated that an assembly of properly chosen achiral oligopeptoids, once cyclized, can mimic the class of bioactive fungal cyclooligomer depsipetides enniatins and beauvericin (hybrid structures composed of α -amino acids and α -hydroxyacids), showing a broad spectrum of anticancer, antihelmintic, antibiotic, antifungal, insecticidal, hypolipidaemic and antiretroviral activities. (3) In order to understand the reasons of the enniatins/beauvericin class properties and with the idea to explore those withheld by the cyclic peptoids scaffold, we designed **1**, **2**, and **3** as structural mimics of enniatin B (enB), enniatin C (enC) and beauvericin, respectively (Figure 1). Analogs **4**, **5** and **6**, although not isomorph with natural enniatins/beauvericin, were included in the study in order to enlarge the scope of the investigation.



Cyclic peptoid	R ₁	R ₂
1 (enB)	<i>i</i> Pr	<i>i</i> Pr
2 (enC)	<i>i</i> Bu	<i>i</i> Pr
3 (bv)	Bn	<i>i</i> Pr
4	<i>i</i> Bu	<i>i</i> Bu
5	Bn	<i>i</i> Bu
6	Bn	Bn

Figure 1. Cyclohexapeptoids synthesized and evaluated in the present work

Experimental data evidenced the intricate conformational and stereochemical properties of the synthesized molecules. In fact, complexation studies by NMR, in the presence of sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaTFPB) indicated that the conformationally stable host/guest metal adducts display architectural ordering comparable to that of the enniatins and beauvericin mycotoxins. Similarly to the natural depsipeptides, the synthetic cyclopeptoid analogs show a correlation between ion transport abilities in artificial liposomes and cytotoxic activity on human cancer cell lines.

The present communication demonstrates that the versatile cyclic peptoid scaffold, for its remarkable conformational and complexing properties, can mimic morphologically related natural products and elicit powerful biological activities.

1. S. A. Fowler, H. E. Blackwell, *Org. Biomol. Chem.* **2009**, 7, 1508-1524
2. F. De Riccardis, I. Izzo, D. Montesarchio, P. Tecilla, *Acc. Chem. Res.*, **2013**, 46, 2781-2790
3. R. Süßmuth, J. Müller, H. von Döhrenb, I. Molnár, *Nat. Prod. Rep.*, **2011**, 28, 99

Development of a green and efficient flow process for the preparation of NH-sulfoximines from sulfides and sulfoxides

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A green and efficient flow process involving an heteroatom transfer (N or/and O) for the synthesis of sulfoximines from sulfides⁽¹⁾ and sulfoxides^(2,3) is presented. Sulfoximines are emerging as drug motifs, ligand or auxiliaries for asymmetric synthesis and directing groups in C-H functionalization as well as agrochemical agents⁽⁴⁾. We explored different N sources using flow reactors: ammonium acetate, ammonium carbamate, ammonium carbonate, ammonia in methanol and aqueous solution in the presence of diacetoxyiodobenzene (DIB) as oxidant. Interestingly the use of an aqueous solution allows the development of a greener protocol for the functionalization of a large variety of sulfides and sulfoxides.

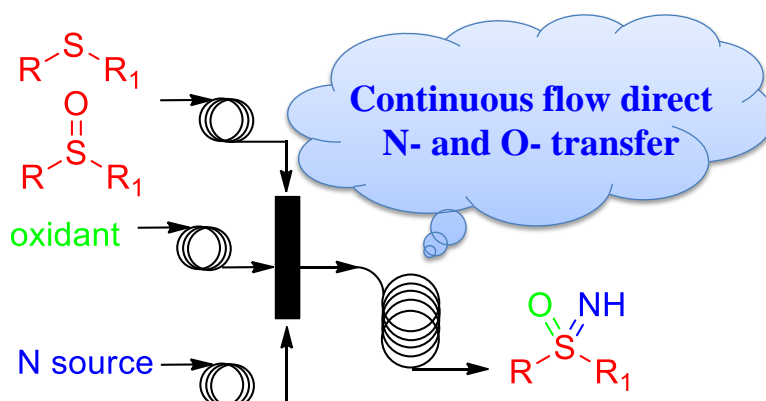


Figura 1. Continuous flow direct N- and O- transfer to sulfides and sulfoxides to give sulfoximines.

References:

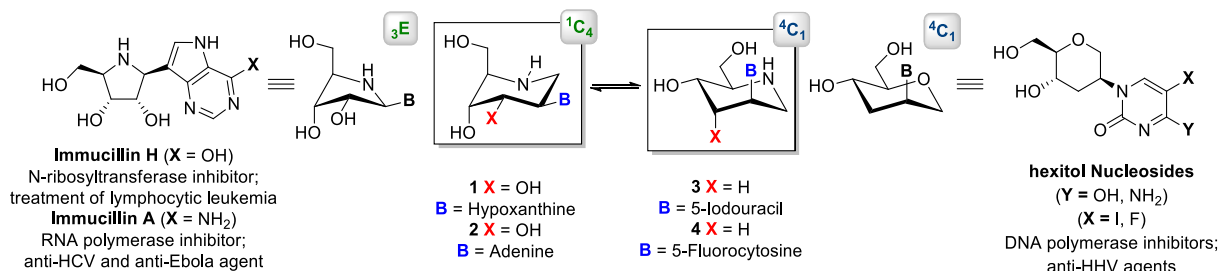
1. A. Tota, M. Zenzola, S. J. Chawner, S. St. John-Campbell, C. Carlucci, G. Romanazzi, L. Degennaro, J. A. Bull, R. Luisi, *Chem. Commun.* 2017, 53, 348-351.
2. M. Zenzola, R. Doran, L. Degennaro, R. Luisi, *J. Bull Angew. Chem. Int. Ed.* 2016, 55, 7203–7207.
3. M. Zenzola, R. Doran, R. Luisi, J. A. Bull, *J. Org. Chem.*, 2015, 80 (12), 6391-6399.
4. W. Dong, K. Parthasarathy, Y. Cheng, F. Pan, C. Bolm, *Chem. Eur. J.*, 2014, 20, 15732-15736.

Synthesis and Biological Evaluation of Novel Piperidinyl Iminosugar-Based Nucleosides

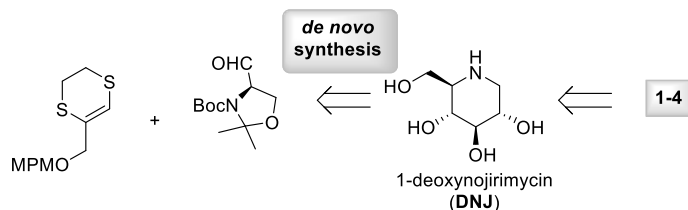
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In recent times, the fusion of two principal concepts behind the research areas of glycomimetics and biomimetics has resulted in the development of a new class of molecules, defined as iminosugar-based nucleosides.(1) On one hand, the structural mimicking of carbohydrates achieved by iminosugars has enabled to identify highly efficient modulators of the activity of carbohydrate processing enzymes. On the other hand, the conformational mimicking of natural nucleosides, achieved with sugar modified nucleoside analogues, revealed as a winning strategy for the treatment of viral infections.(2) Accordingly a number of pyrrolidine-based nucleosides acting as excellent inhibitors of nucleoside processing enzymes have been identified so far, including Immucillin H (PNP inhibitor, $K_i = 56$ pM) and Immucillin A (broad antiviral agent, e.g. anti-HCV). In this context, with the aim to expand the repertoire of such compounds, we have herein explored the synthesis of a variety of piperidinyl nucleosides **1-4**.



Learning from the lesson of anti-HHV hexitol nucleosides,(2) compounds **1-4** are conceived as conformational preorganized nucleosides, exploiting the rigidity of the piperidinyl core to improve inhibition potency and selectivity. Access to nucleosides **1-4** has been devised starting from the well-known glucosidase inhibitor 1-deoxynojirimycin (**DNJ**), (3) efficiently prepared with a general and highly selective procedure by a *de novo* synthetic approach. (4)



Preliminary biological *in vitro* assays of **3** revealed antiviral activity against a variety of DNA viruses (HSV-1 and 2, VZV, HCMV, Vaccinia Virus and Adenovirus).

References: 1 Ho, M. C.; Shi, W.; Rinaldo-Matthis, A.; Tyler, P.C.; Evans, G.B.; Clinch, K.; Almo, S.C.; Schramm, V. *PNAS*, **2010**, *107*, 4805-4812. 2. Ostrowski, T.; Wroblowski, B.; Busson, R.; Rozenski, J.; De Clercq, E.; Bennett, M. S.; Champness, J. N.; Summers, W. C.; Sanderson, M. R.; Herdewijn, P. *J. Med. Chem.* **1998**, *41*, 4343-4353. 3. D'Alonzo, D.; Guaragna, A.; Palumbo, G. *CurrMedChem* **2009**, *16*, 473-505. 4. D'Alonzo, D. *et al.* **2017**, manuscript in preparation.

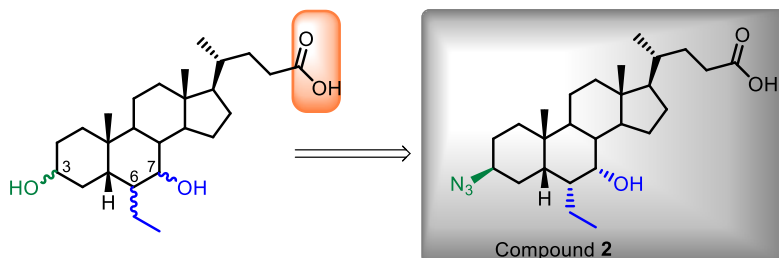
3-azido-6-ethylcholane derivatives as potent and selective FXR agonists

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Considered for many years as the final product of cholesterol metabolism, bile acids (BAs) are experiencing a new life, being recognized as key signaling molecules. They exert their effects by interacting with membrane G-protein coupled receptors, including the bile acid receptor GP-BAR1, and nuclear receptors, mainly the farnesoid X receptor (FXR). In recent years, we have reported the chemical manipulation on chenodeoxycholic acid (CDCA) scaffold, with the aim to improve potency, efficacy and metabolic stability of endogenous BAs, affording several hit compounds with promising pharmacological profiles (1,2,3).

The introduction of an α -ethyl group at C-6 on CDCA profoundly improves the activity of the endogenous BAs, giving the most potent dual FXR/GPBAR1 agonist, the 6-ethylchenodeoxycholic acid (6-ECDCA), also known as obeticholic acid. Its dual activity makes this compound a promising lead in the treatment of primitive biliary cirrhosis (PBC) and steatohepatitis. However, the concomitant activation of GPBAR1 associates with potential side effects, including itching that represents a significant limitation to 6-ECDCA clinical use (4,5). As consequence, several efforts have been shifted towards the development of selective modulators. In the present communication, we have modified 6-ECDCA scaffold installing an azido/amino group at the C-3 position affording a small library with compound **2** as the most potent and selective FXR agonist of this series (6).



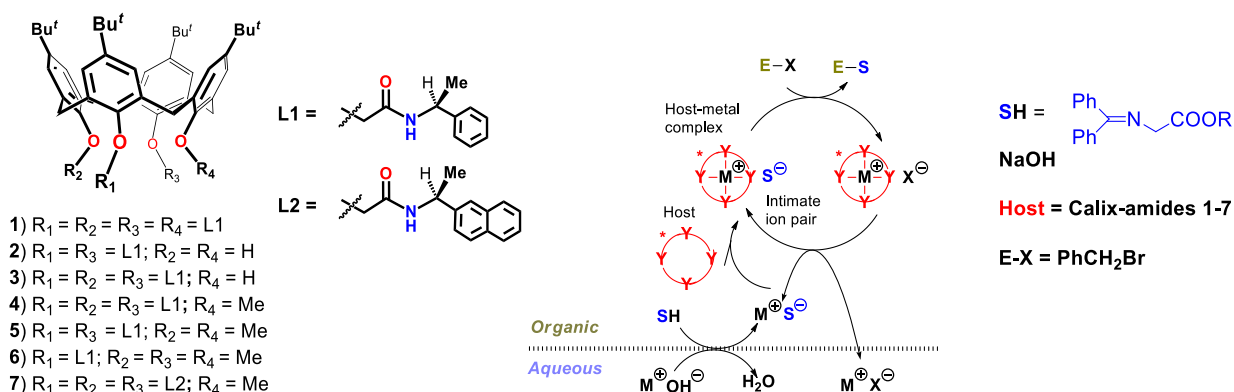
References: 1. Sepe, V., Festa, C., Renga, B., Carino, A., Cipriani, S., Finamore, C., et al. *Sci. Rep.*, **2016**, 6:19008. 2. Finamore, C., Festa, C., Renga, B., Sepe, V., Carino, A., Masullo, D., et al. *Sci. Rep.*, **2016**, 6:29320. 3. Di Leva, F. S., Festa, C., Renga, B., Sepe, V., Novellino, E., Fiorucci, S., et al. *Sci. Rep.*, **2015**, 5:16605. 4. Mason, A., Luketic, V., Lindor, K., Hirschfield, G., Gordon, S., Mayo, M., et al. *J. Hepatol.*, **2010**, 52, S1-S2. 5. Neuschwander-Tetri, B. A., Loomba, R., Sanyal, A. J., Lavine, J. E., Van Natta, M. L., Abdelmalek, M. F., et al. *Lancet*, **2015**, 385, 956-965. 6. Festa, C., De Marino, S., Carino, A., Sepe, V., Marchianò, S., Cipriani, S., et al. *Front. Pharmacol.* **2017**, 8:162.

Asymmetric Phase-Transfer Catalysis by Chiral Calix[4]arene Derivatives

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Calix[*n*]arenes (1) are a well-known class of macrocyclic compounds widely exploited in the field of molecular recognition for their three-dimensional shape and ease of functionalization, which make them good supramolecular hosts. It has long been known that calix[4]arene-amide hosts show a high affinity towards alkali metal cations, in particular K⁺ and Na⁺ (2). These cation-recognition abilities of calixarene-amides have been particularly exploited in many supramolecular applications, whereas their employment in phase transfer catalysis has surprisingly remained unconsidered. In particular, the approach proposed by Shinkai (3) and Taniguchi (4), using the cation-recognition abilities of calixarene-ethers, has not been considered. However, in the last years, examples of calixarene-based PTC have been proposed (5), in which the macrocycle merely acts as a scaffold bearing ammonium moieties as the real phase-transfer groups. To the best of our knowledge, no examples of asymmetric phase transfer catalysis exploiting the cation-recognition abilities of chiral calixarene-amide hosts have been so far reported. In the present communication, we will describe the synthesis of chiral calix[4]arene-amides **1-7**, their recognition properties toward Na⁺ and K⁺ guests as TFPB salts, and their abilities as phase-transfer catalysts in the asymmetric alkylation of *N*-(diphenylmethylene)-glycine esters.



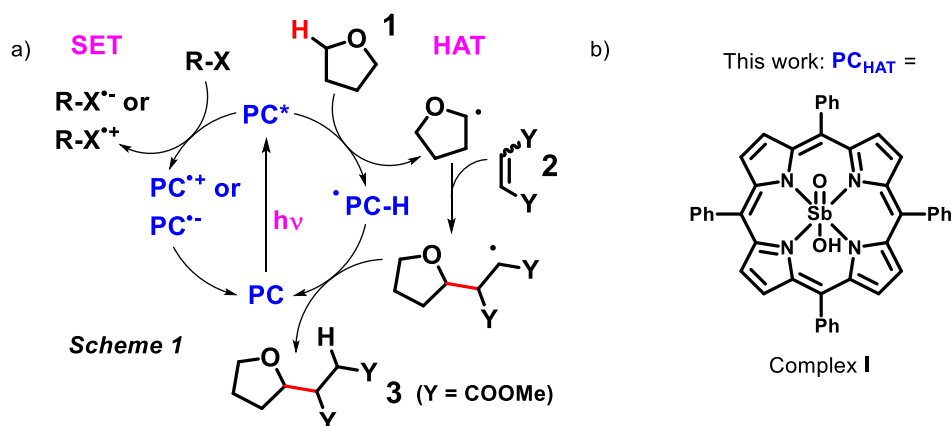
References: 1. C. D. Gutsche, *Calixarenes, An Introduction*, Royal Society of Chemistry, Cambridge, UK, **2008**. P. Neri, J. L. Sessler, M. -X. Wang (Eds), *Calixarenes and Beyond*, Springer, Dordrecht, **2016**. 2. F. Arnaud-Neu, G. Barrett, S. Fanni, D. Marrs, W. McGregor, A. M. McKervey, M. J. Schwing-Weill, V. Vetrogon, S. Wechsler *J. Chem. Soc., Perkin Trans. 2* **1995**, 453–461. F. Arnaud-Neu, M. A. McKervey, J. Schwing-Weill, in *Calixarenes 2001* (Eds.: Asfari, Z., Böhmer, V., Harrowfield, J., Vicens J.) Kluwer: Dordrecht, **2001**, pp. 385–406. P. J. Greenawalt, S. Amemiya *Anal. Chem.* **2016**, *88*, 5827–5835. S. Amemiya *Anal. Chem.* **2016**, *88*, 8893–8901. 3. K. Araki, A. Yanagi, S. Shinkai *Tetrahedron* **1993**, *49*, 6763–6772. 4. H. Taniguchi, E. Nomura *Chem. Lett.* **1988**, *20*, 1773–1776. E. Nomura, H. Taniguchi, K. Kawaguchi, Y. Otsuji *J. Org. Chem.* **1993**, *58*, 4709–4715. E. Nomura, H. Taniguchi, K. Kawaguchi Y. Otsuji *Chem. Lett.* **1991**, *20*, 2167–2170. 5. S. Shimizu, S. Shirakawa, Y. Sasaki, C. Hirai *Adv. Synth. Catal.* **2002**, *344*, 370–378. S. Shimizu, N. Shimada, Y. Sasaki; *Green Chem.* **2006**, *8*, 608–614. (c) P. Srivastava, R. Srivastava *Tetrahedron Lett.* **2007**, *48*, 4489–4493. (d) S. Sayin, M. Yilmaz *RSC Adv.* **2014**, *4*, 2219–2225. (e) M. Yilmaz, S. Sayin, in *Calixarenes and Beyond* (Eds.: Neri, P.; Sessler, J. L.; Wang M. -X.) Springer, Dordrecht, **2016**, pp. 719–741.

Antimony-oxo Porphyrins as Promising Photocatalysts for Visible Light Induced H-Atom Abstraction

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The use of photocatalytic reactions in organic synthesis has recently gained increasing attention due to the mild conditions involved and because they allow unconventional pathways. These reactions are based on the use of a photocatalyst (PC, Scheme 1), a species that is responsible for light absorption and, once in the excited state, for the activation of the substrates of the reaction through a chemical step. (1) Single Electron Transfer (SET) and Hydrogen Atom Transfer (HAT) are the typical activation modes of a PC. The former approach is undoubtedly the most investigated one, where visible light absorbing Ru- and Ir-polypyridyl complexes (PC_{SET}) led to the development of a hot topic, tagged as "photoredox catalysis" (Scheme 1a, left part). By contrast, HAT processes offer the possibility to cleave directly a C-H bond in the substrate (e.g. THF, Scheme 1a, right part). The main limitations to the development of this type of reactions are related to the classes of PCs able to promote HAT steps (PC_{HAT}; currently limited to the families of polyoxometalates and (aromatic) ketones) and to the use of UV light in place of visible light. (2,3)



Addressing the urgent need to develop visible light photocatalysts for promoting HAT processes, we report herein some preliminary results on the use of antimony-oxo porphyrin complexes, (4,5) such as **I** (Scheme 1b), for the formation of C-C bonds. We studied the Giese-type addition of tetrahydrofuran **1** onto unsaturated esters **2** as a model reaction, affording succinate **3** in up to 77% yield. Gratifyingly, the reaction could be extended also to different radical traps, such as unsaturated nitriles. Different light sources can be adopted, including (simulated) solar light and monochromatic LEDs (410 or 455 nm). The process is completely inhibited in the presence of radical-scavengers, such as TEMPO, and, when the reaction is performed with an equimolar mixture of **1** and **1-d₈**, occurs with a kinetic isotopic effect (KIE) of 5.25.

References: 1. Ravelli, D.; Protti, S.; Fagnoni, M. *Chem. Rev.* **2016**, *116*, 9850-9913. 2. Protti, S.; Fagnoni, M.; Ravelli, D. *ChemCatChem* **2015**, *7*, 1516-1523. 3. Capaldo, L.; Ravelli, D. *Eur. J. Org. Chem.* **2017**, *2017*, 2056-2071. 4. Ertl, M.; Wöß, E.; Knör, G. *Photochem. Photobiol. Sci.* **2015**, *14*, 1826-1830. 5. Knör, G. *Coord. Chem Rev.* **2016**, *325*, 102-115.

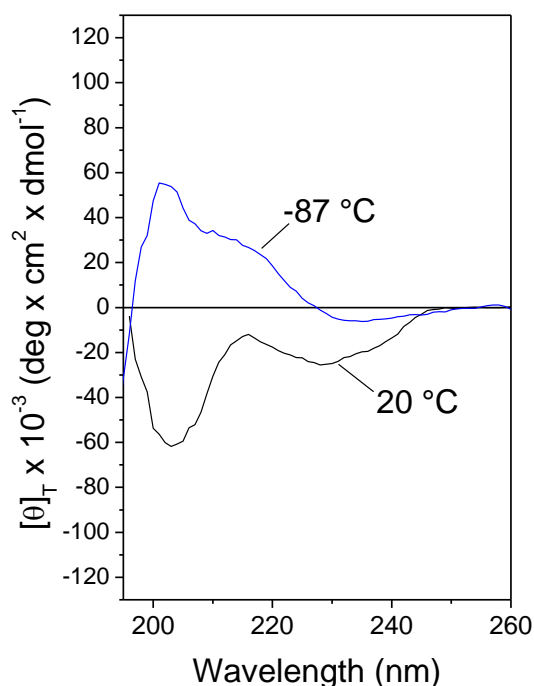
Acknowledgements: D.R. thanks MIUR for financial support (SIR Project "Organic Synthesis via Visible Light Photocatalytic Hydrogen Transfer"; Code: RBSI145Y9R). G.K. is grateful for support by COST action CA15106 "C-H activation in organic synthesis".

C-terminal methyl ester helical peptides can undergo a temperature-driven, reversible screwsense inversion. A spectroscopic study

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The C-terminus of natural peptides is never a methyl ester. However, post-translational modifications inserting esters on membrane proteins have been detected and associated with the ability of the protein to switch its 3D-structure (1). Here we describe how a methyl ester inserted at the C-terminus of the well-known, helical peptaibol trichogin GA IV dramatically reduced the rigidity of its helical 3D-structure. To this aim, we acquired synchrotron radiation circular dichroism spectra of a number of trichogin analogs in organic solvents at cryogenic temperatures, an environment that closely resembles membrane. We found that by replacing the native C-terminal 1,2-aminoalcohol leucinol of trichogin with a leucine methyl ester or free carboxylic acid, at room temperature the helical handedness was inverted from right to left at cryogenic temperatures showing an isodichroic point. Back at room temperature, the native right-handed helical conformation was regained revealing the presence of a thermally-driven peptide helical handedness switch. On the other hand, the temperature-dependence of the peptide conformation using fluorescence and EPR spectroscopies of suitably functionalized analogs revealed that the well-characterized, mixed 3_{10} -/ α -helical structure adopted by trichogin at room temperature was also retained at cryogenic temperatures.



References: 1. Pechlivanis, M.; Kuhlmann, J., BBA-Proteins Proteom. 2006, 1764, 1914.

Synthesis, conformation analysis, and proteolytic stability of helical peptide inhibitors of the VEGF/VEGFR protein-protein interaction

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Angiogenesis is a key target in cancer therapy. With the aim at regulating this process, we recently designed, synthesized and investigated an array of peptides based on the IDNEWRKQTQ sequence of the vascular endothelial growth factor (VEGF)-C. The new peptides were optimized to increase both helix stability and binding affinity towards the VEGF receptors. In particular, we exploited the known helix-inducing capabilities of C^α-tetrasubstituted α-amino acids to stabilize the secondary structure of our peptides. By adding such non-coded residues we gained in proteolytic stability, as well. In addition, we inserted Trp residues at appropriate positions to enhance the binding affinity. The conformational preferences of our peptides were investigated by CD and 2D-NMR in aqueous solution. Data analysis confirmed the onset of helical structures. Interestingly, we observed that the absorption bands in the near-UV of the indole (Trp) chromophore constitute a reliable probe to assess the conformational stability of our helical peptides. In this presentation we will correlate this CD feature to the information extracted from the NMR analysis. Our new VEGFR antagonists exhibit high binding affinity for the receptor, and biological activity against VEGF-mediated angiogenesis.

Tosylhydrazones as Powerful Tools for the Construction of sp^3 - sp^2 and sp^2 - sp^2 Carbon Bonds: A Novel Approach to Conjugated and Skipped 1-Alkoxydienes

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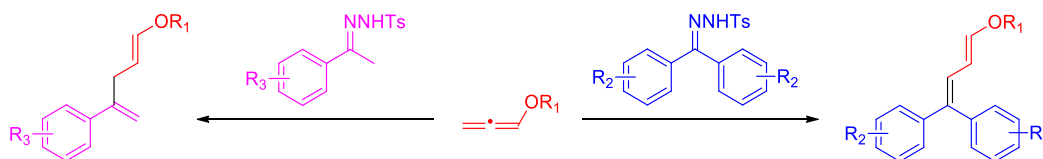
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N-tosylhydrazones have attracted large attention in organic synthesis as safe alternative for the *in situ* generation of unstable diazo compounds. Moreover they are easily accessible, also on large scale, by condensation between *p*-toluenesulfonyl hydrazide and carbonyl compounds, or by sulfonylation of a preformed hydrazone.

Their high synthetic potential arises from the easy generation of many unstable species, with differing reactivity by choosing the appropriate procedure and tuning the reaction conditions. For instance, in the early 50's, Bamford and Stevens discovered that upon treatment with strong bases, tosylhydrazones afford alkenes in high yields.¹ Fifteen years later Shapiro reported that aliphatic tosylhydrazones containing an α hydrogen, react with alkyllithium reagents to yield vinyl lithium intermediates.² Later on, their ability to generate reactive metal carbenes has triggered renewed interest in these reagents. In 2007, Barluenga and co-workers reported the first example of *N*-tosylhydrazones used as nucleophilic partners in palladium catalyzed cross couplings.³

Recently, we started to investigate over the possibility to build 1-alkoxy-1,3-dienes exploiting tosylhydrazones peculiar reactivity. Inspired by Xiao and colleagues, who reported the synthesis of highly substituted butadienes through a palladium catalyzed three component reaction between allenes, aryl iodides and diazocompounds,⁴ we set up a similar reaction using alkoxyallenes.

Unfortunately, due to their different electronic properties, it is not possible to promote a similar multicomponent process. Surprisingly a 4,4'-diaryl-1-alkoxy-1,3-diene is recovered, which clearly appears to be the product of a two component process competing with the expected reaction (Scheme 1, right). Moreover, when the same reaction conditions are applied to acetophenone tosylhydrazones, a completely different regioselectivity is observed (Scheme 1, left).



Scheme 1 General scheme for the Pd catalyzed cross couplings of alkoxyallenes with benzo- and acetophenone tosylhydrazones

References: 1. W. R. Bamford, T. S. Stevens, The Decomposition of Toluene-*p*-sulphonylhydrazones by Alkali, *J. Chem. Soc.* **1952**, 4735–4740. 2. R. H. Shapiro, M. J. Heath, Reaction of Tosylhydrazones with Alkyllithium Reagents. A New Olefin Synthesis. *J. Am. Chem. Soc.* **1967** (89), 5734–5735. 3. J. Barluenga, P. Moriel, C. Valdes, F. Aznar, *N*-Tosylhydrazones as Reagents for Cross-Coupling Reactions: A Route to Polysubstituted Olefins, *Angew. Chem. Int. Ed.* **2007** (46), 5587–5590. 4. Q. Xiao, B. Wang, L. Tian, Y. Yang, J. Ma, Y. Zhang, S. Chen, J. Wang, Palladium Catalyzed Three Component Reaction of Allenes, Aryl Iodides, and Diazo Compounds: Approach to 1,3-Dienes, *Angew. Chem. Int. Ed.* **2013** (52), 9305–9308.

Proteomics Approaches to Elucidate Bioactivity of Monacolin K

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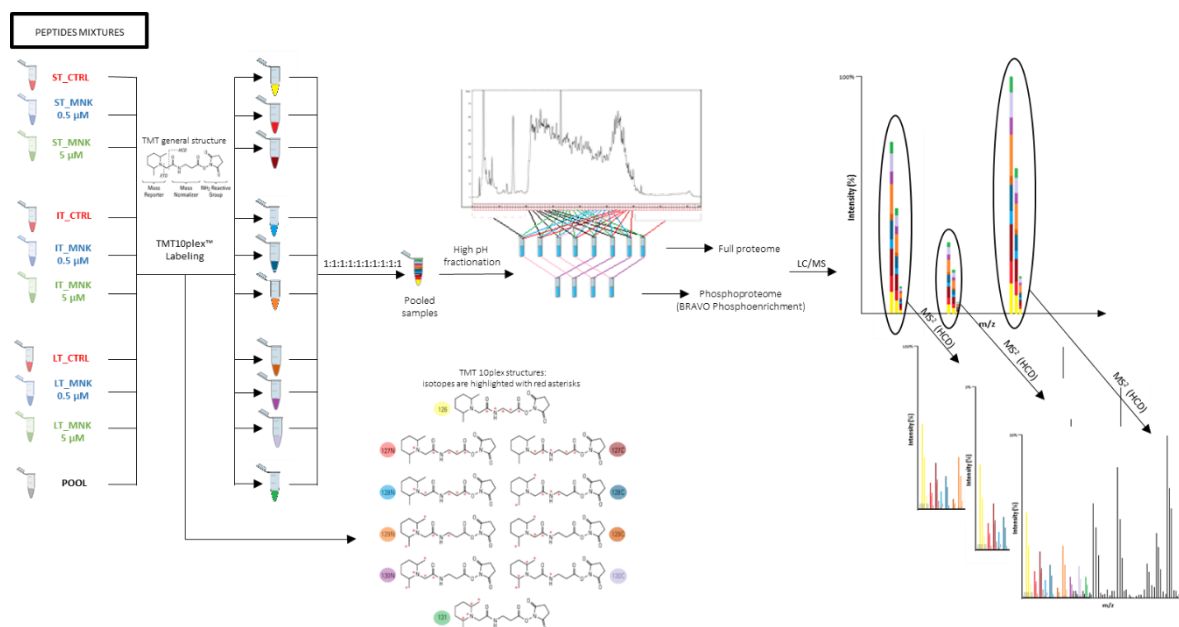
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MS-based proteomics represents a clever tool to disclose unclear molecular bioactivities of small molecules (1,2) such as natural compounds in nutraceuticals. The latter is rising as significant building block in prevention or/and treatment of numerous diseases (3).

Monacolin K (MNK) from *Monascus purpureus* is known as lovastatin, an HMG-CoA reductase inhibitor used to lower hematic concentration of cholesterol. Scientific evidences link statins to antiproliferative and apoptotic effects in a wide panel of cancers. MNK is particularly active on Triple Negative Breast Cancer (TNBC) cell lines such as MDA-MB 231(4). In this study, we investigated how MNK affects protein expression and phosphorylation in MDA-MB 231 cells

Preliminarily, a kinetic proliferation assay was performed using IncuCyte ZOOM[®] system to find out the IC₅₀ of MNK and to set up proteomics experiments. Then, living MDA-MB 231 cells were treated with MNK and harvested at different time points. Each of the peptides mixtures, obtained upon extraction and digestion of proteomes, was tagged with one of the isotopomeric amine- reactive Tandem Mass Tags (TMT 10-plex[™]) and then pooled together (5). After HpH fractionation and phospho-enrichment, in the case of phosphoproteome analysis, UPLC-MS/MS of the obtained multiplexed pools was carried out: bioinformatic analysis of the MS data revealed changes in proteome and phosphoproteome of MDA-MB 231 due to MNK.



References: 1. Aebersold & Mann, *Nature*, **2003**, 422, 198-207. 2. Cravatt *et al.*, *Nature*, **2007**, 450, 991-1000. 3. Hardy *et al.*, *Nutrition*, **2000**, 16, 688-697. 4. Park *et al.*, *BBRC*, **2013**, 439, 275-279. 5. Thompson *et al.*, *Anal. Chem.*, **2003**, 75, 1895-1904.

A [8]Cycloparaphenylene Derivative as Emitter in Triplet-Triplet Annihilation Upconversion

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CycloParaPhenylenes ([n]CPPs) are fully conjugated macrocycles constituted by n para-linked benzene units (Figure), which exhibit size-dependent optical and electronic properties (1,2). Among them, they exhibit the narrowing of the HOMO-LUMO gap as the number of aromatic units decreases (2). Consequently, the emission spectra of CPP derivatives are red-shifted and quantum efficiency decreases as the macrocycle become smaller (2). CPPs, can be considered useful template for the bottom-up synthesis of single wall carbon nanotubes (3). Recently, many efforts have been devoted to study the triplet-triplet annihilation (TTA)-based upconversion processes (4). Upconversion represents a emerging wavelength-shifting technology, useful to convert low energy photons into light adequate for photovoltaic, photocatalysis and bioimaging (5). In TTA-based upconversion systems, the photon excitation of a triplet sensitizer (e.g.: octaethylporphyrin Pd complex, PdOEP in Figure), affords a triplet energy transfer toward an acceptor which give rise to upconverted fluorescence. Cycloparaphenylenes are known as excellent chromophores exhibiting high fluorescence quantum yields, however, to the best of our knowledge, no data is currently available about their abilities to act as emitter (acceptor) into upconversion schemes. Prompted by these considerations, we wish to describe here the synthesis of the new anthracene-incorporated [8]CPP macrocycle **1** (Figure). In addition, details on the conformational features, optoelectronic and upconversion properties of this new derivative will be given.

References: 1. R. Jasti, J. Bhattacharjee, J. B. Neaton, C. R. Bertozzi, *J. Am. Chem. Soc.*, **2008**, *130*, 17646–17647. 2. E. R. Darzi, R. Jasti, *Chem. Soc. Rev.*, **2015**, *44*, 6401–6410. 3. H. Omachi, T. Nakayama, E. Takahashi, Y. Segawa, K. Itami, *Nat. Chem.*, **2013**, *5*, 572-577. 4. S. Balushev, T. Miteva, V. Yakutkin, G. Nelles, A. Yasuda, G. Wegner, *Phys. Rev. Lett.*, **2006**, *97*, 143903-143906. 5. Q. Liu, W. Feng, T. Yang, T. Yi, F. Li, *Nat. Protoc.* **2013**, *8*, 2033 –2044. 6. P. Della Sala, A. Capobianco, T. Caruso, C. Talotta, M. De Rosa, P. Neri, A. Peluso, C. Gaeta, *submitted*.

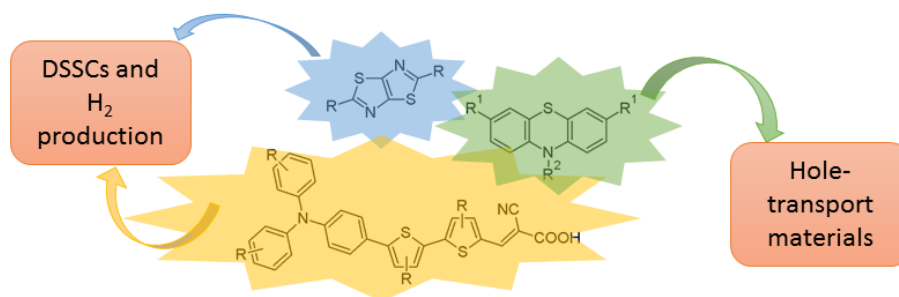
Multi-purpose metal-free dyes for energy and hydrogen production.

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Sunlight is, by far, the most abundant, economic and well distributed energy source over the world. For this reason, many different photovoltaic technologies exploit solar energy in order to produce electric current or eco-friendly fuels as hydrogen (1). Organic chemistry can play a pivotal role in the field of renewable energies because totally organic molecules are often the most suitable candidates as photoactive materials, thanks to their unique optical and electrochemical properties which can be finely tuned through a balanced modification of the structure of the compounds.

Our first interest in this field was the design and the synthesis of organic dyes as photoactive materials for Dye-Sensitized Solar Cells (DSSCs) (2), a very promising photovoltaic technology which is currently finding its market niche where the traditional silicon solar cells cannot be used. Recently we decided to broaden our horizons exploring new applications of our molecules toward other research fields which involve the exploitation of sunlight, such as in the photo-catalyzed production of hydrogen (3), or the employment of solid-state hole-transport materials (ss-HTMs) for DSSCs and PSCs (Perovskite Solar Cells) (4).



Our main interest was that of studying the influence of small structural modifications, such as the substitution of some functional groups or the insertion of alkyl chains in different regions of the molecules, on the physical and electrochemical properties of the dye, and on the efficiency of the final photovoltaic devices.

References:

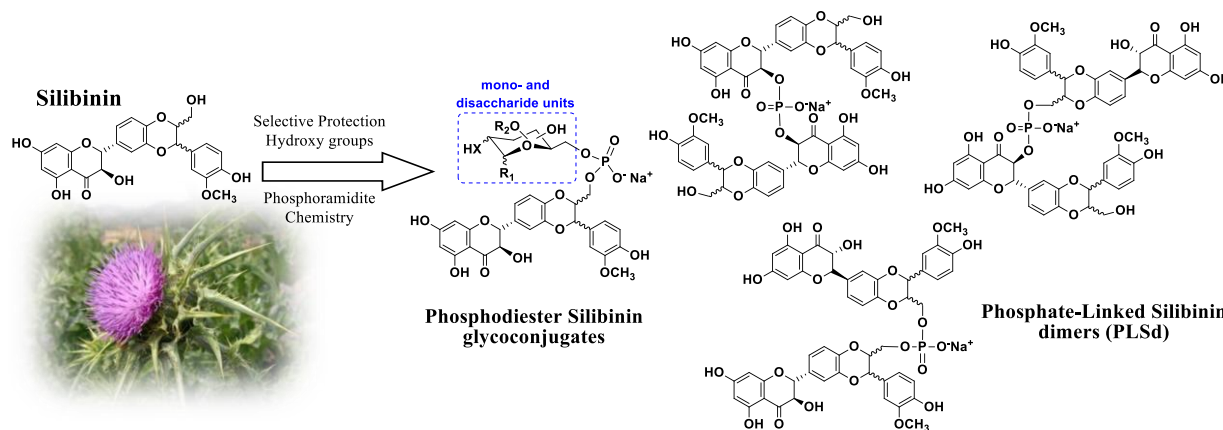
1. Armaroli N., Balzani V. *Chem. Eur. J.*, **2016**, 22, 32.
2. Dessì A., Calamante M., Mordini A., Peruzzini M., Sinicropi A., Basosi R., Fabrizi de Biani F., Taddei M., Colonna D., Di Carlo A., Reginato G., Zani L. *Chem. Commun.*, **2014**, 50, 13952 and *RSC Adv.*, **2015**, 5, 32657.
3. Cecconi B., Manfredi N., Montini T., Fornasiero P., Abboto A. *Eur. J. Org. Chem.*, **2016**, 31, 5194.
4. Seo J., Noh J. H., Seok S. I. *Acc. Chem. Res.*, **2016**, 49, 562.

Silibinin phosphate-based flavonolignans: new emerging synthetic metabolites with interesting pharmacological properties

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Many drug candidates have been reported to possess a strong therapeutic potential *in vitro* but they have failed *in vivo* because of their poor pharmacokinetic behaviour, very often due to the low water solubility. There are many formulations and drug design strategies that can be used to overcome solubility issues. The design and synthesis of soluble *pro-drugs* is one of the most common approach used. In this frame, the phosphate group is a useful tool for the enhancement of aqueous solubility of phenolic and other metabolites, in addition it displayed excellent chemical stability and rapid bioconversion *in vivo* to the parent drug by phosphatases. On the other hand, also the conjugation of specific molecules recognized by a receptor on the target cell could be a successful strategy (1). In our studies, we have combined both aspects through the synthesis of new phosphodiester modified Silibinin with a good water solubility, as well as, attractive antioxidant properties (2,3). In the past decade, Silibinin has received more attention due to its large variety of activities ranging from anticancer and chemopreventive actions (4,5) to hypocholesterolemic, cardioprotective and neuroprotective (6,7) activities. Unfortunately, the bioavailability and the therapeutic efficiency of Silibinin are rather limited by its low water-solubility. In this work, we present the synthesis of a new library of modified Silibinins (Figure) and related studies of their redox behaviour.



Exploiting the selective protection of the hydroxyl groups of the Silibinin, we developed an efficient strategy for the synthesis of Silibinin phosphate-based flavonolignans consisting of phosphodiester glycoconjugates and dimers of Silibinin. The water solubility, the radical scavenger efficiency and the ability to scavenge different reactive oxygen species (ROS) have been evaluated for the new phosphodiester modified Silibinins in comparison to Silibinin. Moreover, the serum stability, and their cytoprotective (X/XO assay on HepG2 cells) behaviours have been studied. The remarkable antioxidant activity and the high water solubility (compared to Silibinin) make Silibinin phosphate-based flavonolignans promising molecules for future studies.

References: 1. J. M. Ferriz, J. Vinsova, *Curr. Pharm. Des.* **2010**, *16*, 2033 – 2052. 2. A. Zarrelli, V. Romanucci, M. Della Greca, L. De Napoli, L. Previtera, G. Di Fabio, *Synlett* **2012**, *24*, 45 – 48. 3. A. Zarrelli, V. Romanucci, C. Tuccillo, A. Federico, C. Loguercio, R. Gravante, G. Di Fabio, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5147 – 5149. 4. R. Gazak, D. Walterova, V. Křen, *Curr. Med. Chem.* **2007**, *14*, 315 – 338. 5. D. Biedermann, E. Vavříková, L. Cvak, V. Křen, *Nat. Prod. Rep.* **2014**, *31*, 1138 – 1157. 6. S. Duan, X. Guan, R. Lin, X. Liu, Y. Yan, R. Lin, T. Zhang, X. Chen, J. Huang, X. Sun, Q. Li, S. Fang, J. Xu, Z. Yao, H. Gu, *Neurobiol. Aging* **2015**, *36*, 1792 – 1807. 7. F. Yin, J. Liu, X. Ji, Y. Wang, J. Zidichouski, J. Zhang, *Neurochem. Int.* **2011**, *58*, 399 – 403.

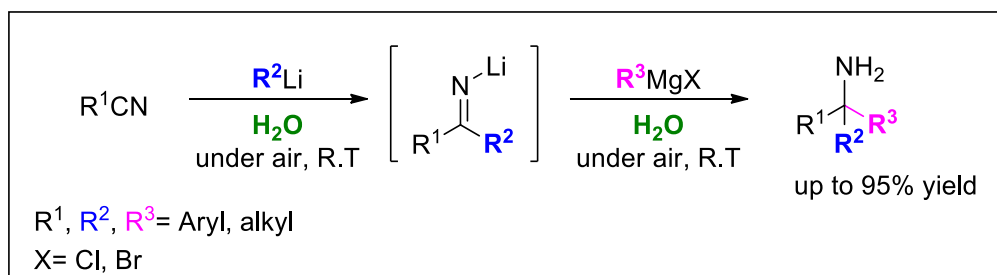
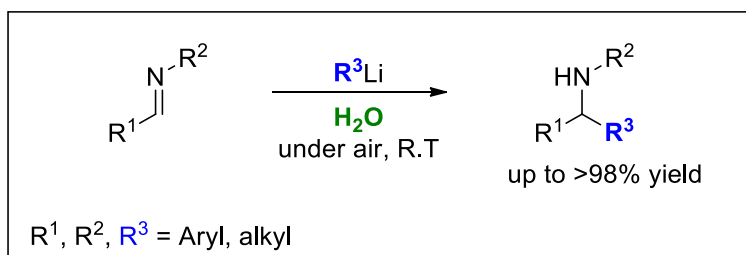
Unprecedented “On-Water” Nucleophilic Addition of Organolithiums and Grignard Reagents to Imines and Nitriles

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Despite their enormous synthetic relevance, the use of polar organolithium and Grignard reagents is greatly limited by their requirements of low temperatures in order to control their reactivity as well as the need of dry organic solvents and inert atmosphere protocols to avoid their fast decomposition. One of most momentous challenges in organic synthesis is to perfect the use of polar organometallics under air at room temperature, also replacing harsh and volatile organic compounds by more environmentally benign solvents (1).

Building on our recent findings (2,3,4), in this Communication we describe an unprecedented nucleophilic addition of Grignard and organolithium reagents to both aliphatic and aromatic imines and nitriles under “on water” conditions (5). It will be shown that, under optimized protocols, the above additions can be conveniently and safely run at room temperature and under air *en route* to secondary amines and tertiary carbinamines, which were isolated in up to >98% yield (Scheme 1). This methodology opens up new opportunities to push even more polar organometallic chemistry towards “green” horizons.



Scheme 1

References: 1. García-Álvarez, J.; Hevia, E.; Capriati, V. *Eur. J. Org. Chem.* 2015, 6779–6799. 4. 2. Mallardo, V.; Rizzi, R.; Sassone, F. C.; Mansueto, R.; Perna, F. M.; Salomone, A.; Capriati, V. *Chem. Commun.* 2014, 50, 8655–8658. 3. Sassone, F. C.; Perna, F. M.; Salomone, A.; Florio, S.; Capriati, V. *Chem. Commun.* 2015, 51, 9459–9462. 4. Cicco, L.; Sblendorio, S.; Mansueto, R.; Perna, F. M.; Salomone, A.; Florio, S.; Capriati, V. *Chem. Sci.* 2015, 7, 1192–1199. 5. Butler, R. N.; Coyne, A. G. *Org. Biom. Chem.* 2016, 14, 9945–9960.

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Asymmetric Synthesis and Antiviral Activity of Novel Carbocyclic Nucleosides

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Cyclohexenyl nucleosides (**Figure 1**) represent well-known biomimetic agents, working as bioactive nucleoside analogues, either at monomeric and oligomeric level (1) or as substrates/templates for enzymatic replication (2). These properties are due to the capacity by the cyclohexenyl ring to act as a conformational bioisostere of natural deoxyribose. Indeed, the flexible nature of cyclohexenyl nucleosides, rapidly fluctuating between the low energy ²H₃ and ³H₂ conformations, enables a close resemblance with the bioactive sugar ring puckers (²T₃ and ³T₂) of natural nucleosides (**Figure 1**). Not surprisingly, when evaluated as antiviral agents, both D- and L-cyclohexenyl nucleosides (**1** and *ent*-1) exhibited comparable *in vitro* anti-HHV (*Human Herpes Virus*) properties than those of some of the most efficient drugs currently in use on the market (1).

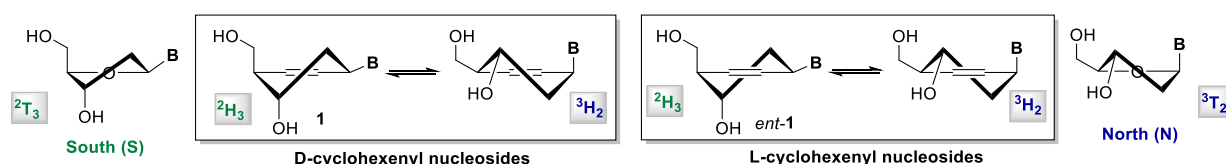


Figure 1. Bioactive D- and L-cyclohexenyl nucleosides **1** and *ent*-1.

With the aim to expand the repertoire of these bioactive nucleosides, we are currently exploring the antiviral properties of novel cyclohexenyl nucleosides **2** and *ent*-2, lacking the OH group at C5' position and therefore being conceived as chain terminators. Herein, the asymmetric synthesis of **2** and *ent*-2 (B = Pu or Py) starting from achiral cyclohexanone is reported (**Figure 2**). Main attention has been devoted to the key Tsuji-Trost rearrangement step of **3** and *ent*-3, whose unprecedented stereoconvergent outcome has been studied by chemical methods, as well as, by spectroscopic and *in silico* analysis.

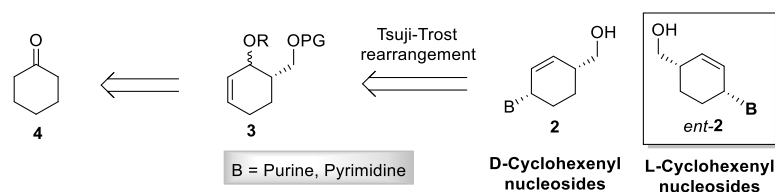


Figure 2. Synthesis of novel D- and L-cyclohexenyl nucleosides **2** and *ent*-2.

Preliminary *in vitro* assays against a variety of HHV infections are also presented, revealing interesting antiviral properties, especially against TK⁻ strains.

References: 1. Reference n. 1 Herdewijn, P. *Antiviral Res.* **2006**, *71*, 317-321. 2. Reference n. 2 Pinheiro, V. B.; Taylor, A. I.; Cozens, C.; Abramov, M.; Renders, M.; Zhang, S.; Chaput, J. C.; Wengel, J.; Peak-Chew, S.-Y.; McLaughlin, S. H.; Herdewijn, P. *Science* **2012**, *336*, 341-344.

Elucidating the role of tanshinone IIA and cryptotanshinone in neuroinflammation through molecular docking studies

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Alzheimer's disease (AD) is a common form of dementia mainly characterized by the deposition of neurofibrillary tangles and β -amyloid (A β) peptides in the brain and a neuro-inflammatory state (1). Beside synthetic drugs, the use of natural compounds represents a valid therapeutic alternative for the treatment of AD. Among these, the root of *Salvia miltiorhiza* Bunge (also known as Danshen) used for the treatment of cardiovascular, cerebrovascular disease and CNS functional decline in Chinese traditional medicine is one of the most representative examples (2). Thus, we have investigated the role of tanshinone IIA (TIIA) and cryptotanshinone (CRY), two of the main components of the Danshen, in neuroinflammation by a multidisciplinary approach. Biological data showed a reduced activation of COX-2 and iNOS and an inhibition of the NF- κ B/I κ B- α signaling pathway (3). Therefore, we examined the ability of these compounds to bind NF- κ Bp65 with an in silico methodology. In particular, we performed molecular docking experiments of the active secondary metabolites on NF- κ Bp65 and we concluded that CRY and TIIA interact in similar way with it (Figure 1). In addition, because no structure containing NF- κ Bp65 has been crystallized yet, we decided to use the software SiteMap (4) to highlight the possible binding sites on the target surface. Interestingly, the most probable one (Figure 1, top), was located in the DNA-binding domain and the docking results showed that both molecules interact with Arg30, which has been previously proven to be an important site of methylation in the NF- κ Bp65 activation process (5). These suggest that CRY and TIIA may be used in the treatment of AD and could act as direct inhibitors of NF- κ Bp65.

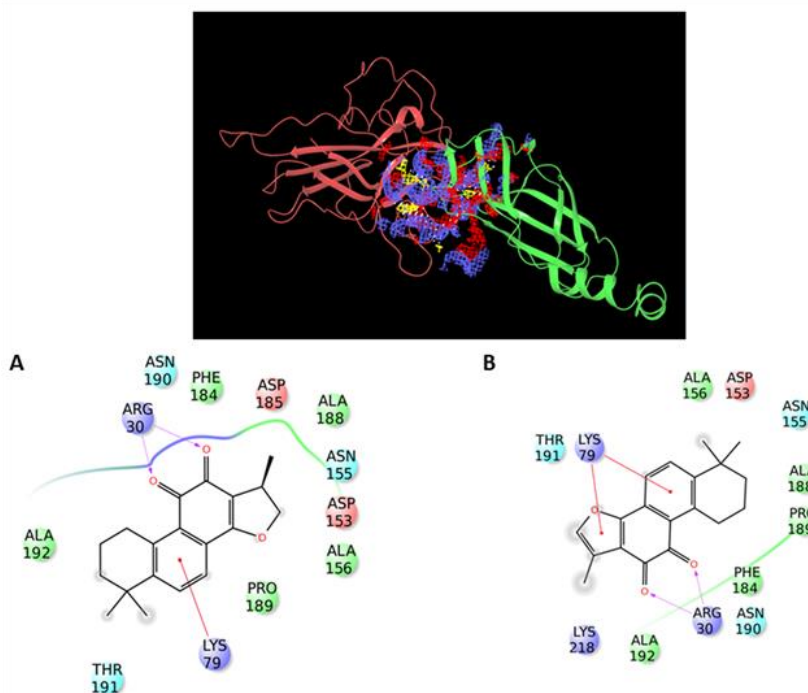


Figure 1. Binding site on NF- κ Bp65 (top) and binding mode of CRY (A) and TIIA (B).

References: 1. Lleo, A.; Greenberg, S.; Growdon, J, *Annu. Rev. Med.* **2006**, *57*, 513-533. 2. Teng, Y.; Zhang, M. Q.; Wang, W.; Liu, L. T.; Zhou, L. M.; Miao, S. K.; Wan, L. H., *BMC Complement. Altern. Med.* **2014**, *14* (1), 23. 3. F. Maione; M. Piccolo; S. De Vita; M. G. Chini; C. Cristiano; C. De Caro; P. Lippiello; M. C. Miniaci; R. Santamaria; C. Irace; V. De Feo; A. Calignano; N. Mascolo; G., Bifulco, *Pharm. Res.* **2017** (submitted). 4. SiteMap, Schrödinger, LLC, New York, NY, **2016**. 5. Reintjes, A.; Fuchs, J. E.; Kremser, L.; Lindner, H. H.; Liedl, K. R.; Huber, L. A.; Valovka, T., *Proc. Natl. Acad. Sci.* **2016**, *113* (16), 4326-4331.

Microwave synthesis and preliminary evaluation of 2-amino-3,4-dihydropyrimidine BACE-1 inhibitors

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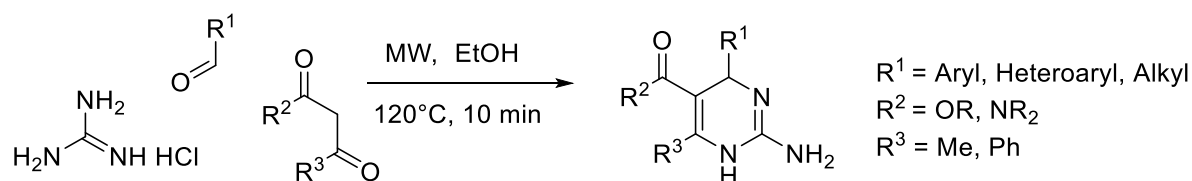
The guanidine functional group is one of the most widely used motifs in the design and synthesis of new compounds with appealing pharmacological properties. This structural unit is present in fact in a large number of natural products (1) and bioactive compounds, (2) playing important roles in medicinal chemistry.

Of particular interest is the incorporation of this moiety into a dihydropyrimidine scaffold. Functionalized 3,4-dihydropyrimidines are accessible in a single step from readily available starting materials by Biginelli reaction, a three component cyclocondensation (3) in which urea or thiourea are reacted with an aldehyde and a β -ketoester.

A large choice of optimized experimental protocols with variations in the three building blocks is available in the literature, (3) giving access to 2-oxo- and 2-thioxodihydropyrimidine derivatives that have exhibited a large spectrum of biological properties.

On the contrary, very few general Biginelli protocols based on the use of guanidine, and leading to the corresponding substituted 2-amino-3,4-dihydropyrimidines are reported in the literature.

Due to the great potential of this functional group when included in an heterocyclic scaffold and in the frame of a research aimed at finding low molecular weight compounds of medicinal interest, we found a simple and practical method for the microwave assisted Biginelli cyclocondensation of guanidine hydrochloride with aldehydes and β -dicarbonylic compounds, affording a large set of differently functionalized 2-amino-3,4-dihydropyrimidines in short reaction times and good yields.



These compounds were found to display a marked *in vitro* inhibitory activity towards BACE 1, an aspartyl protease involved into the pathogenesis of Alzheimer Disease,(4) with IC₅₀ values in the micromolar and sub-micromolar range.

References: 1. Berlinck, R.G.S. and Romminger, S. *Nat. Prod. Rep.* **2016**, *33*, 456-490. 2. Berlinck, R. G. S. and Kossuga, M. H. *Nat. Prod. Rep.* **2005**, *22*, 516-521. 3. Nagarajaiah, H.; Mukhopadhyay, A.; Narasimha Moorth, J.; *Tetrahedron Lett.*, **2016**, *57*, 5135-5148. 4. Finder, V. H. *J. Alzheimers Dis.*, **2010**, *22*, 5-19.

Combinatorial approach for the discovery of novel microsomal prostaglandin E₂ synthase-1 (mPGES-1) inhibitors

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Microsomal Prostaglandin E synthase 1 (mPGES-1) has been recognized as a novel, promising target for anti-inflammatory and anticancer drugs development being involved in a number of pathologic conditions including arthritis, cancer and Alzheimer's disease (1). mPGES-1 is the terminal enzyme in the prostaglandin (PG) biosynthesis pathway and catalyzes the conversion of prostaglandin H₂ (PGH₂) to prostaglandin E₂ (PGE₂). It is an inducible enzyme and its expression is increased in response to pro-inflammatory stimuli. This feature makes mPGES-1 extremely interesting for drugs development because its inhibition is connected to the suppression of inducible PGE₂ responsible for inflammatory and tumor pathologies that should reduce the typical side effects of the COX-2 inhibitors commercially available (2). Thanks to the resolution human mPGES-1 X-ray structure (3), and starting from our previous results (4-6), we report the structure based drug design of new inhibitors against mPGES-1 through a combinatorial approach. We have selected two different 'privileged structures': a) 2-aminobenzothiazoles and b) 1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one scaffolds, which can be easily manipulated to provide a number of highly functionalized potential ligands. Starting from the analysis of the synthetic procedures (7, 8), in fact, we have combined (Enumerate phase) (9) and evaluated (Virtual Screening Workflow) (9) all the commercially available synthons *in silico* before the chemical synthesis, obtaining in this way a large libraries (millions of compounds) that have been prepared and screened against mPGES-1 (dedicated software: CombiGlide, Schrödinger LLC.) (9). The possible inhibitors have been selected by a qualitative computational filter, based on the accordance with specific key interactions with the receptor counterparts, predicted free energy of binding and ligand efficiency, leading to the identification of a focused set of compounds selected for the subsequent phases of chemical synthesis and biological evaluation (cell free and cell-based assays). Following this workflow, we have identified a set of new mPGES-1 inhibitors, all endowed with low micromolar activity. Moreover, the ongoing lead optimization phases will be step-by-step supported by the prediction of the pharmacokinetic properties (dedicated software: QikProp, Schrödinger LLC.) (9), essential to discard the compounds with unfavorable predicted ADME properties that fall outside the normal range of known drugs, eliminating unnecessary testing on compounds that will ultimately fail.

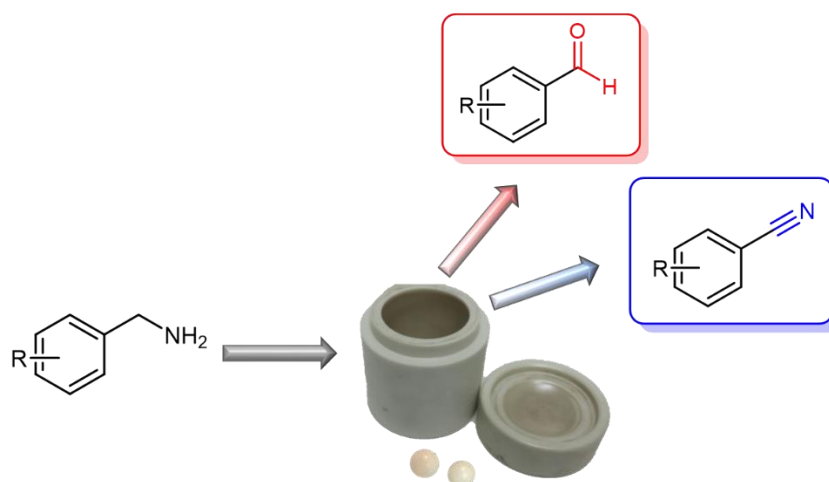
References: 1. Koeberle, A.; Werz, O. *Biochem. Pharmacol.* **2015**, *98*, 1. 2. Nakanishi, M.; Gokhale, V.; Meuillet, E. J.; Rosenberg, D. W. *Biochimie* **2010**, *92*, 660-664. 3. Luz, J. G.; Antonysamy, S.; Kuklish, S. L.; Condon, B.; Lee, M. R.; Allison, D.; Yu, X. P.; Chandrasekhar, S.; Backer, R.; Zhang, A.; Russell, M.; Chang, S. S.; Harvey, A.; Sloan, A. V.; Fisher, M. J. *J. Med. Chem.* **2015**, *58*, 4727. 4. Maione, F.; Cantone, V.; Pace, S.; Chini, M. G.; Bisio, A.; Romussi, G.; Pieretti, S.; Werz, O.; Koeberle, A.; Mascolo, N.; Bifulco, G. *Br. J. Pharmacol.* **2016**. DOI: 10.1111/bph.13545. 5. Iranshahi, M.; Chini, M. G.; Masullo, M.; Sahebkar, A.; Javidnia, A.; Yazdi, M. C.; Pergola, C.; Koeberle, A.; Werz, O.; Pizza, C.; Terracciano, S.; Piacente, S.; Bifulco, G. *J. Nat. Prod.* **2015**, *78*, 2867. 6. Chini, M. G.; De Simone, R.; Bruno, I.; Riccio, R.; Dehm, F.; Weinigel, C.; Barz, D.; Werz, O.; Bifulco, G. *Eur. J. Med. Chem.* **2012**, *54*, 311. 7. Piscitelli, F.; Ballatore, C.; Smith, A. B. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 644. 8. Viviano, M.; Milite, C.; Rescigno, D.; Castellano, S.; Sbardella, G. *Rsc Adv.* **2015**, *5*, 1268. 9. Schrödinger, Suite 2017, LLC, New York, NY, **2017**.

Oxidation of amines to carbonyl compounds and nitriles by ball milling

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The oxidation of amines is a powerful method to produce various important synthetic intermediates such as carbonyl compounds and nitriles (1,2,3). The classical methodologies suffer of many drawbacks (4,5) such as use of toxic metal-containing reagents, toxic solvents and overoxidation of carbonyl compounds. To overcome these problems we have investigated a new mild, efficient, metal-free and solvent-free oxidation of primary amines to aldehydes, ketones and nitriles under ball-milling conditions at room temperature. This approach is simple, convenient and uses inexpensive and commercially available reagents. In addition this method is compatible with various functional groups and requires easily accessible starting materials. Simple filtration of the reaction mixture through pad of silica gel affords pure aldehydes, ketones and nitriles products.



References:

1. K. C. Nicolau, C. J. N. Mathison, T. Montagnon, *J. Am. Chem. Soc.* **2004**, *126*, 5192-5201.
2. V. V. Patil, E. M. Gayakwad, G. S. Shankarling, *J. Org. Chem.* **2016**, *81*, 781-786.
3. Y. Wang, H. Kaboyashi, K. Yamaguchi, N. Mizuno, *Chem. Commun.* **2012**, *48*, 2642-2644
4. S. S. Rawalay, H. Shechter, *J. Org. Chem.* **1967**, *32*, 3129-3131
5. S. Sobhani, S. Aryanejad, M. F. Maleki, *Helv. Chim. Acta* **2012**, *95*, 613-617.

New triimidazole derivatives: intriguing cases of photoluminescence behavior

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Solid-state luminogens have been the subject of great interest because high tech applications of light emitting materials very often require their use in the condensed phase. Unfortunately, frequently, weakly or even non-emissive solid materials are obtained from highly emissive molecules due to the notorious aggregation caused quenching phenomenon. However, since the pioneering work of Tang (1), many efforts have been spent on the isolation of compounds characterized by the opposite behavior, referred to as Aggregation Induced Emission (AIE). In parallel, a strong effort has been devoted to the search of organic molecules with long-lived excited states which enable exciton migration over long distances for increased production of free charges (2). Very recently, An et al. reported ultra-long phosphorescent emission features in structures of planar organic molecules coupled in H-aggregates, which provide an effective means of stabilizing and protecting the triplet excitons formed through intersystem crossing (3). The stabilized excited state, which functions as an energy trap at a lower energy level, may delocalize on several neighboring molecules, offering suppressed radiative and non-radiative deactivation decay rates in favour of long-lived excited states and ultralong phosphorescence. Here we report three simple pure organic AIE compounds, namely cyclic triimidazole (triimidazo[1,2-*a*:1',2'-*c*:1'',2''-*e*][1,3,5]triazine) and its mono- and di-brominated derivatives, showing at room temperature in powder simultaneous molecular fluorescence and phosphorescence and aggregated ultralong phosphorescence (4). The nature of the emissive behavior is verified and interpreted through complete photophysical characterization in solution, powders and matrix dispersed thin films and by theoretical calculations and structural determination. Our experimental data reveal that luminescence lifetimes up to 1 s, which are several orders of magnitude longer than those of conventional organic fluorophores, can be realized under ambient conditions thus expanding the class of organic materials for phosphorescence applications.

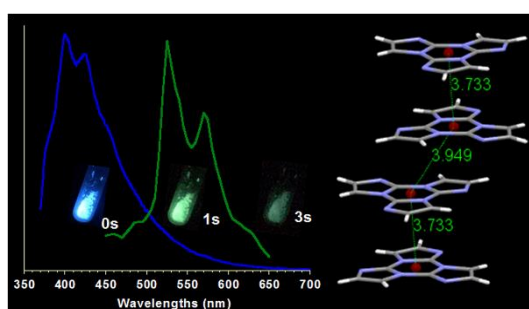


Figure 1. Photophysical behavior of powders of cyclic triimidazole

References: 1. Luo, J. D.; Xie, Z. L.; Lam, J. W. Y.; Cheng, L.; Chen, H. Y.; Qiu, C. F.; Kwok, H. S.; Zhan, X. W.; Liu, Y. Q.; Zhu, D. B.; Thang, B. Z.. Chem. Commun. 2001, 1740–1741. 2. Baroncini, M.; Bergamini, G.; Ceroni, P.. Chem. Commun. 2017, 53, 2081–2093. 3. An, Z.; Zheng, C.; Tao, Y.; Chen, R.; Shi, H.; Chen, T.; Wang, Z.; Li, H.; Deng, R.; Liu, X.; et al.. Nat. Mater. 2015, 14, 685-690. 4. Lucenti, E.; Forni, A.; Botta, C.; Carlucci, L.; Giannini, C.; Marinotto, D.; Previtali, A.; Righetto, S.; Cariati, E.. J. Phys. Chem. Lett. 2017, 8, 1894-1898

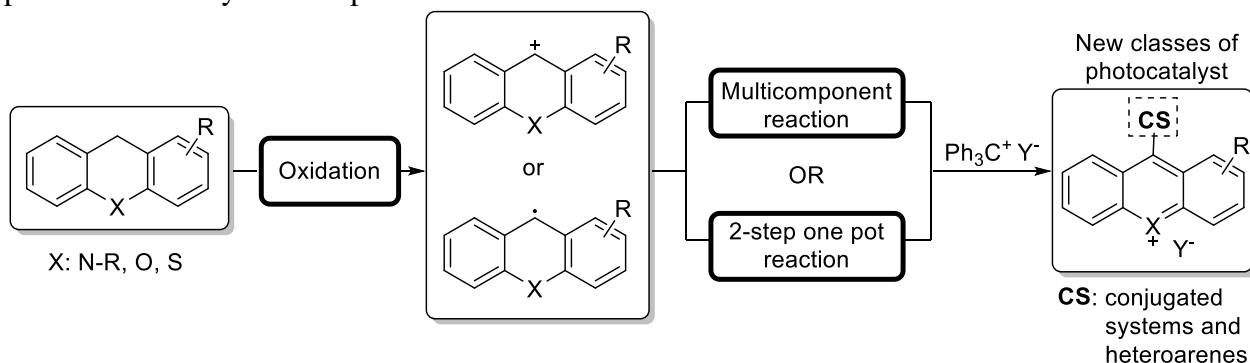
Rational Design of Ready-to-Shape New Classes of Organo-Photocatalysts

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Over the past last decade, the renewed interest around photoredox catalysis resulted in a continuous flux of many valuable light-induced synthetic transformations.(1,2) Even though there are several advantages of a photoredox-mediated approach respect to standard thermal processes, most common catalysts are based on expensive noble transition metals, such as iridium and ruthenium.(1) Moreover, they might contaminate the products, which is especially undesirable in the synthesis of pharmaceuticals. Thus, the use of organo-photocatalysts represents a valuable and attractive alternative, mainly because organic dyes are cheaper, harmless and easy to handle than the corresponding metal-based photocatalysts.(2) As follows, it is evident the advantage coming within the employment of such organic photosensitizers, but the exiguous variety of structures, which are based essentially on fluorescein, rhodamine, eosin and 9-mesityl-10-methylacridinium salt platforms, limit the possible applications. For this reason, new classes of organo-photocatalysts are highly demanding to both discover new synthetic solutions and improve the performance in standard catalytic photoredox reactions.

Following this perspective, we present herein several innovative one-pot strategies to achieve new classes of easily tunable and ready-to-shape (thio)xanthene or acridine-based photocatalysts, in which a Csp³-H oxidative functionalization is involved as key step of the synthetic approach.(3,4) Furthermore, to show the potential and the versatility of such new structures, various applications in photoredox-catalysis are reported.



References: 1. C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, 113, 5322. 2. N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, 116, 10075. 3. A. Gini, T. Brandhofer and O. García Mancheño, *Org. Biomol. Chem.*, 2017, 15, 1294. 4. T. Stopka, L. Marzo, M. Zurro, S. Janich, E.-U. Würthwein, C.G. Daniliuc, J. Alemán and O. García Mancheño, *Angew. Chem. Int. Ed.* 2015, 54, 5049.

Visible light induced C-H α,α -difluoroacetophenone functionalization of electron-rich arenes: A viable option for difluoromethyl functionalization

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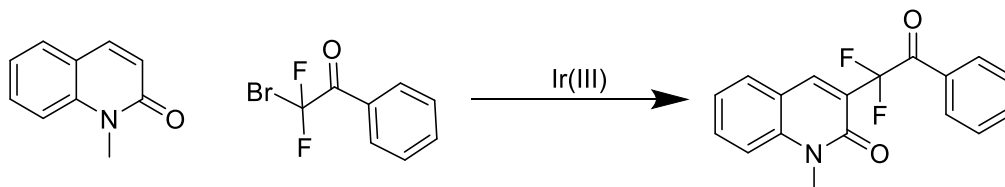
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The difluoromethyl group imparts interesting features attractive in medicinal chemistry. As a lipophilic hydrogen bond donor, it offers the rare feature to simultaneously provide hydrogen bonding interfaces and increased cell membrane permeability.(1)

In recent years a number of reactions have been developed to synthesize difluoromethylated compounds. Many of these methods require activated arenes(2) limiting scope(3,4) and regioselectivity. Baran(5) reported a new reaction that generates CF₂H radical to functionalize the more electron-deficient position in arenes owing to its electronic properties.

To complement these developments, we report a methodology that, in an efficient way, can regioselectively functionalizes the more electron-rich position of arenes (and heteroarenes). An electrophilic CF₂R radical has been developed that substitutes in this desirable position.

Inspired by photoredox catalysis which avoids potentially hazardous radical initiators, we have found that the easily prepared α -bromo- α,α -difluoroacetophenone functions as a useful reagent for the introduction of the difluoroacetophenone,. These products are then readily converted to the difluoromethyl group. Ir(III) photocatalysts were studied and found successful for this easily operated CH functionalization of complex molecules. Our investigations and advances will be described.



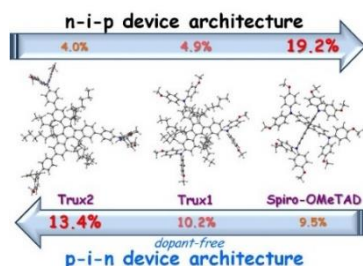
References: 1. Erickson, A. J.; McLoughlin, J. I. *J. Org. Chem.* **1995**, *60*, 1626-1631. 2. Ge, S.; Chaladaj, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4149-4152. 3. Su, Y.-M.; Hou, Y.; Yin, F.; Xu, Y.-M., Li, Y.; Zheng, X.; Wang, X.-S. *Org. Lett.* **2014**, *16*, 2958-2961. 4. He, C.-Y.; Kong, J.; Li, X.; Li, X.; Yao, Q.; Yuan, F.-M. *J. Org. Chem.* **2017**, *82*, 910-917. 5. Fujiwara, Y.; Dixon, J. A., Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494-1497.

Rational Design of Molecular Hole Transporting Materials for Perovskite Solar Cells: Direct versus Inverted Device Configurations

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Organic-inorganic lead halide perovskites have rapidly become one of the hottest topic in photovoltaics. Their use requires the presence, in devices, of hole-transporting materials (HTMs) to extract the photo-generated holes from the perovskite, and transport them to the electrode (1). The molecular tailoring of HTM for perovskite solar cells, however, still lacks in solid design criteria (2). Aiming at providing guidelines in this field, in marked contrast with the 3-D structure of the state-of-the-art Spiro-OMeTAD, truxene-based HTMs **Trux1** and **Trux2** have been employed for the first time in PSCs fabricated with a direct (n-i-p) or inverted (p-i-n) architecture, exhibiting a peculiar behavior with respect to the referential HTM.



Notwithstanding the efficient hole extraction from the perovskite layer exhibited by **Trux1** and **Trux2** in direct configuration devices, their photovoltaic performances were detrimentally affected by their poor hole transport. Conversely, a remarkable improvement of the photovoltaic performances in dopant-free inverted configuration devices compared to Spiro-OMeTAD (13.4% respect to 9.5% for **Trux2** and Spiro-OMeTAD, respectively) was recorded, ascribable to the use of thinner HTM layers. The results of our investigations indicate the 3-D charge distribution of Spiro-OMeTAD radical cation as the cause of the excellent behavior of this HTM reference, favoring the hole transport across adjacent molecules. On the other hand, the trend of the photovoltaic response observed for p-i-n architecture devices was completely reversed: since in this configuration the use of a very thin HTM layer was allowed and the perovskite absorber was assembled onto the organic layer, a more favorable perovskite/HTM interface was generated due to the tailored 2-D structure of the truxene-based HTMs boosting the performances of **Trux2** in comparison with the Spiro-OMeTAD reference device.

References: 1. N. J. Jeon, J. H. Noh, W. S. Yang, Y. C. Kim, S. Ryu, J. Seo, S. I. Seok, *Nature*, **2015**, *517*, 476-80. 2. Saliba, S. Orlandi, T. Matsui, S. Aghazada, M. Cavazzini, J. P. Correa-Baena, P. Gao, R. Scopelliti, E. Mosconi, K.-H. Dahmen, F. De Angelis, A. Abate, A. Hagfeldt, G. Pozzi, M. Graetzel, M. K. Nazeeruddin, *Nat. Energy*, **2016**, *1*, 15017-23.

Flow synthesis of cyclobutanones via [2 + 2] cycloaddition of keteneiminium salts and ethylene gas

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In recent years, the interest of pharmaceutical and agrochemical companies toward small ring compounds, as flexible building blocks susceptible to further molecular elaboration, has increased, leading to the development of new synthetic methods based on sustainable processes (1,2). Among these compounds, substituted cyclobutanones represent a very interesting target (3), as they are associated with a reactive versatility (4), mainly due to their ring strain (3) (ca. 25 kcal/mol). Here, a flow chemistry process for the synthesis of 2-substituted cyclobutanones, via [2 + 2] cycloaddition reaction of keteneiminium salts and ethylene gas, is discussed (5). To realize the process, the flow machine was equipped with the “tube-in-tube” reactor (6), an advantageous gas-feeding technology for gas-liquid chemical reactions (Figure 1). The synthesis was carried out on substituted N,N'-diallylamides, using rapid and mild reaction conditions to access a diverse array of products with good to excellent yield (47-99 % of yield), alongside a good level of functional group compatibility.

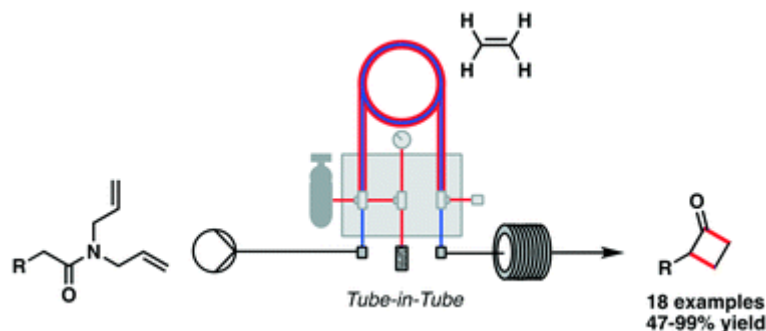


Figure 1. Flow reaction set-up used for the synthesis of 2-substituted cyclobutanones.

References: 1 (a) A. Guan, C. Liu, X. Yang, M. Dekeyser, *Chem. Rev.* **2014**, *114*, 7076; (b) C. Lamberth, S. Jeanmart, T. Luksch, A. Plant, *Science* **2013**, *341*, 742. 2. (a) T. Rodrigues, D. Reker, P. Schneider, G. Schneider, *Nat. Chem.* **2016**, *8*, 531; (b) A. Figueras, R. Miralles-Lluma, R. Flores, A. Rustullet, F. Busqè, M. Figueredo, J. Font, R. Alibes, J. D. Marechal, *Chem Med Chem* **2012**, *7*, 1044. 3. D. Bellus, B. Ernst, *Angew. Chem. Int. Ed.* **1988**, *27*, 797. 4. (a) M. H. Shaw, J. F. Bower, *Chem. Comm.* **2016**, *52*, 10817; (b) H. M. Ko, G. Dong, *Nat. Chem.* **2014**, *6*, 739; (c) M. Murakami, T. Itahashi, Y. Ito, *J. Am. Chem. Soc.* **2002**, *124*, 13976; (d) B. Brown, L. S. Hegedus, *J. Org. Chem.* **2000**, *65*, 1865. 5. C. Battilocchio, G. Iannucci, S. Wang, E. Godineau, A. Kolleth, A. De Mesmaeker, S. V. Ley, *React. Chem. Eng.* **2017**, DOI: 10.1039/c7re00020k. 6. (a) M. Brzozowski, M. O'Brien, S.V. Ley, A. Polyzos, *Acc. Chem. Res.* **2015**, *48*, 349; (b) C. Shotten, D. Plaza, S. Manzini, A. P. Nolan, S. V. Ley, D. L. Browne, A. Lapkin, *ACS Sustainable Chem. Eng.* **2015**, *3*, 1453; (c) J. C. Pastre, D. L. Browne, M. O'Brien, S. V. Ley, *Org. Process Res. Dev.* **2013**, *17*, 1183; (d) S. L. Bourne, M. O'Brien, S. Kasinathan, P. Koos, P. Tolstoy, D. X. Hu, R. W. Bates, B. Martin, B. Schenkel, S. V. Ley, *ChemCatChem* **2013**, *5*, 159.

Looking for a new, isoluminol-based, molecule with improved chemiluminescence properties: a SAR study

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Chemiluminescence methods have become established in both routine clinical analysis and for clinical research applications. Historically, luminol and isoluminol were the first chemiluminescent compounds to be used as labels to be conjugated to reporter molecules (peptides, proteins, antibodies) but they were surpassed in some applications by the more sensitive acridinium esters. However, isoluminol has been successfully employed in a significant number of commercially available in vitro immunoassays, such those marketed for use with DiaSorin's fully automated analyzers, LIAISON[®] (<http://diasorin.com>).

Generally, chemiluminescent labels with increased light output are highly desirable since they allow enhanced immunoassay sensitivities. With the aim of developing a new, isoluminol-based, molecule with enhanced chemiluminescence properties, we report here a Structure-Activity-Relationship (SAR) study carried out around the N-(4-aminobutyl)-N-ethylisoluminol (ABEI) core. Starting from previous studies (1,2,3), we explored different substituents in position 5 of the isoluminol ring (Fig. 1). As result, we found that several substituents are able to confer an increased chemiluminescence signal. In particular, a gain up to more than 10-fold was observed for propyl-based substituents (i.e. sulfopropyl-, phosphopropyl-, methoxypropyl-), when the corresponding ABEI derivatives are used as labels in model assays. Moreover, the hydrophilic nature of these substituents is an interesting feature, since it should help to reduce the non-specific binding of the reporter molecule and allow its higher labeling without the risk of aggregation or precipitation. We believe that the use of such new isoluminol derivatives will lead to improved immunoassay performance, in terms of sensitivity and specificity. Further investigations are currently ongoing.

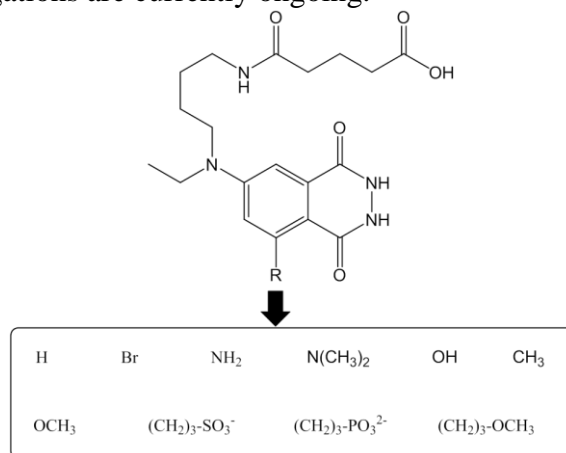


Fig. 1 The N-(4-aminobutyl)-N-ethylisoluminol (ABEI) structure and substituents used in the SAR study. The glutaric acid spacer was introduced to allow the labeling on reporter molecules.

References: 1. Dodeigne C. et al, *Talanta* **2000**, 415–439; 2. Belanger A. et al, *Can. J. Chem.* **1987**, 65, 1392-1396; 3. Brundrett R. B. et al, *JACS* **1974**, 96, 24, 7497-7502

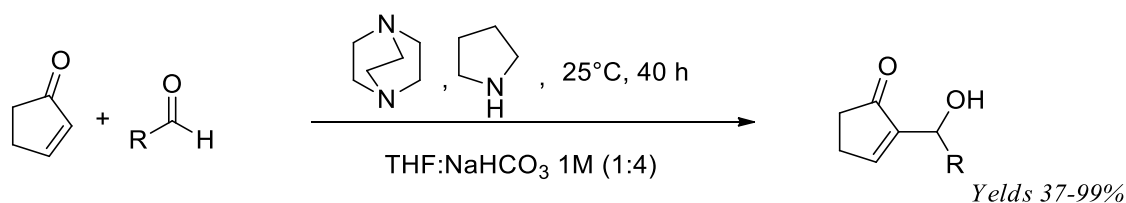
Efficient iminium-catalyzed Morita-Baylis-Hillman reaction on cyclopent-2-enone

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The Morita-Baylis-Hillman (MBH) reaction is an atom-economic carbon-carbon bond-forming reaction between the β position of an electron poor alkene and different carbon electrophiles under the influence of a catalyst or catalytic system. The product of a MBH reaction is a very interesting compound because of its polyfunctional character which can be used in the total synthesis of complex organic molecules or as a building block in diversity oriented Synthesis (DOS) strategies.

Several electron poor alkenes have been used in this reaction such as acrylic acid derivatives, nitro alkenes, α - β unsaturated ketones, however the cyclic enones in particular cyclic pent-2-enone prove to be challenging substrate as only few examples of efficient catalytic systems on this compound have been reported in the literature². In our work we proposed a new mild catalytic system based on the concomitant presence of an iminium catalyst, derived from a secondary amine, and a basic water solution of NaHCO₃ for the reaction of cyclic pent-2-enone with several aldehydes, obtaining 16 compounds in moderate to excellent yields (37-99%).



1 D. Basavaiah, A. J. Rao, T. Satyanarayana *Chem Rev*, **2010**, 110, 5447.

2 a) R. Gatri, M. M. El Gaied, *Tetrahedron Lett* **2002**, 43, 7835; b) K.P. Guerra, C. A. M. Afonso *Tetrahedron*, **67**, **2011**, 7835; c) A. Bugarin, B.T. Connell *J. Org. Chem.*, **2009**, 74, 4638.

Design and Synthesis of GlcNAc-6-P Analogues Targeting Hexosamine Biosynthetic Pathway (HBP) with promising antitumor activity.

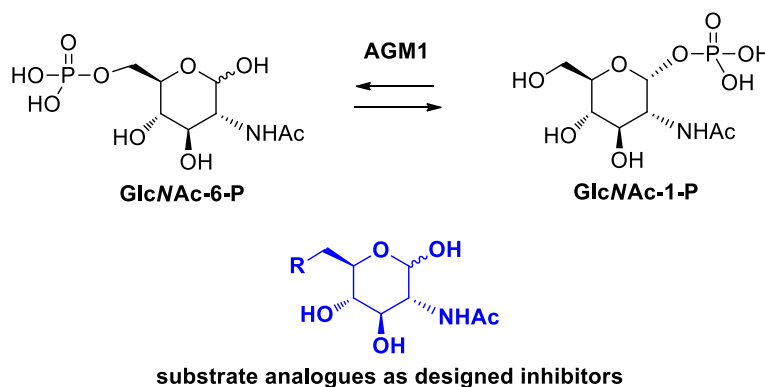
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The Hexosamine Biosynthetic Pathway (HBP) is an important pathway essential in human body involved in the proliferation, survival and ability to migrate of many cancer cells lines, among which are particularly interested in pancreatic cancer cells. This pathway requires nutrients such as glutamine and glucose for the synthesis of UDP-*N*-acetyl-D-glucosamine, the substrate for *N/O*-glycosylation. The comprehension of the molecular bases of the role of the HBP could help in the identification of compounds able to interfere with this pathway, thus representing a possible strategy to arrest or kill pancreatic ductal adenocarcinoma (PDAC) cancer cells, in which protein and lipid glycosylation are actively involved in cell proliferation, cell migration and metastasis.

N-acetylglucosaminophosphate mutase (AGM1) is a key enzyme of the pathway, which catalyzes the conversion of *N*-acetylglucosamine-6-phosphate into *N*-acetylglucosamine-1-phosphate (figure 1). In the present work our aim is to interfere with the synthesis of UDP-GlcNAc through the inhibition of AGM1. To this aim we designed and synthesized a library of potential AGM1 inhibitors based on substrate/product structural similarities.

Biological evaluations in cellular cultures have identified a promising lead compound, which is under evaluation in animal models.



This work was supported by AIRC (IG2014 Id15364)

References

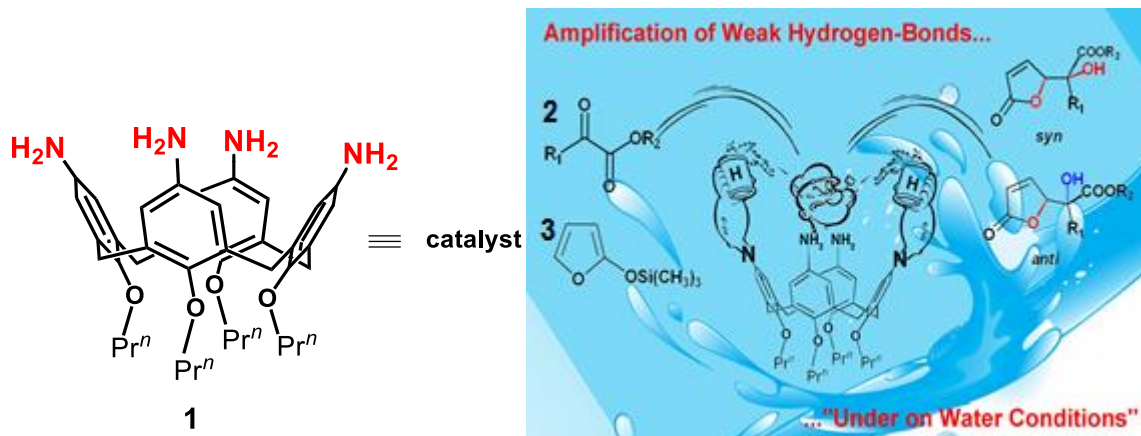
1. Palorini R, Cammarata FP, Balestrieri C, et al. Glucose starvation induces cell death in K-rastransformed cells by interfering with the hexosamine biosynthesis pathway and activating the unfolded protein response. *Cell Death Dis* 2013; 4: e732.
2. Banerjee PS, Hart GW, Won Cho J. Chemical Approach to study O-GlcNAcylation. *Chem Soc Rev* 2013; 42: 4345-4357.

Calix[4]arene Mediated Catalysis Under “On-water Conditions”: Hydrophobic Amplification of Weak Hydrogen-Bonds

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In the last thirty years, calixarene macrocycles (1) have gradually gained a special role in a wide range of supramolecular applications. At this regard, many efforts have been devoted to the design and synthesis of calixarene derivatives as catalysts for organic reactions (2), and among them the development of environmentally-oriented catalytic strategies has been particularly investigated. In a pioneering work, Sharpless (4) introduced the expression “on-water conditions” to denote the rate acceleration observed in organic reactions when insoluble reactants are vigorously stirred in H₂O suspension. Under “on-water conditions” the supramolecular affinities between reactants and catalyst play a key role. In fact, it is known that the hydrophobic effect forces the reactants and the catalyst to aggregate and thus amplifying the secondary interactions between them and favoring the molecular collisions. In the present communication, we will show that under “on-water conditions”, even weaker H-bond donor groups, such as amino-groups in **1** are effective to activate the substrate **2** in the Vinylogous Mukaiyama Aldol Reaction between **2** and **3** (see Figure below), on the basis of the hydrophobic amplification of H-bonds (5). Details on the catalytic efficiency of **1** and on the its recognition abilities toward the substrate **2** will be given.



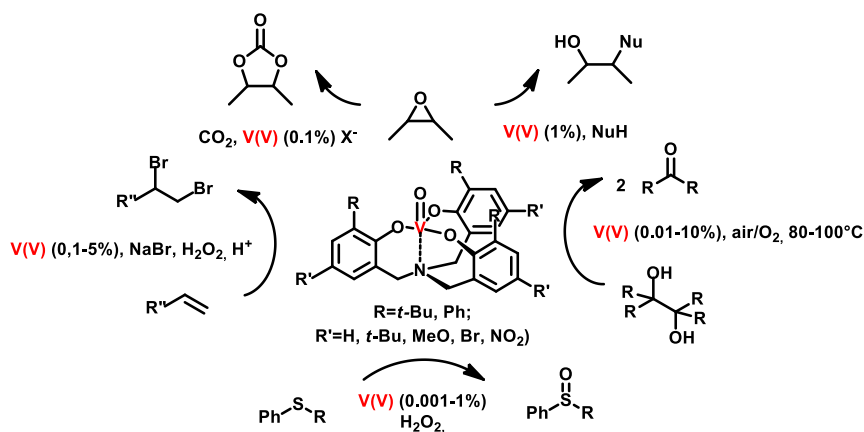
1. C. D. Gutsche, *Calixarenes, An Introduction*, Royal Society of Chemistry, Cambridge, UK, **2008**. P. Neri, J. L. Sessler, M. –X. Wang (Eds), *Calixarenes and Beyond*, Springer, Dordrecht, **2016**.
2. H. Homden, C. Redshaw, *Chem. Rev.* **2008**, *108*, 5086–5130. M. Yilmaz, S. Sayn, in *Calixarenes and Beyond* (Eds.: P. Neri, J. L. Sessler, M. –X. Wang) Springer, Dordrecht, **2016**, pp. 719-741.
3. M. De Rosa, P. La Manna, A. Soriente, C. Gaeta, C. Talotta, P. Neri, *RSC Adv.* **2016**, *6*, 91846–91851.
4. S. Narayan, J. Muldoon, M. J. Finn, V. V. Fokin, H. Kolb, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2005**, *44*, 3275-3279.
5. M. De Rosa, P. La Manna, A. Soriente, C. Gaeta, C. Talotta, N. Hickey, S. Geremia, P. Neri. *Chem. Eur. J.* **2017**, DOI: 10.1002/chem.201701247.

Aminotriphenolates as Privileged Ligands in Catalysis

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Triphenolamines (TPA) are highly symmetric, modular molecules that form stable metal complexes with a wide variety of transition and main group elements.¹ These complexes are highly active catalysts in important reactions like polymerizations, olefin metathesis, CO₂/epoxide cycloadditions, and oxygen transfer processes.⁽¹⁾ Here we will report our latest results related to V(V)-TPA catalysed processes. The activity of V(V)-TPA as V-haloperoxidase model (2) and as catalyst in the aerobic carbon-carbon cleavage of vicinal diols and more complex lignin substructures (3) will be described together with the activation of epoxides towards amine nucleophiles and CO₂ for cyclic carbonate synthesis.⁽⁴⁾



References: 1. Mba, M.; Zonta, C.; Licini, G., Patai Series, *The Chemistry of Metal Phenolates* (2014). 2. Badetti, E.; Romano, F.; Marchiò, L.; Taşkesenlioğlu, S.; Daştan, A.; Zonta, C.; Licini, G. *Dalton Trans.*, **2016**, 45, 1460. 3. Amadio, E.; Di Lorenzo, R.; Zonta, C.; Licini, G. *Coord. Chem. Rev.* **2015**, 301-302, 147. 4. C. Miceli, J. Rintjema, E. Martin, E. C. Escudero-Adán, C. Zonta, G. Licini, A. W. Kleij, *ACS Catal.* **2017**, 7, 2367–2373

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Polydopamine: a versatile bioinspired material for multipurpose applications

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Mussels can strongly attach to diverse substrates with high binding strength, even on wet surfaces. This observation led to a better understanding of the wet adhesion property of mussels. It was found that 3,4-dihydroxy-L-phenylalanine (DOPA) and lysine-enriched proteins near the plaque substrate interface are the major origins of the extraordinarily robust adhesion. (1,2,3,4)

On the basis of these findings, polydopamine (PDA), due to the molecular structure similarity to that of DOPA, moved into the spotlight as a novel coating material in 2007. (5) PDA presents numerous advantages: first of all PDA can be easily obtained from self-polymerization of dopamine in alkaline or oxidants contained aqueous solutions and adhere onto almost any solid surfaces without surface pretreatment (6), as seen with mussels, it can be easily deposited on virtually all types of inorganic and organic substrates, including superhydrophobic surfaces, with controllable film thickness and durable stability. Moreover this film is rich in catechol groups, which endows the PDA versatile chemical reactivity for biopolymer, biomimetic mineralization and metal nanoparticles (MNPs) in situ growth (5).

Last, but not least, polydopamine is also a major pigment of naturally occurring melanin (eumelanin), consequently, polydopamine displays many striking properties of naturally occurring melanin in optics, electricity, and magnetism, and, most importantly, it processes excellent biocompatibility. Herein, we first report that, upon dopamine polymerization in the presence of the protein, RC (a) is incorporated, (b) is capable to generate the charge-separated state, and (c) even to perform its natural photocycle (figure 1). It proved, indeed, to be effective in reducing quinone molecules to quinol by withdrawing electrons from cytochrome c. As an example of biotechnological application, a photoelectrochemical cell based on polydopamine-immobilized RC onto ITO has also been designed and successfully employed to generate photocurrents arising from the reduction of the electron-donor ferrocenemethanol.

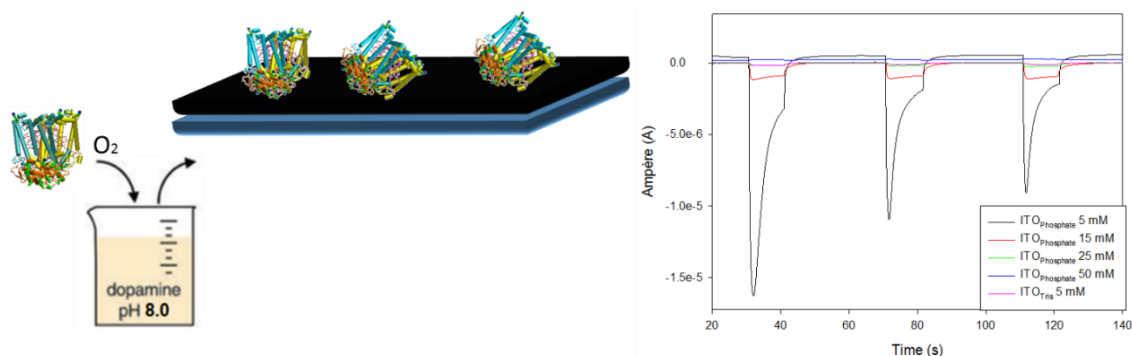


Figura 1

References: 1. Waite, J. H. CHEMTECH 1987, 17, 692. 2. Waite, J. H.; Tanzer, M. L. Science 1981, 212, 1038. 3. Harrington, M. J.; Masic, A.; Holten-Andersen, N.; Waite, J. H.; Fratzl, P. Science 2010, 328, 216. 4. Waite, J. H.; Qin, X. X. Biochemistry 2001, 40, 2887. 5. Lee, H.; Dellatore, S. M.; Miller, W. M.; Messersmith, P. B. Science 2007, 318, 426. 6. Cheng, Chong, et al. "Biomimetic assembly of polydopamine-layer on graphene: Mechanisms, versatile 2D and 3D architectures and pollutant disposal." *Chemical engineering journal* 228 (2013): 468-481. 5. Yan, Yinghua, et al. "Hydrophilic polydopamine-coated graphene for metal ion immobilization as a novel immobilized metal ion affinity chromatography platform for phosphoproteome analysis." *Analytical chemistry* 85.18 (2013): 8483-8487.

Lipophilic core-shell Fe₃O₄@SiO₂@Au nanoparticles into nano-micelles for magnetic resonance and photoacoustic dual-imaging.

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Metal nanoparticles represent promising agents for both cancer treatment and diagnosis, opening up the novel field of theranostic (therapy and diagnostic). There is anyway an urgent need for multiple imaging technology in order to overcome the intrinsic limitations of every single imaging modality. Iron oxide nanoparticles are well known for their properties as contrast agents in magnetic resonance imaging (MRI) (¹), while gold nanoparticles, have been recently investigated as promising photoacoustic imaging (PAI) contrast agents (²). The formation of a single nanosystem containing both the two nanostructures may allow an easy two imaging modality.

In this study metallic nanoparticles consisting of multiple shells of iron oxide, silica and gold were synthesized (Fe₃O₄@SiO₂@Au) and accurately characterized. The obtained Fe₃O₄@SiO₂@Au NPs were coated with a specifically designed organic ligand by exchange ligand reaction to guarantee their stability and solubility in organic solvents. The organic ligand synthesized for this purpose presents a thiol as ending group, in order to maximize interaction with the gold surface. The resulted coated nanoparticles are finally suitable for entrapment into biocompatible polymeric matrix to form a targetable water soluble nanocarrier for nanomedicine applications (³).

In conclusion, the final nanosystem is decorated with folic acid moieties and successfully tested in vivo for Photoacoustic (PA) and MRI detection of ovarian cancer.

References:

- ¹ Baldi, G., Ravagli, C., Mazzantini, F., Loudos, G., Adan, J., Masa, M., Psimadas, D., Fragogeorgi, E.A., Locatelli, E., Innocenti, C., Sangregorio, C., Comes Franchini, M. (2014). In vivo anticancer evaluation of the hyperthermic efficacy of anti-human epidermal growth factor receptor-targeted PEG-based nanocarrier containing magnetic nanoparticles. *International journal of nanomedicine*, 9, 3037.
- ² Locatelli, E., Monaco, I., Comes Franchini, M. (2015). Surface modifications of gold nanorods for applications in nanomedicine. *RSC Advances*, 5(28), 21681-21699.
- ³ Locatelli, E., Comes Franchini, M. (2012). Biodegradable PLGA-b-PEG polymeric nanoparticles: synthesis, properties, and nanomedical applications as drug delivery system. *Journal of Nanoparticle Research*, 14(12), 1316.

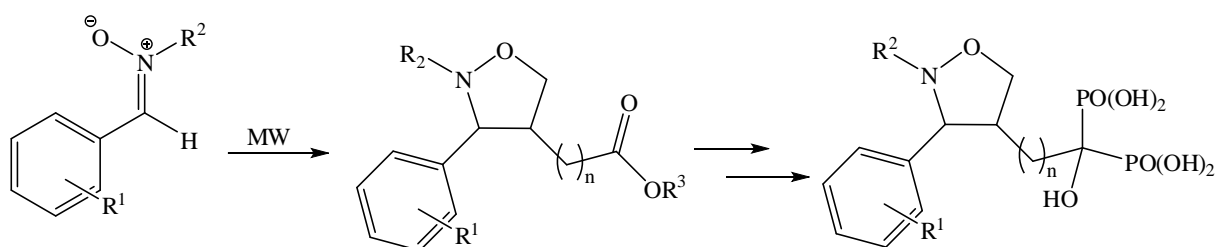
Synthesis of isoxazolidinyl-*gem*-bisphosphonic acids and study of protein-ligands interactions.

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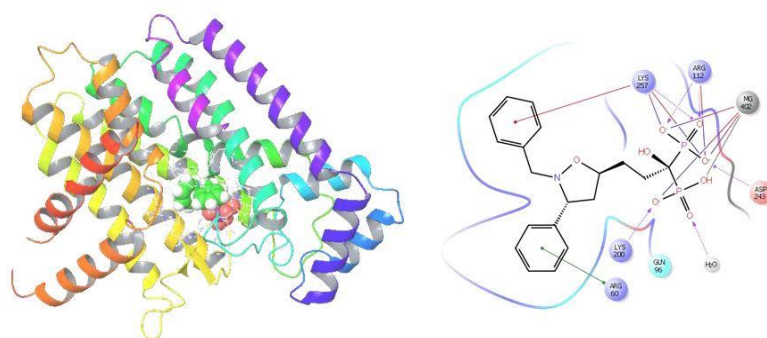
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Isoxazolidines mimic natural nucleosides exerting antitumor activity (1). The addition of a *gem*-bisphosphonate group on the heterocyclic ring increases the cytotoxicity of the obtained substrates that can be applied in clinical treatment of bone metastases and osteoporosis (2,3). In particular, this class of molecules inhibits the Farnesyl Pyrophosphate Synthase (FPPS) and the Geranylgeranyl Diphosphate Synthase (GGPP), targets of bisphosphonates for treatment of bone-related disorders (4).

In this work we will present the synthesis of a new family of isoxazolidinyl-*gem*-biphosphonic acids with potential pharmacological activity.



Molecular modelling calculations and STD-NMR experiments have been used to predict and determine the affinity of our ligands towards human FPPS, as well as for characterization of the ligands binding modes. Moreover, the results of activity against Farnesyl Pyrophosphate Synthase (FPPS) and the Geranylgeranyl Diphosphate Synthase (GGPP) will be illustrated.



References:

1. Bortolini, O.; D'agostino, M.; De Nino, A.; Maiuolo, L.; Nardi, M.; Sindona, G. *Tetrahedron*, **2008**, 64, 8078.
2. Guenin, E.; Ledoux, D.; Oudar, O.; Kraemer, M. *Anticancer Research*, **2005**, 25, 1139.
3. Bortolini, O.; Mulani, I.; De Nino, A.; Maiuolo, L.; Nardi, M.; Russo, B.; Avnet, S. *Tetrahedron*, **2011**, 67, 5635.
4. Merino, P.; Maiuolo, L.; Delso, I.; Algieri, V.; De Nino, A.; Tejero, T. *RSC Advances*, **2017**, 7, 10947.

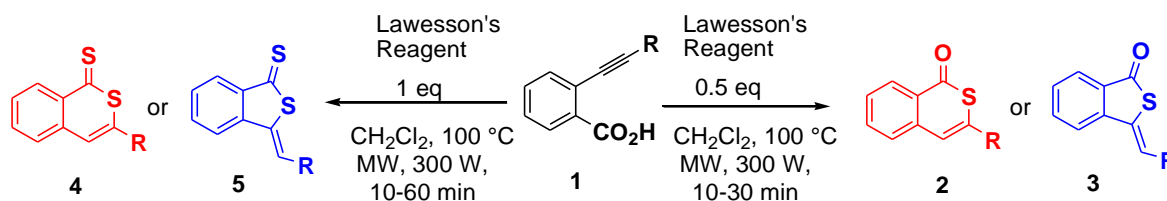
Synthesis of sulfureted heterocycles with herbicidal activity

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The widespread development of weed resistance towards the most common herbicides is pushing the research in developing of new synthetic molecules, characterized by high phytotoxic activity and multi-target action. In this contest, we have synthesized some sulfureted heterocycle derivatives with promising herbicidal activity *in vitro*.

The synthetic approach towards 1*H*-isothiochromene-1-ones **2**, (*Z*)-benzo[*c*]thiophene-1(3*H*)-ones **3**, 1*H*-isothiochromene-1-thiones **4** and (*Z*)-benzo[*c*]thiophene-1(3*H*)-thiones **5** is based on divergent tandem thionation-heterocyclization processes starting from readily available 2-alkynylbenzoic acids **1**.



Scheme 1

Reactions were carried out under microwave (MW) irradiation at 300W, at $100\text{ }^\circ\text{C}$, using 0.5 equiv. (for the synthesis of **2** and **3**) or 1 equiv. (for the synthesis of **4** and **5**) of the Lawesson's reagent as the thionation. Products were obtained in good isolated yields (60-95%).

All the newly synthesized compounds were assayed *in-vitro* on seedlings growth of *Arabidopsis thaliana*, a model plant species. The results have pointed out that almost all molecules exerted a phytotoxic activity on both root and shoot. In fact, plants showed a reduction on shoot development (ED_{50} values $\leq 64\text{ }\mu\text{M}$) accompanied by a high decrease on pigment content. Moreover, the compounds strongly altered the root growth and morphology with ED_{50} values $\leq 266\text{ }\mu\text{M}$ and $\leq 185\text{ }\mu\text{M}$ for primary root length and lateral root number, respectively. Finally, some of molecules significantly affected root anatomy and cells organization. Taken together these results suggest that the synthesized sulfur-containing heterocyclic derivatives represent interesting classes of chemicals with high phytotoxic activity. Further *in-situ* experiments are in progress to evaluate their potential in weed management.

Tuning morphological architectures generated through living supramolecular assembly of a helical foldamer end-capped with two complementary nucleobases

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Two appropriately functionalized nucleobases, thymine and adenine, have been covalently linked at the N- and C- termini, respectively, of two α -aminoisobutyric acid-rich helical peptide foldamers, aiming at driving self-assembly through complementary recognition⁽¹⁾. A crystal-state analysis (by X-ray diffraction) on the shorter, achiral foldamer **1** unambiguously shows that adenine···thymine base pairing, through Watson-Crick intermolecular H-bonding, does take place between either end of each peptide molecule (Fig. 1, upper part). In the crystals, π -stacking between base pairs is also observed⁽²⁾. Evidence for time-dependent foldamer···foldamer associations for the longer, chiral foldamer **2** (Fig. 1, lower part) in solution is provided by circular dichroism measurements.

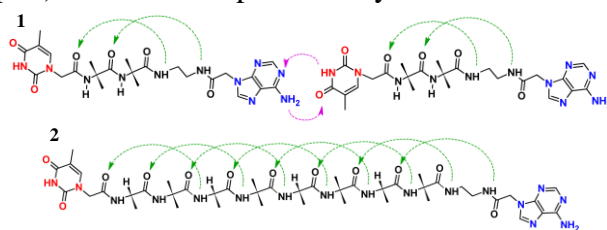


Fig. 1 Chemical structure of the achiral foldamer **1** and the chiral foldamer **2** (with a schematic representation of their expected inter- and intramolecular H-bonding interactions).

The self-assembly of foldamer **2**, through living supramolecular polymerization, eventually leads to the formation of twisted fibers⁽³⁾. Such a supramolecular organization can be affected by addition of either pristine adenine or thymine, that acts as a “terminator” by selectively matching a pairing nucleobase at one end of the foldamer. The co-assembly of foldamer **2** with a porphyrin-derivatized thymine, under appropriate experimental conditions, leads to the formation of vesicles which, in turn, can be converted to the fiber morphology by changing the environmental polarity. Conversely, dendrimeric, star polymer-like microstructures are generated when the supramolecular assembly of foldamer **2** is seeded by adenine-capped gold nanoparticles (Fig. 2)⁽⁴⁾.

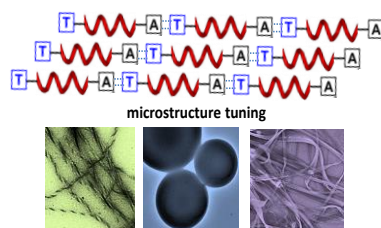


Fig. 2 Representation of the packing mode and the related 3D microstructures obtained.

References: 1. B. J. Cafferty, I. Gallego, M. C. Chen, K. I. Farley, R. Eritja, and N. V. Hud, *J. Am. Chem. Soc.*, 2013, **135**, 2447; 2. M. R. Jones, N. C. Seeman and C. A. Mirkin, *Science*, 2015, **347**, 840; 3. S. Hecht and I. Huc, *Foldamers: Structure, Properties and Applications*, Wiley-VCH: Weinheim, 2007; 4. G. Marafon, D. Mosconi, D. Mazzier, B. Biondi, M. De Zotti and A. Moretto, *RSC Adv.*, 2016, **6**, 73650.

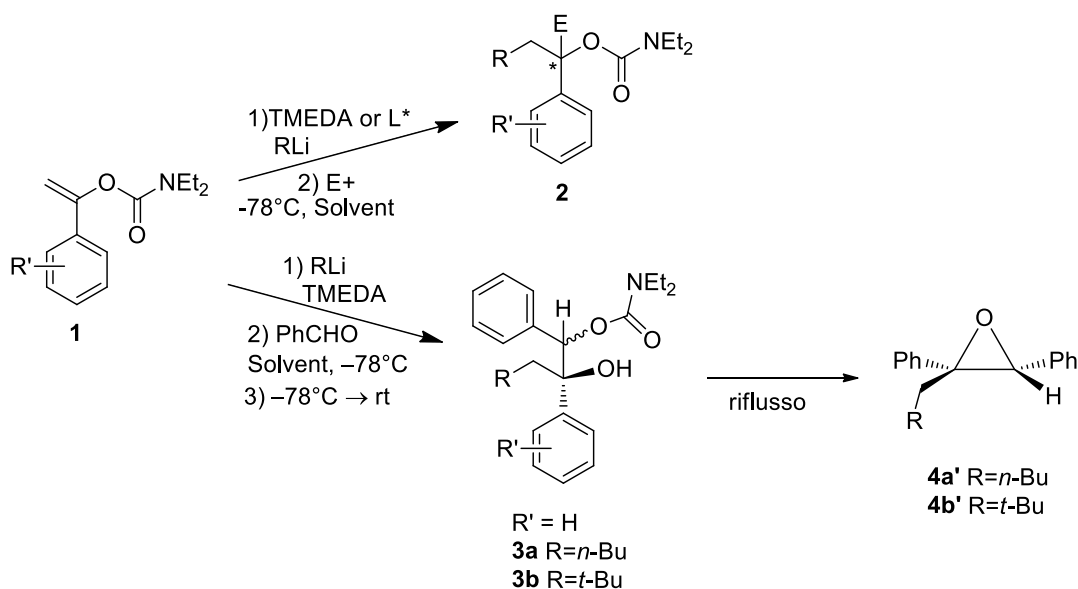
Enantioselective Carbolithiation of α -Arylcarbamates

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Carbolithiation of styrene double bonds is a practical methodology with a broad synthetic potential. In fact, the subsequent tandem reaction with carbon electrophiles allows the construction of two new C-C bonds, leading to highly functionalized systems. Despite its synthetic appealing, this class of reactions has not been much investigated because of the difficulty to control the organolithium intermediate which, reacting with a second molecule of the olefin, can trigger an unwanted anionic polymerization process. For a synthetic use of carbolithiation reactions a stabilization of the benzyllithium intermediate is then required. This can be made by *intra* or *inter*-molecular organolithium coordination which, leading to an anion stabilization, prevents the polymerization.⁽¹⁾ This coordination occurs in the presence of coordinating groups bearing Lewis-base moieties and/or in the presence of bidentate ligands such as diamines. Aim of this study was to investigate the carbolithiation of 1-aryl-1-alkenyl *N,N'*-diethylcarbamates (**1**), a reaction poorly described in literature, and its extension to the preparation of optically active products.⁽¹⁾ After the carbolithiation step, the organolithium intermediate was reacted with several electrophiles, obtaining trisubstituted benzyl carbamates (**2**), direct precursors of tertiary benzylic alcohols. The tandem carbolithiation-trapping with electrophiles was also carried out in enantioselective manner, in the presence of chiral diamines,⁽²⁾ obtaining enantioenriched tertiary benzyl carbamates. When PhCHO was used as an electrophile, a diastereomeric mixture of product **3** was obtained (3:1 by ¹H NMR) which, after heating at reflux, gave rise to an intramolecular cyclization eventually leading to the single *cis* epoxide **4**.⁽¹⁾ Also the enantioselective version of this reaction was investigated to provide an original approach to the synthesis of enantiomerically enriched *cis*-2-alkyl-2,3-diarylepoxides.



References: 1. Superchi, S.; Sotomayor, N.; Miao, G.; Joseph, B.; Campbell, M. G.; Snieckus, V. *Tetrahedron Lett.* **1996**, 37, 6061. 2. Peters, J. G.; Seppi, M.; Fröhlich, R.; Wibbeling, B.; Hoppe, D. *Synthesis* **2002**, 3, 381.

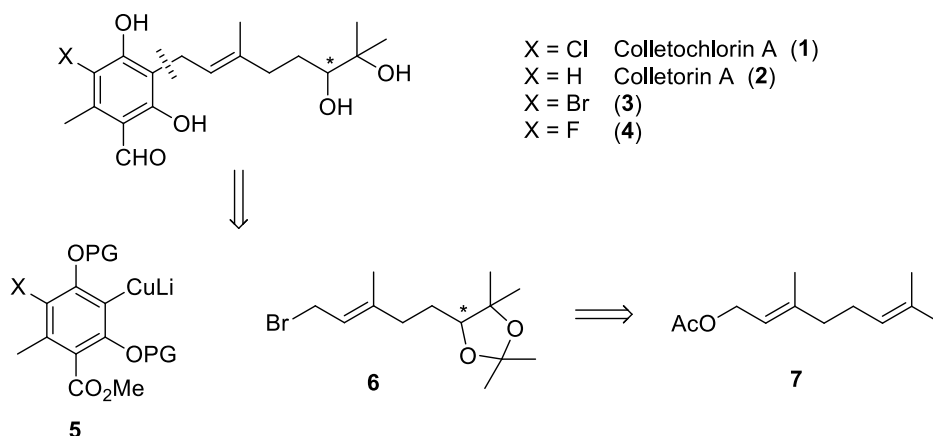
Asymmetric synthesis of the natural products colletochlorin A and colletorin A and their halogenated synthetic analogues

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Fungal bioactive metabolites are an excellent source of pharmaceuticals, antifungal, and herbicidal compounds. Among these, the 3-diprenyl orsellinaldehyde derivatives colletochlorins and colletorins are a class of phytotoxic metabolites isolated from *Colletotrichum nicotianae*, a fungus causing anthracnose in tobacco plants.(1) Such compounds share as a common structural feature a multi-substituted polyphenolic ring and a terpenoid side chain. Moreover, in some of them, the terpenoid side chain bears one or more stereogenic centers, which may possibly affect their biological activity. For most of these metabolites the bioactive properties are still underexplored, mainly for their scarce availability from natural sources. This is the case of colletochlorin A (**1**) and colletorin A (**2**) (2), for which the absolute configuration is also still unknown. Herein we describe the first asymmetric synthesis of both enantiomers of **1** and **2** with the aim to study the effect of the absolute stereochemistry on their biological activity. Moreover, the brominated and fluorinated unnatural analogues **3** and **4** were also prepared in optically active form to investigate the effect of the halogen substituents on their biological properties. The synthetic approach is based on the disconnection of the structure of colletochlorin A, colletorin A and their analogues into an aromatic precursor (**5**) and an optically active side chain (**6**). The enantioselective key step is the Sharpless asymmetric dihydroxylation of the geranyl acetate (**7**) (3), which is followed by a coupling of the chiral side chain with the poly-substituted aromatic moiety. The desired products were then obtained in good overall yields and high enantioselectivity (94-98% ee).



References: 1. C. M. García-Pajón, I. G. Collado, *Nat. Prod. Rep.*, **2003**, *20*, 426–431. 2. a) Y. Kosuge, A. Suzuki, S. Hirata, S. Tamura, *Agric. Biol. Chem.*, **1973**, *37*, 455–456. b) Y. Kosuge, A. Suzuki, S. Tamura, *Agric. Biol. Chem.*, **1974**, *38*, 1265–1267. 3. a) K.K. Wan, J.P. Litz, D.A. Vosburg, *Tetrahedron:Asymmetry* **2010**, *21*, 2425–2428. b) D. Xu, C.Y. Park, K.B. Sharpless, *Tetrahedron Lett.* **1994**, *35*, 2495–2498.

The role of structural and medium effects on hydrogen atom transfer from alcohols and diols to alkoxy radicals

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The centrality of hydrogen atom transfer (HAT) processes is out of question, being one of the most fundamental reactions taking place in many chemical and biological processes, from radical-induced oxidative stress, to a number of new synthetically useful C-H bond functionalization procedures. Among the reactive species involved in these reactions, alkoxy radicals have gained major attention, and the cumyloxy radical ($\text{PhC}(\text{CH}_3)_2\text{O}^\bullet$, CumO $^\bullet$) has proven to be a very good reagent for the study of these reactions (1). CumO $^\bullet$ can be easily generated by UV photolysis of the corresponding commercially available peroxide, can tolerate a wide range of experimental conditions and is characterized by an absorption band in the visible region and a lifetime in the microsecond time regime, that make the direct measurement of HAT rate constants by the means of the laser flash photolysis technique particularly convenient.

Recent studies (1,2) carried out in our laboratory showed how substrate structure and medium effects could be used to finely tune the reactivity and selectivity in HAT processes from aliphatic C-H bonds. Due to the ubiquitous presence of hydroxyl functional groups in natural, commercially and biologically relevant compounds, alcohols and diols were one of the substrates of choice to broaden our comprehension of HAT reactivity and selectivity. Along this line, we have carried out a detailed time-resolved kinetic study on the reactions of a series of alcohols, 1,2-diols and 1,3-diols with CumO $^\bullet$, taking into particular account the role of added alkali and alkaline earth metal ion salts on the HAT reactivity. The results of these studies will be discussed.

References: 1. Salamone, M; Bietti, M. *Acc. Chem. Res.* **2015**, 48, 2895-2903. 2. Salamone, M.; Carboni, G.; Bietti, M. *J. Org. Chem.* **2016**, 81 19, 9269–9278.

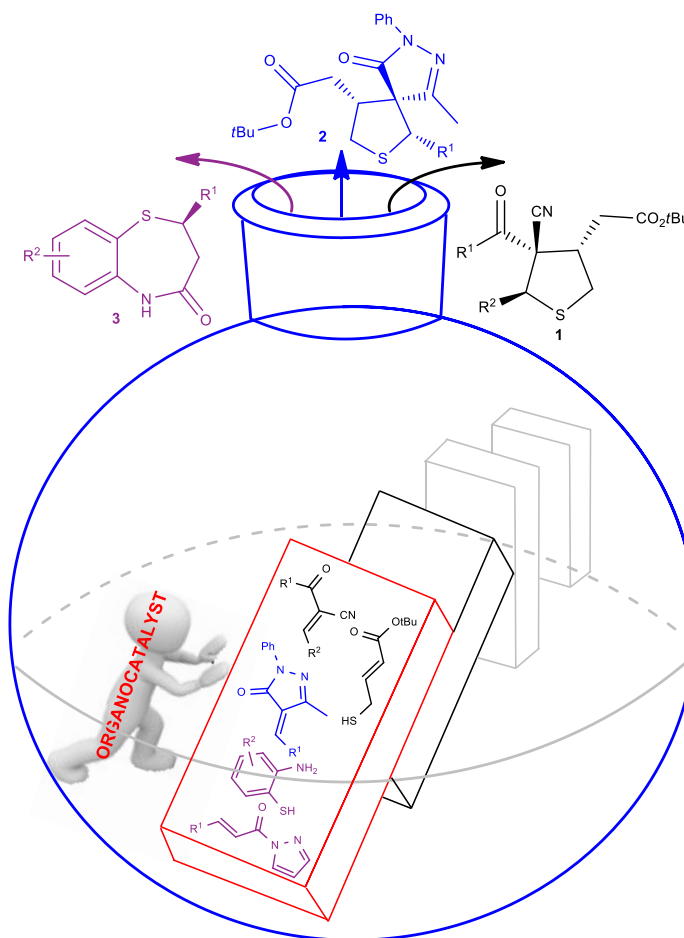
Organocatalytic Domino Methodologies to Access Important Sulfur Heterocycles: from Tetrahydrothiophenes to 1,5-Benzothiazepines

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Organocatalytic one-pot and domino methodologies represent one of the most important achievements in organic synthesis in recent years (1,2). Small chiral organic molecules, such as squaramides and thioureas derived from simple chiral amines, are able to promote two or more successive chemical transformations in one reactor. These catalysts through the "invisible strings" of hydrogen bonds are able to orchestrate highly organized transition states accelerating and driving the sequence of reactions with high stereocontrol. Access to differently functionalized chiral cyclic molecules, bearing one or more stereocenters, is possible without purification or separation of the intermediates. The importance of these methodologies is even more evident when applied to the synthesis of relevant biological and pharmaceutical compounds. Among sulfur containing heterocyclic compounds, particularly relevant are tetrahydrothiophenes, as naturally occurring products, targets exploited in medicinal chemistry and ligands in asymmetric catalysis. In this communication we are going to illustrate the stereoselective syntheses of highly functionalized tetrahydrothiophenes bearing three contiguous stereocenters, one of them quaternary, such as **1** (3) and more challenging spirotetrahydrothiophenes **2** (4), both of them obtained via a cascade double Michael reaction promoted by a readily available amine thiourea. The first methodology to prepare enantioenriched popular drugs N-unprotected 1,5-benzothiazepines **3**, will be also described (5). An one-pot sequence involving an organocatalyzed sulfa-Michael reaction of α,β -unsaturated N-acyl pyrazoles with 2-aminothiophenols followed by silica-gel-catalyzed lactamization has been successfully exploited to develop a concise preparation of the antidepressant drug (*R*)-(-)-thiazesim.



References: 1. Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. 2. Mayano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703. 3. Meninno, S.; Croce, G.; Lattanzi, A. *Org. Lett.*, **2013**, *15*, 3436. 4. Meninno, S.; Overgaard, J.; Lattanzi, A. *Synthesis*, **2017**, *49*, 1509. 5. Meninno, S.; Volpe, C.; Lattanzi, A. *Chem. Eur. J.* **2017**, *23*, 4547.

Dicationic Ionic Liquids (DILs): synthesis, characterization and applications

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The reduction, fixation, and use of carbon dioxide (CO₂) is one of the major and urgent challenges the scientific community has demanded to address. Among the several strategies to face this problem, capture and storage of CO₂ in geological storages (for example saline aquifers or deep ocean storage) is considered at present the best option, while CO₂ utilization remains an underexploited opportunity.

(1)

However, CO₂ could be seen as an attractive option in the preparation of new added-value products. In fact, from a synthetic perspective, CO₂ is a non-toxic, safe, and economical C1 synthon and some methodologies to employ it in the preparation of valuable chemicals have been developed. (2) One of the typical viable routes is the synthesis of cyclic carbonates via the cycloaddition of CO₂ with different epoxides. Cyclic carbonates have been already used as organic solvents and in the synthesis of polycarbonates, pharmaceutical medicines and fine chemical products.

Ionic liquids (ILs) have been proven as efficient homogeneous catalysts for the synthesis of cyclic carbonates. Many task-specific ILs, combined with Lewis acids (3), are used in the cyclic carbonates formation.

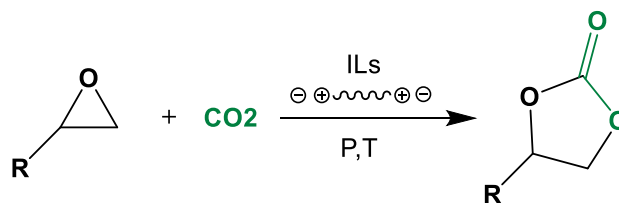


Fig1. Schematic synthesis of cyclic carbonates.

Herein the preparation of a series of different di-cationic ionic liquids (DILs) is presented. The synthesized DILs were fully characterized (¹H-, ¹³C-NMR, FT-IR) and their thermal behavior was analyzed (thermo gravimetric analysis and differential scanning calorimetry). Finally, the effect of the structure of the DILs, (eg distance between anions/cations, type of spacer, nature of cation) on the cyclic carbonates synthesis was investigated to determine their optimal structure and their role in the catalytic cycle.

References: 1. D. Y. C. Leung, G. Caramanna, M. M. Maroto-Valer, *Renewable and Sustainable Energy Reviews*. 2014, 39, 426-443. 2. M. Mikkelsen, M. Jørgensen and F. C. Krebs. *Energy Environ. Sci.*, 2010, 3, 43-81. 3. D. Kim, Y. Moon, D. Ji, H. Kim, D.H. Cho. *ACS Sustainable Chem. Eng.*, 2016, 4, 4591-4600.

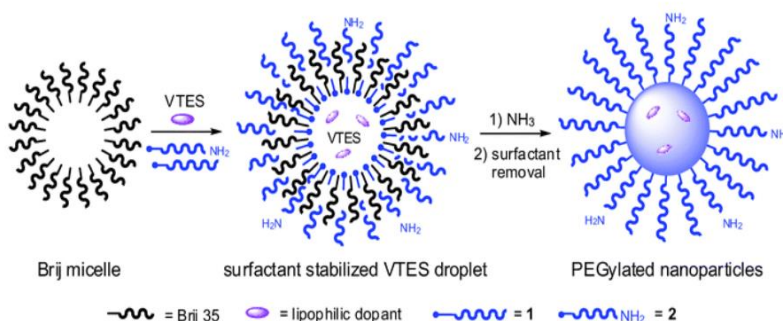
Synthesis of multifunctional ORMOSIL nanoparticles for drug delivery

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The probability to develop a cancer disease has been growing for the last century and although there are many therapies to treat it, cancer progresses in such manner that our knowledge is not extensive enough. Nanomedicine has emerged for its use in drug delivery, diagnosis, imaging, as well as therapy and thus nanoparticles have been used (1). Silica nanoparticles have been developed in the last years due to their great features for drug delivery(2,3), therefore in this project we synthesized organic modified silica nanoparticles loaded with an anticancer drug that were targeted to tumor cells and biocompatible.



The synthesis consist in a one pot reaction (4) in which surfactant micelles in water act as template for the nanoparticles, forming a mesoporous hydrophobic core in which our anticancer drug was loaded. Increased biocompatibility was obtained by functionalizing the nanoparticles with PEG and substituted PEG that was further conjugated with hyaluronic acid. The purpose of the use of hyaluronic acid relies on the interaction with CD44 antigen which participates in the tumor metastasis. Biological test indicated a higher effect of the drug loaded nanoparticles conjugated with hyaluronic acid compared with the free drug and unconjugated nanoparticles.

Hence, we synthesized organic modified silica nanoparticles in a one pot reaction that were loaded with an anticancer drug and functionalized with PEG conjugated with hyaluronic acid showing a significant cancer cell death.

- References: 1. Ranganathan, R., Madanmohan, S., Kesavan, A., Baskar, G., Krishnamoorthy, R., Santosham R., Ponraju, D., Rayala, S., Venkatraman, G., *Int J Nanomedicine*. **2012**, *7*, 1043–1060.
 2. Bharti, C., Nagaich, U., Kumar Pal, A., Gulati, N., *Int J Pharm Investig*. **2015**, *5*, 124–133.
 3. Echevarria, I. M., Selvestrel, F., Segat, D., Guarino, G., Tavano, R., Causin, V., Reddi, E., Papini, E., Mancin, F., *J. Mat. Chem.*, **2010**, *10*, 2780-2787.
 4. Selvestrel, F., Moret, F., Segat, D., Woodhams, J. H., Fracasso, G., Echevarria, I. M., Baù, L., Rastrelli, F., Compagning, C., Reddi, E., Fedeli, C., Papini, E., Tavano, R., Mackenzie, A., Bovis, M., Yaghini, E., MacRobert, A. J., Zanini, S., Boscaini, A., Colombatti, M., Mancin, F., *Nanoscale*, **2013**, *5*, 6106-6116.

Discovering the biological target of 5-epi-Sinuleptolide with a combination of proteomic approaches

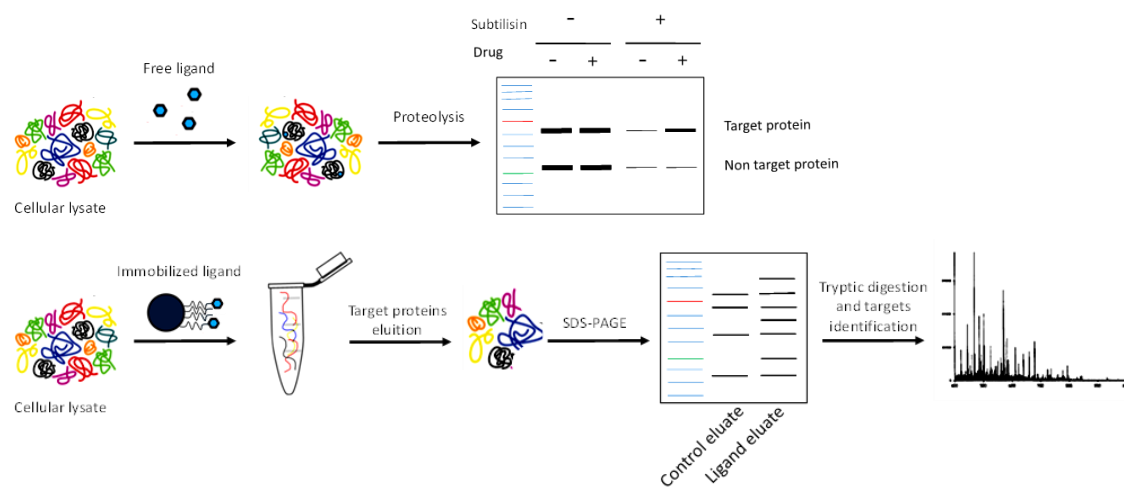
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The marine surroundings include around half of the world's biodiversity and is a huge resource of structurally relevant and biologically active compounds (1). The soft coral *Sinularia* produces a rich collection of secondary metabolites with a range of biological activities such as antimicrobial, anti-inflammatory, and cytotoxic (2). Among them, 5-epi-sinuleptolide (5-epi-SNEP) was selected as ideal candidate for a target discovery analysis through a combination of functional proteomic approaches.

Our strategy was based on two complementary approaches: 1) 5-epi-SNEP has been covalently bound on a solid matrix and used as a bait, fishing out its specific interactors from a complex mixture as a cell lysate by affinity. Once eluted, fished cellular targets have been identified by means of high resolution MS, bioinformatic analyses and immunoblotting (3); 2) in parallel, we applied a drug affinity responsive target stability approach (DARTS) on the native unmodified metabolite (4). The DARTS principle is based on the evidence that a protein might become less susceptible to proteolysis when is drug-bound than when it is drug-free. Both approaches pointed to the identification of *actin* proteins as the main 5-epi-SNEP cellular targets. Finally, a biological investigation on its effect on the cytoskeleton assembly showed the ability of 5-epi-SNEP to induce the disruption of the actin cytoskeleton and the formation of F-actin amorphous aggregates, without affecting the cell viability.



References:

1. Jha, R.K. et al. *Mar. Drugs* **2004**, *2*, 123-146.
2. Kamel, H.N. et al. *M. Pharmaceutical Biology* **2005**, *43*, 253-269.
3. Margarucci, L. et al. *Mol. BioSystems* **2011**, *7*, 480-485.
4. Lomenick, B. et al. *PNAS* **2009**, *106*, 21984-21989

Data-driven Ionic Liquids Modelling: a Design Opportunity for Task-specific Applications

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In the field of ionic liquids (ILs) theory-driven modelling approaches aimed at the best fit of all available data by a unique often non-linear model have been widely adopted to develop Quantitative Structure Property Relationships (QSPR) models. Data-driven procedures have recently been proposed as a complementary approach (1).

Cheminformatics and chemometrics procedures were applied to develop QSPR soft models of local validity predicting ILs toxicities (2,3,4), E_{NR} solvent polarity (5) and important physicochemical properties such as heat capacity (6), viscosity (1), density (1), conductivity (1) and decomposition temperature (1). This approach uses simultaneously cations and anions VolSurf+ structural descriptors which can be easily interpreted.

As experiments can hardly explore the enormous chemical space covered by ILs, data-driven modelling complements theory-driven approaches for interpretation and correlation purposes and may represent an unexploited opportunity for experimentalists in ILs industrial design.

References: 1. A. Paternò, L. Goracci, S. Scirè, and G. Musumarra, *ChemistryOpen*, 2017, 6, 90 – 101. 2. A. Paternò, G. Bocci, L. Goracci, S. Scirè, and G. Musumarra, *SAR QSAR Environ. Res.*, 2016, 27, 1-15. 3. A. Paternò, G. Bocci, G. Cruciani, C.G. Fortuna, L. Goracci, S. Scirè, and G. Musumarra, *SAR QSAR Environ. Res.*, 2016, 27, 221-244. 4. A. Paternò, S. Scirè, and G. Musumarra, *Tox. Res.*, 2016, 5, 1090-1096. 5. A. Paternò, F. D'Anna, C. G. Fortuna, and G. Musumarra, *Tetrahedron*, 2016, 72, 3282-3287. 6. A. Paternò, R. Fiorenza, S. Marullo, G. Musumarra, and S. Scirè, *RSC Adv.*, 2016, 6, 36085-36089.

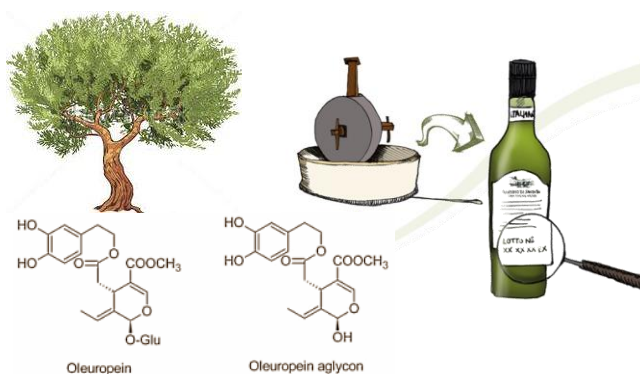
Unconventional synthetic methods towards new food additives from waste derived by olive oil industry

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People who closely follow the Mediterranean diet live longer than other Europeans and Americans due to the lower incidence of chronic and degenerative diseases; Virgin Olive Oil (VOO) is the main beneficial factor responsible for nutritional benefits of Mediterranean diet.¹

The beneficial effect connected to the olive oil consumption is directly dependent on its composition. Beside a correct ratio of saturated and unsaturated fatty acids, olive oil contains an important percentage of phenols, most of them displaying antioxidant activity. In particular, olive oil is characterized by the presence of secoiridoids phenols. The most important secoiridoid in olive oil industry is oleuropein possessing a lot of biological and pharmacological properties² and mostly present in olive leaves, a waste of one of the more extensive agricultural production in our region. Metabolic derivatives of oleuropein are aglycones derivatives and hydroxytyrosol that have demonstrated important biological activity.³⁻⁶



In this context, our recent research was focused to exploit the oleuropein and demethyl oleuropein, derived by wastes from olive oil industry, in environmentally friendly extraction processes. The same compounds were used as precursors for the obtainment new natural food additives through innovative synthetic methods.

References: 1. Tripoli, E., Giammanco, M., Tabacchi, G., Di Majo, D., Giammanco, S., La Guardia, M. (2005). Nutrition Research Review, 18, 98–112. 2. Reference n. 2. Bulotta, S., Corradino, R., Celano, M., D'Agostino, M., Maiuolo, J., Oliverio, M., Procopio, A., Iannone, M., Rotiroti, D., & Russo, D. (2011). Food Chemistry, 127, 1609–1614. 3. Procopio, A., Alcaro, S., Nardi, M., Oliverio, M., Ortuso, F., Sacchetta, P., Pieragostino, D., & Sindona, G. (2009). Journal of Agricultural and Food Chemistry, 57, 11161–11167. 4. Procopio, A., Sindona, G., Gaspari, M., Costa, N. & Nardi, M. (2008) International Patent PCT/IT2008/000303). 5. Sindona, G., Caruso, A., Cozza, A., Fiorentini, S., Lorusso, B., Marini, E., Nardi, M., Procopio, A., & Zicari, S. (2012). Current Medicinal Chemistry, 19, 4006–4013. 6. Nardi M., Bonacci S., De Luca G., Maiuolo J., Oliverio M., Sindona G., Procopio A. Food Chemistry 162 (2014) 89–93

Metaboliti secondari bioattivi prodotti da funghi patogeni di piante forestali

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Le formazioni boschive in Italia sono minacciate da un crescente numero di specie fungine invasive. In particolare, i risultati di recenti ricerche indirizzate allo studio delle cause della grave moria di querce che sta interessando ampie regioni del territorio nazionale hanno evidenziato il ruolo preminente svolto da *Diplodia corticola*, un patogeno altamente aggressivo. Le infezioni di questo fungo hanno un grande impatto ecologico, in quanto compromettono sia la vitalità sia la produttività delle piante. Allo stesso tempo, due nuove specie fungine, *Diaporthella cryptica* e *Sardiniella urbana* associate rispettivamente ad una grave sindrome che colpisce il nocciolo e il bagolaro stanno causando gravi morie in Sardegna (1, 2). Considerata la grande valenza ecologica di questi ecosistemi forestali e dei gravi danni causati da questi funghi, si è ritenuto opportuno approfondire le conoscenze sulla bio-ecologia di queste specie e, in particolare, sui fattori di virulenza coinvolti nel processo di patogenesi. Dalle ricerche finora condotte è emersa la capacità di *D. corticola* di produrre in vitro una pletera di metaboliti secondari bioattivi, alcuni dei quali di particolare interesse anche sotto il profilo applicativo. I metaboliti fitotossici finora isolati appartengono a diverse classi di composti naturali quali: diterpeni pimarani, cicloeseni epossidi, furanoni e piranoni (3, 4). Degna di nota è la potenzialità applicativa come antitumorale della sphaeropsidina A, metabolita appartenente alla classe dei diterpeni pimarani, che ha mostrato in vitro una notevole attività contro tumori maligni come il melanoma (5). Oltre la sphaeropsidina A, altri metaboliti, come il diorcinolo e il diplopyrone B, possiedono un grande potenziale applicativo in virtù della loro efficacia nei confronti di importanti patogeni appartenenti al genere *Phytophthora*, le cui infezioni su piante forestali sono controllate attualmente solo con pochi fungicidi di sintesi.

Nella presente comunicazione saranno presentati i risultati ottenuti sull'isolamento e la caratterizzazione chimica e biologica di metaboliti bioattivi prodotti dalle due nuove specie fungine *D. cryptica* e *S. urbana*.

References:

1. Linaldeddu B.T., Deidda A., Scanu B., Franceschini A., Alves A., Abdollahzadeh J., Phillips A.J.L.; Phylogeny, morphology and pathogenicity of *Botryosphaeriaceae*, *Diatrypaceae* and *Gnomoniaceae* associated with branch diseases of hazelnut in Sardinia (Italy). *European Journal of Plant Pathology* 146(2): 259–279 (2016).
2. Linaldeddu B.T., Alves A., Phillips A.J.L. *Sardiniella urbana* gen. et sp. nov., a new member of the *Botryosphaeriaceae* isolated from declining *Celtis australis* trees in Sardinian streetscapes. *Mycosphere* 7 (7): 893–905 (2016).
3. Masi M., Maddau L., Linaldeddu B.T., Cimmino A., D'Amico W., Scanu B., Evidente M., Tuzi A., Evidente A.; Bioactive secondary metabolites produced by the oak pathogen *Diplodia corticola*. *Journal of Agricultural and Food Chemistry* 64: 217-225. (2016).
4. Cimmino A., Maddau L., Masi M., Evidente M., Linaldeddu B.T., Evidente A.; Further secondary metabolites produced by *Diplodia corticola*, a fungal pathogen involved in cork oak decline. *Tetrahedron* 72(43): 6788-6793 (2016).
5. Aude Ingels, Carina Dinhof, Abhishek D. Garg, Lucia Maddau, Marco Masi, Antonio Evidente, Walter Berger, Bieke Dejaegher, Véronique Mathieu; Computed determination of the in vitro optimal chemocombinations of sphaeropsidin A with chemotherapeutic agents to combat melanomas; DOI 10.1007/s00280-017-3293-x; *Cancer Chemother Pharmacol* (2017).

An expeditious and greener synthesis of functionalized cyclopentenones in deep eutectic solvents.

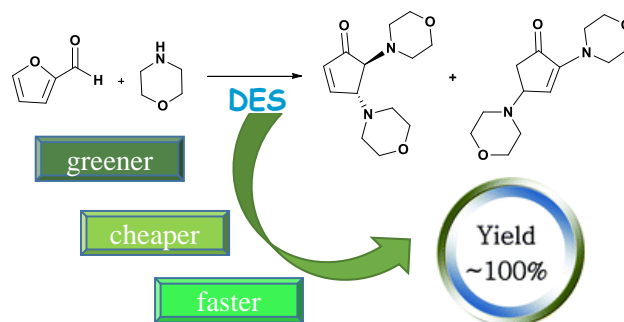
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In recent years, cyclopentenones have been the target of various synthetic efforts because their five member-ring structure is a characteristic of many compounds with a broad range of biological properties.¹

Conventionally, the cyclopentenone unit has been synthesized starting from furfuraldehyde and primary and secondary amines but most of the reported methods suffer of some disadvantages, such as use of toxic solvents or catalysts, harsh reaction conditions, environmental problems, undesirable wastes, unsatisfactory yield, and tedious work-up procedures.

Therefore, the potential important biological activity of compounds related to bifunctionalized cyclopentenones derivatives has demanded alternative, environmentally friendly strategies to synthesize bifunctionalized cyclopentenones.²



In recent years much attention has been devoted to deep eutectic solvents (DESs) as new sustainable alternatives to traditional solvents and ionic liquids.³ Compared to ionic liquids, DESs are generally cheaper to make, are less toxic and are often biodegradable. Thus, DESs can be used as low-cost, safe and efficient solvents. We report here a practical, inexpensive, rapid and green method for the preparation of cyclopentenones derivatives in deep eutectic solvents.

References: 1. S. P. Simeonov, J. P. M. Nunes, K. Guerra, V. B. Kurteva, C. A. M. Afonso *Chem. Rev.*, 2016, **116**, 5744. 2. A. Procopio, P. Costanzo, M. Curini, M. Nardi, M. Oliverio, G. Sindona, *ACS Sustain Chem Eng.* 2013, **1**, 541. 3. A. P. Abbott, G. Capper, D. L. Davies, R. K. Rasheed, V. Tambyrajah *Chem Commun* 2003, **1**:70.

Synthesis of nitro-functionalized *N*-heteroaromatic condensed systems

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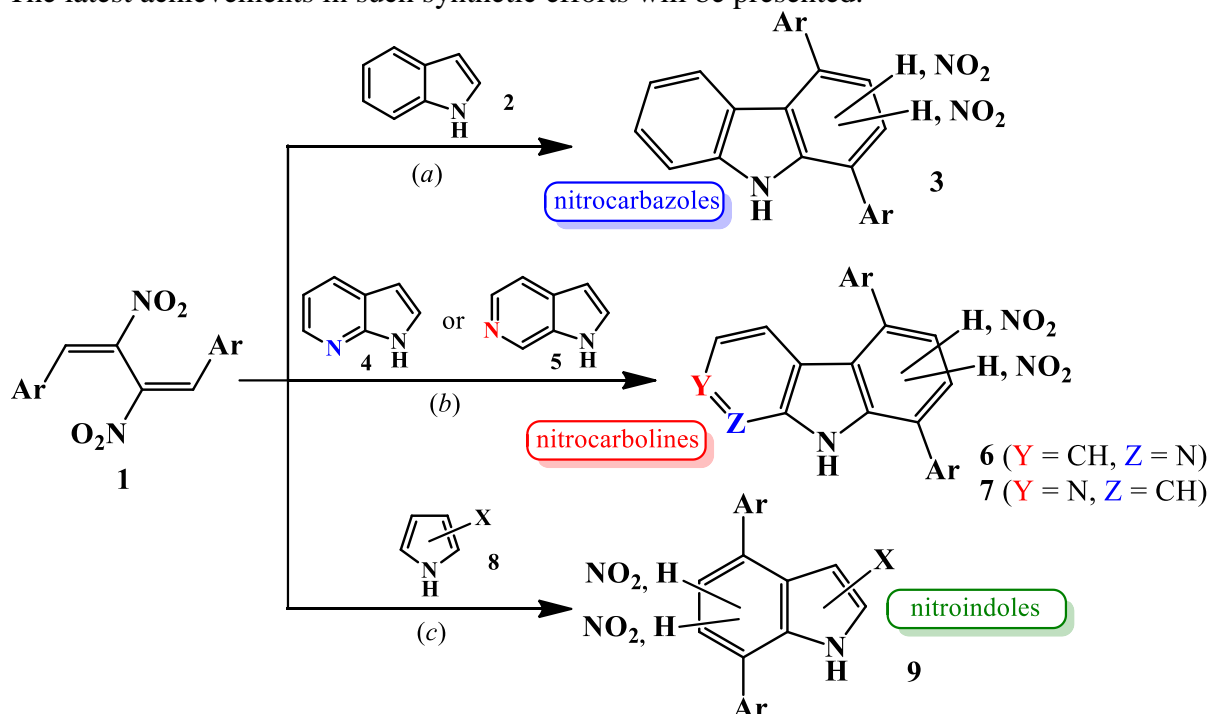
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The long-standing synthetic efficacy of dinitrobutadienes **1** (1) has been more recently applied to the preparation of nitrocarbazoles **3**, via a sequence of two Michael-type additions (inter- and intra-molecular), followed by aromatization through nitrous acid elimination and/or oxidation processes (Scheme, path *a*) (2).

The extension of the same reactivity of dienes **1** to azaindoles **4** or **5** (path *b*), as well as to pyrroles **8** (path *c*), would provide an appealing access to new entries, otherwise not simply attainable, in the biologically and technologically exploited field of nitroheteroaromatics and derivatives therefrom.

The latest achievements in such synthetic efforts will be presented.



References: 1. Bianchi, L.; Carloni-Garaventa, A.; Maccagno, M.; Pani, M.; Petrillo, G.; Scapolla, C.; Tavani, C. *Tetrahedron* **2015**, *71*, 7550-7556, and references therein. Ballini, R.; Araujo, N.; Gil, M. V.; Roman, E.; Serrano, J. A. *Chem. Rev.* **2013**, *113*, 3493-3515. Bianchi, L.; Maccagno, M.; Petrillo, G.; Sancassan, F.; Spinelli, D.; Tavani, C. 2,3-Dinitro-1,3-butadienes: Versatile Building Blocks from the Ring Opening of 3,4-Dinitrothiophene, in *Targets in Heterocyclic Systems: Chemistry and Properties*; Attanasi, O.A., Spinelli, D., Eds.; Società Chimica Italiana: Rome, Italy, 2007; Vol. 10, pp 1-23. 2. Bianchi, L.; Giorgi, G.; Maccagno, M.; Petrillo, G.; Scapolla, C.; Tavani, C. *Tetrahedron Lett.* **2012**, *53*, 752-757. Bianchi, L.; Maccagno, M.; Pani, M.; Petrillo, G.; Scapolla, C.; Tavani, C. *Tetrahedron* **2015**, *71*, 7421-7435.

Targeting Gastrin-Releasing Peptide Receptor expressing tumors: synthesis and characterization of new potential diagnostic and therapeutic molecular tools.

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Gastrin-Releasing Peptide Receptors (GRPR) are transmembrane G-proteins coupled receptors that trigger different signaling transduction pathways, resulting, among which, in the stimulation of cell proliferation. Although GRPR are poorly distributed in normal tissues, it has been shown that they are significantly involved in the pathogenesis of different human cancers (1), including lung (small and non-small cell type), breast, prostate, exocrine pancreas, head and neck squamous cell, and glioblastoma cancers. In addition, they are recently emerged as tumoral marker in early prostate and breast cancers diagnosis (2). For these reasons, the research of new GRPR ligands as antagonists or carriers for cytotoxic and imaging molecular tools might be a promising strategy for the treatment and diagnosis of human tumoral malignancies (3).

The main aim of our work is the design, synthesis and elucidation of the structure-activity relationship of new ligands able to act as GRP agonist or antagonist.

Here we presents the synthesis of a non-peptidic library of novel GRPR ligands based on a preliminary rational drug-design computational study. In particular, we synthesized a library of ligands based on a rigid and spatially defined selected glycidic scaffold, differing for the nature of potential pharmacophoric moieties. Since GRP and analogous peptides promote the activation of Phospholipase C (PLC) signaling pathway, the biological activity of the synthesized compounds was preliminarily screened by evaluating their ability to increase the level of cytosolic Ca²⁺ (agonist activity) or to contrast the stimulation mediated by natural ligands (e.g. bombesin, Bn) (antagonist activity) in a human prostate carcinoma cell line (PC-3) over-expressing the receptor.

This work was supported by AIRC (MFAG-17030 Targeting of Gastrin-Releasing Peptide receptor expressing tumors: NMR characterization of Bombesin/GRP-R interaction)

References

1. Ramos-Álvarez, I.; Moreno, P.; Mantey, S. A.; Nakamura, T.; Nuche-Berenguer, B.; Moody, T. W.; Coy, D. H.; Jensen, R. T., Insights into bombesin receptors and ligands: Highlighting recent advances. *Peptides* **2015**, *72*, 128-144.
2. (a) Mansi, R.; Fleischmann, A.; Macke, H. R.; Reubi, J. C., Targeting GRPR in urological cancers[mdash]from basic research to clinical application. *Nat Rev Urol* **2013**, *10* (4), 235-244; (b) Morgat, C.; MacGrogan, G.; Brouste, V.; Vélasco, V.; Sevenet, N.; Bonnefoi, H.; Fernandez, P.; Debled, M.; Hindie, E., Expression of Gastrin-Releasing Peptide Receptor (GRPR) in Breast Cancer and its Association with Pathological, Biological and Clinical Parameters: A Study of 1432 Primary Tumors. *Journal of Nuclear Medicine* **2017**.
3. Hohla, F.; Schally, A. V., Targeting gastrin releasing peptide receptors: New options for the therapy and diagnosis of cancer. *Cell Cycle* **2010**, *9* (9), 1738-1741.

An unconventional helical push-pull system for solar cells

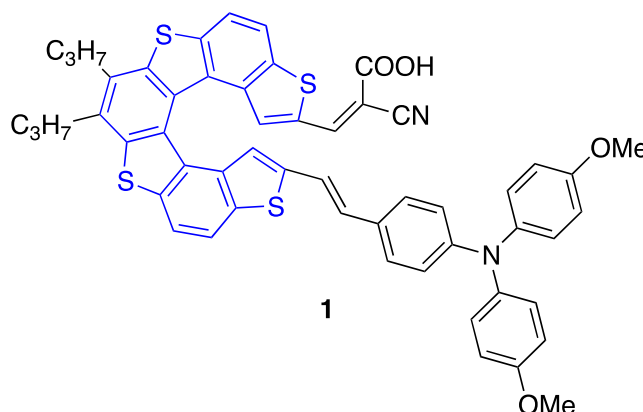
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Tetrathiahelicenes (7-THs), formed by thiophene and benzene rings *ortho*-fused in an alternating fashion, belong to an intriguing class chiral helical-shaped molecules, that have received much attention thanks to manifold applications in different areas of science (1). In fact, the configurationally fixed helical arrangement of the π -system confers to helicenes a peculiar topology, and provides unique electronic and optical properties suitable for applications in optoelectronics (2), biomolecular recognition (3), and catalysis (4,5,6). Moreover, the selective functionalization of the α -position(s) of the terminal thiophene ring(s) of the 7-TH allows the introduction of a variety of substituents (7), which can modulate specific properties, including electronic properties. Exploiting our well-established know-how in the synthesis and functionalization of 7-TH derivatives, we have synthesized a novel push-pull system (**1**, Figure 1), in which the thiahelical skeleton represents the π -conjugated-bridge spacer.



The optical and electrochemical properties of **1** have been studied, and its performance as organic dye in dye-sensitized solar cells (DSSCs) has been preliminary investigated.

References: 1. Licandro, E.; Cauteruccio, S.; Dova, D. *Adv. Heterocycl. Chem.* **2016**, *118*, 1-46. 2. Bossi, A.; Licandro, E.; Maiorana, S.; Rigamonti, C.; Righetto, S.; Stephenson, G. R.; Spassova, M.; Botek, E.; Champagne, B. *J. Phys. Chem. C* **2008**, *112*, 7900-7907. 3. Xu, Y.; Zhang, Y. X.; Sugiyama, H.; Umamo, T.; Osuga, H.; Tanaka, K. *J. Am. Chem. Soc.* **2004**, *126*, 6566-6567. 4. Cauteruccio, S.; Loos, A.; Bossi, A.; Blanco Jaimes, M. C.; Dova, D.; Rominger, F.; Prager, A.; Drew, A.; Licandro, E.; Hashmi, A. S. K. *Inorg. Chem.* **2013**, *52*, 7995-8004. 5. Cauteruccio, S.; Dova, D.; Benaglia, M.; Genoni, A.; Orlandi, M.; Licandro, E. *Eur. J. Org. Chem.* **2014**, 2694-2702. 6. Dova, D.; Viglianti, L.; Mussini, P. R.; Prager, S.; Dreuw, A.; Voituriez, A.; Licandro, E. *Asian J. Org. Chem.* **2016**, *5*, 537-549. 7. Rigamonti, C.; Ticozzelli, M. T.; Bossi, A.; Licandro, E.; Giannini, C.; Maiorana, S. *Heterocycles* **2008**, *76*, 1439-1470.

Metal chelators for the multi-target therapy of Alzheimer's Disease: isolation/synthesis and preliminary biological evaluation of new natural and synthetic compounds

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Alzheimer's Disease (AD) is widely recognized as a social problem. Nowadays, only five drugs are FDA approved for the therapy of this widespread neurodegenerative disease, however, with poor results. Three of them (Donepezil, Rivastigmine, Galantamine) are acetylcholinesterase (AChE) inhibitors, Memantine is a NMDA receptor antagonist (1), whereas the fifth medication is a combination of Donepezil with Memantine. Because of the multiple origin of this pathology, a multi-target strategy is currently strongly pursued by physicians. This approach is based on the identification of multifunctional molecules designed in order to act simultaneously on at least two disease targets with the aim of achieving synergistic actions and of improving the therapeutic efficacy (1,2). Currently, inhibition of AChE and monoaminoxidase, NMDA receptor antagonism, antioxidant activity, inhibition of Abeta amyloid plaques (A β) aggregation, and chelation of copper, iron and/or zinc cations are among the most heavily investigated drug targets (1). Recent evidence, in particular, have shown that the removal and/or redistribution of metal ions at the level of the nervous system can significantly reduce the formation of A β and thus of reactive oxygen species, which are typical of the first stages of AD and other neurodegenerative diseases (3).

Considering that many synthetic and natural compounds possess anti-oxidant, anticholinesterase and/or metal chelation activity (4), several scaffolds have been selected in order to design new derivatives. A list of secondary metabolites of fungi, in particular, have been isolated and preliminarily tested with the aim of finding new hit compounds for future Structure-Activity Relationship studies. In addition, starting from the structure of Donepezil and two selected synthetic scaffolds, new hybrid derivatives have been synthesized aimed at obtaining a better AChE inhibitory activity, an anti-oxidant activity, and the inhibition of A β aggregation. In this communication, the synthetic procedures for the preparation of these compounds, jointly with the results of preliminary biological studies, will be discussed.

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Project ID: I2PCTF6.*

References: 1. Piemontese L. Neu. Regen. Res. 2017, 405-6. 2. Chaves S., Piemontese L., Hirematad A., Santos M.A. Curr. Med. Chem., 2017, 10.2174/0929867324666170330092304. 3. M.A. Santos, K. Chand S. Chaves, Coord. Chem. Rev. 2016, 287-303. 4. Habtemariam S. Curr. Med. Chem. 2016, 860-873.

The unexpected driving role played by substituent groups in the molecular recognition of aromatic derivatives performed through Argentation Chromatography.

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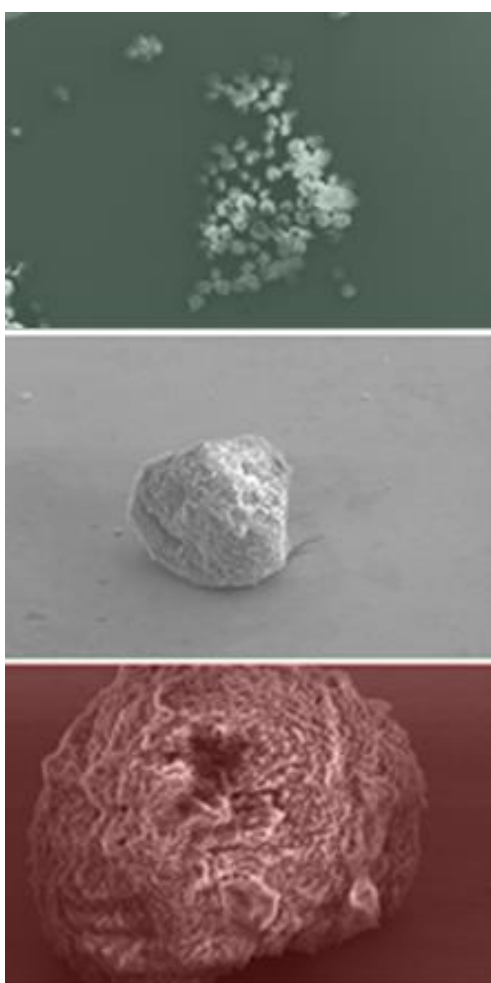
Argentation Chromatography (AC) is widely used nowadays as a powerful tool to separate complex mixtures of analytes containing unsaturated and/or aromatic fragments. Typically, the older types of stationary phases (SPs) employed in this kind of technique were based on either the direct process of impregnating of the silica surface with silver cations, or by the use of strong cation exchange resins. More recently, a new typology of SPs has been developed, in which the silver metal is covalently bonded to mercaptopropyl silica gel (MPSG-Ag). With respect to the older ones, which are prone to undergo both silver ion leaching and easy reduction of the metal cation, (from Ag^+ to Ag^0) (1, 2), the MPSG-Ag SPs display a consistent improvement of chemical stability. The general mechanism with which, in AC techniques, the silver atom interacts with the π -electrons of unsaturated species has been thoroughly clarified, allowing to rationalize the retention pattern of such type of compounds on the basis of several simple rules related to chain length, number, configuration and position of the involved double bonds (3,4,5,6). Differently, to our knowledge, they were never achieved analogous information about the chromatographic retentive behaviour of the same technique towards aromatic analytes as a function of the effect exercised by groups directly bound onto the aromatic ring. In the perspective to afford a contribution to fill this gap, here we present the results of chromatographic and computational studies in which a series of benzene derivatives, substituted with either electron withdrawing or electron donating G_i groups, have been resolved through the AC technique using a MPSG-Ag SP. In this way, clear indications (emerging from a quantum-mechanical DFT analysis that has fully rationalized the observed experimental trend) have been gained about the mechanism by which the various G_i substituents have proven to modulate, in an unexpected way, the ability of the MPSG-Ag SP in retaining and discriminating the aromatic species at which they are linked.

References: 1. J. C. Aponte, J. T. Dillon, R. Tarozo, Y. Huang. *J. Chromatogr. A*, 2012, 1240, 83-89. 2. J. T. Dillon, J. C. Aponte, R. Tarozo, Y. Huang. *J. Chromatogr. A*, 2012, 1240, 90-95. 3. O. K. Guha, J. Janak. *J. Chromatogr.*, 1972, 68, 325-343. 4. P. H. Kasai, D. McLeod, T. Watanabe. *J. Am. Chem. Soc.*, 1980, 102, 179-190. 5. S.D. Ittel, J.A. Iberis, *Advances of Organometallic Chemistry*, 1976, 14, 33-61. 6. C.L. de Ligny, *Advances in Chromatography*, 1976, 14, 265-304.

Facile Preparation of Metal Ions Loaded Sporopollenin Grains from Pollens, and Characterization

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SEM micrograph of functionalized pollen grains. The pristine structure is preserved.

Pollen grains are 3D microstructures that can act as scaffolds or templates and can be exploited for applications in different fields including drug delivery (1). To this aim, their structural component sporopollenin must be isolated. Recently, some of us reported a novel procedure for the separation of sporopollenin from the other pollen components, using room temperature ionic liquids (ILs) (2).

Here, we present the results of functionalization protocols involving ILs including anions such as $[\text{FeCl}_4]^-$, and we show that sporopollenin can retain a considerable amount of metal ions. We explored the use of different metals including iron, copper and zinc. The chemical and morphological main features of our systems are studied with a multitechnique approach, using X-ray photoemission spectroscopy (XPS), Fourier transform IR (FTIR) spectroscopy, elemental analysis and scanning electron microscopy (SEM). Preliminary studies suggest the onset of magnetic order in selected samples.

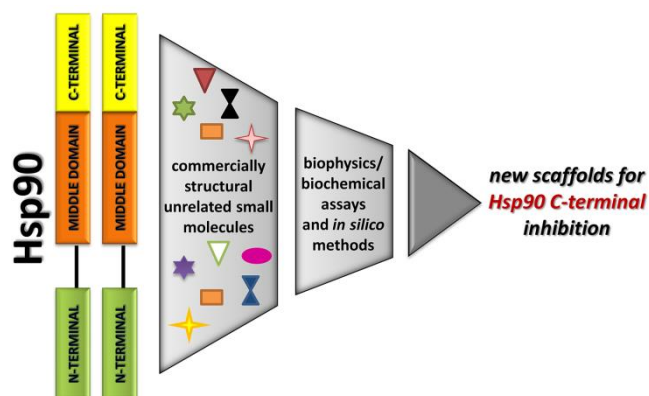
From the chemical point of view these systems can be useful as in heterogeneous catalysts. Some preliminary results will be presented.

References: 1.T.S. Shim, S.-H. Kim and S.M. Yang *Elaborate design strategies toward novel microcarriers for controlled encapsulation and release Part. Part. Sys. Char.*, 2012, **30**, 9-45. 2. C. Chiappe, G.C. Demontis, V. Di Bussolo, M. J. Rodríguez Douton, F. Rossella, C.S. Pomelli, S. Sartini and S. Caporali. *From pollen grains to functionalized microcapsules: a facile chemical route using ionic liquids Green Chem.*, 2017,**19**, 1028-1033.

Hsp90 C-terminal domain: identification of new molecular entities

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Heat shock proteins (Hsps) are effective anti-apoptotic proteins involved in vital mechanisms of cancerous cells (1), and among them, the Hsp90 inhibition represents a powerful strategy in cancer therapy (2). In recent years, many natural and synthetic Hsp90 N-terminal inhibitors have been developed and have entered clinical trials, while only a few C-terminal inhibitors have been identified so far. In contrast to N-terminal modulators, the C-terminal inhibitors represent promising therapeutic alternatives for targeting malignant cells,

because they do not induce the deleterious pro-survival heat shock response (HSR) (3). On these bases, in order to expand the number of Hsp90 C-terminal inhibitors, a set of twenty seven commercially available small molecules, endowed with different structural features, was subjected to surface plasmon resonance (SPR) screening on recombinant Hsp90 α (4). Among these, sixteen compounds showed high affinity of binding for the Hsp90 chaperone with low K_D values, and after an evaluation on their anti-proliferative activity against tumor cell lines and limited proteolysis experiments, we have disclosed two new hits targeting the C-terminal domain. On these bases, in order to rationalize the biological activity reported above, all the compounds filtered out by SPR experiments were docked onto closed active crystal structure of Hsp90 α homologue (PDB code: 2CG9) (5), focusing the conformational searches in the putative ligand-binding sites disclosed by the limited proteolysis experiments. In details, we have performed molecular docking experiments using the induced fit docking protocol (Schrödinger Suite) (6), to account for flexibility of ligands and receptor. Our structural results disclose the halogen bonding as fundamental key interaction suitable for the design of novel Hsp90 inhibitors. In conclusion, through a multidisciplinary approach, we have identified two new attractive hits for Hsp90 C-terminal inhibition that provide an excellent opportunity to expand the chemical space associated with this domain.

References: 1. G. Jago, A. Hazoume, R. Seigneuric and C. Garrido, *Cancer Lett.*, 2013, **332**, 275. 2. T. Taldone, S. O. Ochiana, P. D. Patel and G. Chiosis, *Trends Pharmacol. Sci.*, 2014, **35**, 592. 3. X. Wang, M. Chen, J. Zhou and X. Zhang, *Int. J. Oncol.*, 2014, **45**, 18. 4. S. Terracciano, A. Russo, M. G. Chini, M. C. Vaccaro, M. Potenza, A. Vassallo, R. Riccio, G. Bifulco and I. Bruno, *Chem. Commun.*, 2017, submitted. 5. M. M. U. Ali, S. M. Roe, C. K. Vaughan, P. Meyer, B. Panaretou, P. W. Piper, C. Prodromou and L. H. Pearl, *Nature*, 2006, **440**, 1013. 6. Induced Fit Docking, protocol 2015-2, Glide version 6.4, Prime version 3.7, Schrödinger, LLC, New York, NY, 2015.

Conformational Analysis and Absolute Configuration of Axially Chiral 1-aryl and 1,3-diaryl-xanthines

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One of the most important feature of life is its intrinsic chirality. For this reason, specular chiral system interacts differently with biological systems.

The xanthine scaffold is known to be the forefather of a class of biological active molecules(1). Despite its biological activity, poor attention has been given in the dynamic conformations of this scaffold. The motivation of this lack of studies has to be researched in the chemistry of the scaffold itself: it is not possible to install an ordinary center of chirality without modify one of its essential functional groups. However, it is possible to install chiral axes. The xanthine backbone is a planar framework in which an aryl substituent linked in the 1 or 3 position is driven out of the xanthine plane because of the steric hindrance, caused by the two carbonyls (2). Depending on the hindrance of the *ortho*-substituents, the resulting conformational enantiomers are expected to be either stereo labile or configurationally stable (atropisomers). In Figure 1 are shown the series of 1-aryl and 1,3-bis aryl-xanthines studied.

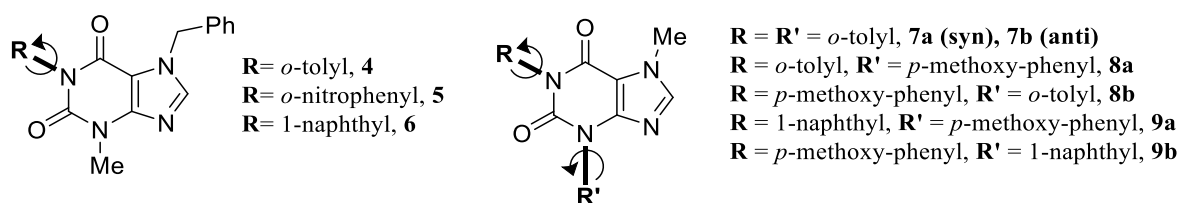


Figure 1. 1-aryl and 1,3 bis aryl-xanthines prepared.

This work aims to investigate the stereodynamics of some 1-aryl and 1-3-bis-aryl xanthines and to evaluate the steric requirements needed to produce stable heteroaromatic atropisomers or diastereoisomers, with one or two C_{sp2}-N stereogenic axes.

With these parameters in hands, it will be possible to design chiral xanthines, stable at room temperature, that can eventually interact differently with biological environment.

References: 1. C. J. Kelly, *American Journal of Clinical Nutrition*, **2005**, *82*, 486. 2. R. J. He, S. M. Ching, Y. L. Lam *J. Comb. Chem.*, **2006**, *8*, 923.

Synthesis and Photo-Physical Properties of Dopamine-Inspired Iridium Complexes for OLED Applications

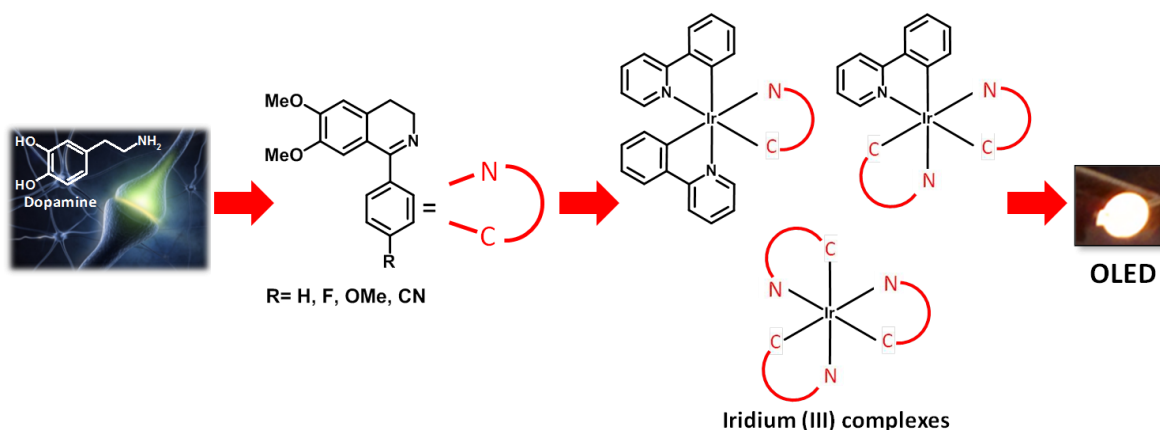
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The recent advances in the field of organic light emitting diodes (OLEDs) have been focused mainly on the need to combine the main strengths of this technology, that is the versatility (i.e. wide color tuning, ultrathin, flexible and large area devices) and the eco-compatibility (low-energy consumption), with the efficiency and the lifetime of the devices, with the aim of making OLEDs very appealing and competitive with respect to the inorganic LEDs. In the last few years, another issue has been explored in connection with the growing expansion and impact of the green electronic field, that is the challenge of integrating natural or nature-inspired materials within organic electronic devices, and so in OLEDs.

In the frame of a research plan aimed at studying the role of melanins, the dark pigment found in mammalian skin, hair and eyes, in organic electronics (1,2), we have recently explored the potentiality of new heterocyclic platforms designed taking inspiration from the mammalian pigments as electroluminescent materials for OLED applications.

Herein we report on the synthesis of a new set of phosphorescent iridium(III) complexes prepared by using ligands obtained from dopamine, the catecholic neurotransmitter and monomer precursor of the melanic polydopamine pigment (Figure 1). All the compounds obtained have been subjected to structural characterization and investigation of the photo-physical and electronic properties. Moreover, a comparative study has been carried out to delineate the role of different kind of functional groups on tuning the wavelength of the emitting light. The performances of the OLED devices fabricated with the synthesized iridium(III) complexes are also discussed.



References

1. Pezzella A. et al. *Materials Horizons* 2015, 2, 212-220
2. Manini, P. et al. *ChemPlusChem* 2015, 80, 898

Visible light driven, metal-free preparation of aromatic amides from arylazo sulfones.

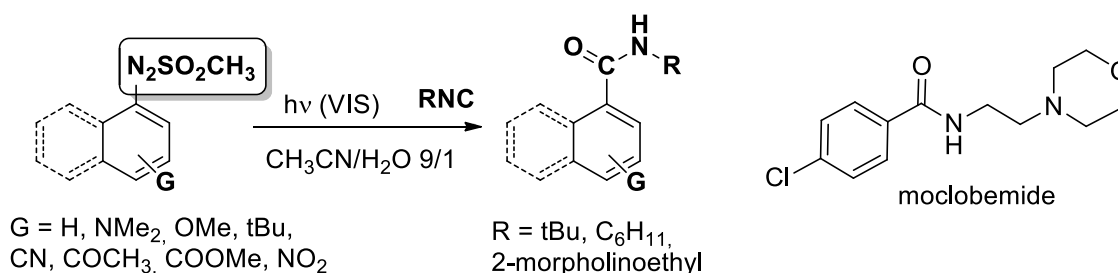
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The amide group is present in around 25% of top-selling pharmaceuticals. In particular, aromatic amides exhibit multifaceted bioactivity, and different compounds belonging to this class have been investigated, among others, as anticancer and antiviral agent (1). Typical approaches for the synthesis of such compounds are based on the formation of a C-N bond (via activation of carboxylic acids or their derivatives in the presence of amines) (2) as well as on the construction of an Ar-C bond, e.g. via aminocarbonylation of (hetero)aryl halides (3).

We present herein the synthesis of aromatic amides via photochemical metal-free carboamidation of arylazo mesylates in the presence of isocyanides in aqueous organic solvent.

The proposed method exploited the peculiar reactivity of thermally stable arylazo sulfones (which are in turn easily synthesized from the corresponding diazonium salts) to generate aryl radicals upon visible light exposure (4).



Scheme 1

The process allowed for the achievement of a wide range of synthetic targets, including hetero- and polyaromatic derivatives, and was also applied to the smooth preparation of antidepressant moclobemide (5).

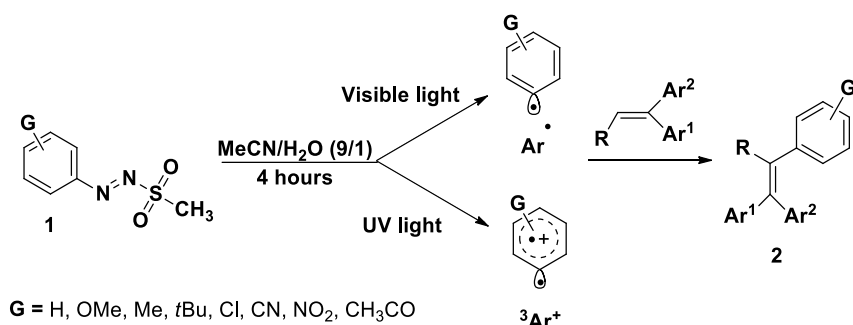
References: 1. See for instance: T. Ai, R. Willett, J. Williams, R. Ding, D. J. Wilson, J. Xie, D.-H. Kim, R. Puertollano, L. Chen, *ACS Med. Chem. Lett.* **2017**, *8*, 90–95; A. Buchynskyy, J. R. Gillespie, M. A. Hulverson, J. McQueen, S. A. Creason, R. M. Ranade, N. A. Duster, M. H. Gelb, F. S. Buckner, *Bioorg. Med. Chem.* **2017**, *25*, 1571–1584. 2. J. W. Comerford, J. H. Clark, D. J. Macquarrie, S. W. Breeden, *Chem. Comm.* **2009**, *18*, 2562–2564. 3. T. Kawamoto, A. Sato, I. Ryu, *Chem. Eur. J.* **2015**, *21*, 14764–14767. 4. S. Crespi, S. Protti, M. Fagnoni, *J. Org. Chem.*, **2016**, *81*, 9612–9619. 5. M. Malacarne, S. Protti, M. Fagnoni, *Manuscript in preparation*.

From arylazo mesylates to triarylethylenes: a solar light metal-free synthesis

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Recently organic chemists have made many efforts in the development of synthetic routes to triarylethylenes (TAEs), which structure is diffuse in nonsteroidal estrogen agonists and antagonists for the treatment of disorders such as breast cancer, osteoporosis and cardiovascular diseases.(1) Most protocols reported in literature involves transition metal catalyzed cross-coupling reactions and the cost and toxicity of the organometallic species along with the harsh conditions required are serious drawbacks.(2) In order to overcome these limitations we proposed herein a sunlight driven, metal-free synthesis of TAEs starting from arylazo mesylates (**1**, Scheme 1). These are thermally stable derivatives of aryl diazonium salts (3) bearing a coloured, photolabile moiety that exhibited a wavelength-dependent photochemistry. Indeed, aryl radicals (Ar^\bullet) and triplet aryl cations ($^3\text{Ar}^+$) (4) can be selectively generated by tuning the light source (visible light for the former ones and UVA light for the latter ones).(5) Both intermediates are generated upon solar light exposition and, in the presence of aromatics or heteroaromatics, the corresponding (hetero)biaryls were obtained in satisfactory yields.(5) In the present protocol, a straightforward uncatalyzed metal-free synthesis of TAEs (**2**) was efficiently achieved via solar light exposition of a solution of **1** in acetonitrile/water mixture in the presence of (substituted) 1,1-diphenylethylenes. The reaction was insensitive to both the nature (electron-donating or withdrawing) and the relative position of the aromatic substituent on **1** thus allowing to obtain a wide range of TAE cores.



Scheme 1

References

1. Farzaneh, S.; Zarghi, A. *Sci. Pharm.* **2016**, *84*, 409-427.
2. Berthiol, F.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2003**, 1091-1096.
3. Kamigata, N.; Kobayashi, M. *Sulfur Rep.* **1982**, *2*, 87-128.
4. (a) Dichiarante, V.; Fagnoni, M. *Synlett* **2008**, 787-800. (b) Qrareya, H.; Raviola, C.; Protti, S.; Fagnoni, M.; Albini A. *J. Org. Chem.*, **2013**, *78*, 6016-6024.
5. Crespi, S.; Protti, S.; Fagnoni, M. *J. Org. Chem.* **2016**, *81*, 9612-9619.

This work has been supported by Fondazione Cariplo, project 2015-0756 "Visible Light Generation of Reactive Intermediates from Azosulfones".

A Hydrogen Borrowing approach to Pyrrolobenzodiazepines.

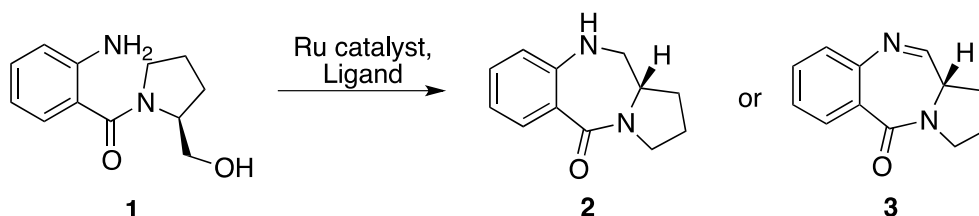
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The pyrrolo[2,1-c][1,4]benzodiazepines (PBDs) are a family of sequence-selective DNA minor-groove binding crosslinking agents originally discovered in *Streptomyces* species. They are significantly more potent than systemic chemotherapy drugs with potential applications in the field of antibiotic and anticancer therapies. Recent results showed that PBDs can be effectively employed also for antibody drug conjugate target therapy.(1)

As synthetic approaches to PBDs are generally multistep complex procedures, we explored the possibility to simplify some synthetic steps applying a hydrogen borrowing (HB) mechanism to the closure of the PDB ring. Different Ru catalysts were screened on the simple amino alcohol **1** giving the cyclic compounds **2** or **3** depending on the catalyst or ligand nature. (Scheme 1). This one-pot reaction takes place with a mechanism that involves a double change in the state of oxidation of the atoms, in line with the principle of redox economy.(2)



Scheme 1.

Once optimized the best conditions to obtain the general structure of PDBs, we investigated the scope of the reaction on differently functionalized analogues of **1** developing also a protecting group free synthesis of a PDB containing natural product.

1. Montaj, J.; Jackson, P. J. M.; Rahman, K.; Thurston, D. E. *Angew. Chem. Int. Ed.* **2016**, *55*, 2-29.
2. Burns, N. Z.; Baran, P. S.; Hoffman, R. W. *Angew. Chem. Int. Ed.* **2009**, *48*, 2854-2867.

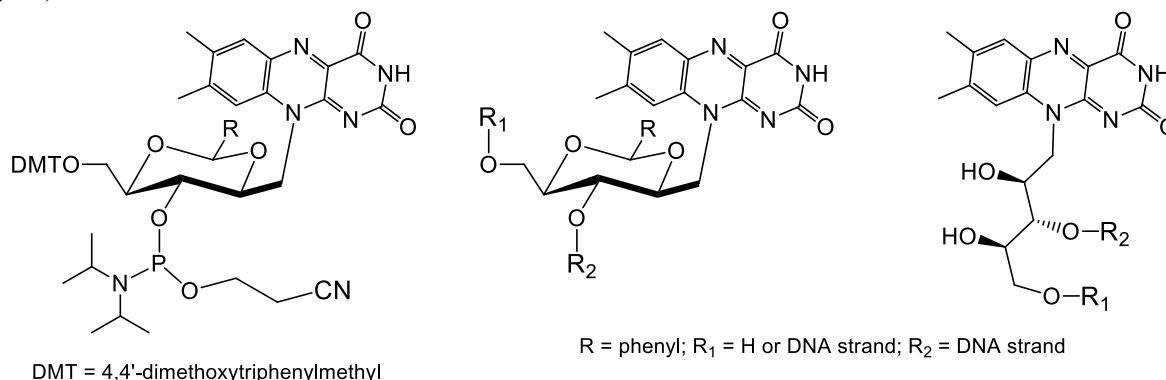
Synthesis of a new Riboflavin-nucleotide and its insertion into G-quadruplex forming ODNs with anti-HIV activity

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In the last years, G-rich oligonucleotides (GROs) able to form G-quadruplexes, have attracted considerable interest in biological and therapeutic fields (1). G-quadruplex are among the most studied DNA structures because they are thought to be involved in important biological processes such as the modulation of gene expression; in addition they present a large variety of biological properties ranging from anticancer to antiviral activities. In all cases, the G-quadruplex formation is a crucial prerequisite for the biological effects.

Recently, we reported the synthesis and full characterization of a mini-library of G quadruplex ODNs carrying aryl groups at the 5'-end through a phosphodiester bond and endowed with prominent anti-HIV activity (2,3,4). In this frame, we report here, the synthesis of new Riboflavin-Nucleoside (RF, Vitamin B) building block in which the ribityl chain is rigidified by 2',4' benzylidene group, the 5'-OH function is protected with DMT group and the 3' position is functionalized with phosphoramidite (Figure).



The new Riboflavin building block is incorporated into different ODN sequences able to form G-quadruplex structures using the well known phosphoramidite chemistry.

This research project has been encouraged by recent studies on the use of RF as useful tool for both *in vivo* and *in vitro* studies: the Riboflavin is internalized through RF transporters and is one of the most efficient natural photosensitizers (5).

Several modified ODN sequences have been synthesized with a solid phase synthetic approach in good yields; their biophysical and biological characterization has been carried out in order to evaluate the effect of RF-nucleotide insertion into G-quadruplex arrangements and their anti-HIV activity.

1. Neidle, S. Therapeutic Applications of Quadruplex Nucleic Acids; Academic Press Elsevier: Oxford (UK), **2012**.
2. G. Di Fabio, J. D'Onofrio, M. Chiapparelli, B. Hoorelbeke, D. Montesarchio, J. Balzarini, L. De Napoli, Chem. Commun. **47** (2011) 2363–2365.
3. V. Romanucci, D. Milardi, T. Campagna, M. Gaglione, A. Messere, A. D'Urso, E. Crisafi, C. La Rosa, A. Zarrelli, J. Balzarini, G. Di Fabio, Bioorg. Med. Chem. **22** (2014) 960–6.
4. V. Romanucci, M. Gaglione, A. Messere, N. Potenza, A. Zarrelli, S. Noppen, S. Liekens, J. Balzarini, G. Di Fabio, Eur. J. Med. Chem. **89** (2015) 51–58.
5. N. Beztsinna, Y. Tsvetkova, M. Bartneck, T. Lammers, F. Kiessling, I. Bestel, Bioconjug. Chem. **27** (2016) 2048–2061.

Detecting new drugs through NMR chemosensing

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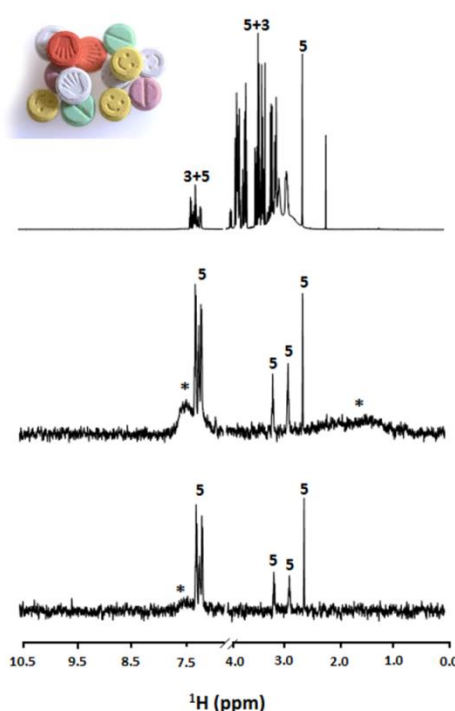
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A designer drug is an analog of a controlled substance designed to mimic the pharmacological effects of the original drug, while avoiding its classification as illegal and/or its detection in standard drug tests. In particular, several notable recreational drugs are members of the substituted phenethylamines class.

In order to detect new substituted phenethylamines, we apply our recently reported “NMR chemosensing” method. The rationale of this method rests upon the slow diffusion rate of the 2-nm gold core nanoparticles (AuNPs) compared to small analytes, and on the intermolecular dipolar interactions as a pathway to transfer magnetization between two interacting species (1,2,3). The NMR chemosensing experiment starts with a diffusion filter which dephases the magnetization of all the small, fast diffusing species in the sample while retaining that of the NPs. This magnetization is then transferred via NOE to the small analytes interacting with the NPs monolayer, and the resulting signals are detected (3). The main advantage is the fact that the signal

produced by the sensing system is the full NMR spectrum of the analyte: this allows not only the detection and quantification of the analyte, but also its unambiguous identification.

Hence, we designed and synthesised new AuNPs able to interact selectively with the target molecules. The use of this AuNPs as NMR chemosensor, allowed the detection in water of amphetamine analogues, together with the identification of their molecular structure.



References: 1. Rastrelli, F. Jha, S. Mancin, F. *J. Am. Chem. Soc.* **2009**, *28*, 14222 2. Perrone, B. Springhetti, S. Ramadori, F. Rastrelli, F. Mancin, F. *J. Am. Chem. Soc.* **2013**, *135*, 11768 3. Salvia, MV. Ramadori, F. Springhetti, S. Diez-Castellnou, M. Perrone, B. Rastrelli, F. Mancin, F. *J. Am. Chem. Soc.* **2015**, *137*, 886

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Synthesis of C2-modified chiral PNA using Minimally Protected Submonomer Synthesis

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PNAs (Peptide Nucleic Acids, figure a) are synthetic analogues of DNA where the phosphate backbone is substituted by amide bonds. They have been used in several applications, in diagnostics and therapeutics (1). PNAs can be obtained using peptide synthesis, mainly with Boc/Z or Fmoc/Bhoc strategies using commercially available monomers, but modified PNA on the backbone, the nucleobase or on both, useful for introducing new properties, can be obtained by synthesizing appropriate precursors (2). Previously, our group showed that the insertion of a stretch of C-2 backbone-modified monomers (figure b) with D-stereochemistry can increase the sequence-selectivity of the interaction of PNA with DNA, especially when recognition of a single point mutated DNA sequence is required (3,4). This “Chiral Box” can therefore be very useful in sensor development aiming at tumor-related point mutations, such as those of the KRas or NRas genes.

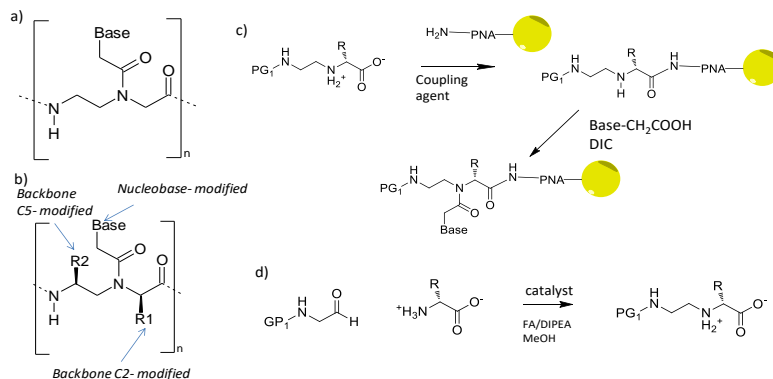


Figure. a) PNA structure; b) modification sites; c) minimally protected submonomer synthesis; d) one-step submonomer synthesis from Fmoc-glycinal.

In this communication we present a simplified route to C2-modified “Chiral Box” PNA by submonomeric strategy (figure c). The procedure is based on a minimal protection approach, using the PNA backbone with only terminal amino group Fmoc-protection. This submonomer can be obtained using a simplified (figure d) metal-catalyzed reductive amination procedure (5). Incorporation into the PNA chain can be obtained, without branching side reactions, by careful choice of the coupling agent and coupling conditions; subsequent coupling with the desired nucleobase provides the incorporation of the modified PNA monomer. The optical purity of the submonomer and the effect on it of the subsequent coupling have been evaluated using a model reaction with phenylalanine methyl ester, by ¹H and ¹³C NMR. This work was carried out in the frame of the H2020 ULTRAPLACAD project aimed to early diagnosis of colorectal cancer.

References:

- Nielsen, P. E. *Acc. Chem. Res.* **1999**, *32*, 624–630.
- Manicardi A.; Bertucci, A.; Rozzi, A.; Corradini, R. *Org. Lett.* **2016**, *18*, 5452–5455.
- Menchise, V.; De Simone, G.; Tedeschi, T.; Corradini, R.; Sforza, S.; Marchelli, R.; Capasso, D.; Saviano, M.; Pedone, C. *Proc. Natl. Acad. Sci. U. S. A.* **2003**, *100*, 12021–12026
- Corradini, R.; Sforza, S.; Tedeschi, T.; Totsingan, F.; Manicardi, A.; Marchelli, R. *Curr. Topics Med. Chem.* **2011**, *11*, 1535.
- Chao, W. Pettman, A., Bacsá, J.; Xiao, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 7548–7552.

Microsomal Prostaglandin E2 Synthase-1 potential inhibitors: design, synthesis and biological evaluation.

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Microsomal prostaglandin E2 synthase-1 (mPGES-1) is a member of the MAPEG (Membrane-Associated Proteins in Eicosanoid and Glutathione metabolism) proteins family and represents an important target for anti-inflammatory and anticancer drugs discovery and development.(1) This membrane homotrimer is an inducible GSH-dependent enzyme involved in the arachidonic acid cascade; in particular, it is responsible for the conversion of COX-derived unstable peroxide PGH₂ in PGE₂, a key bioactive lipid mediator of a variety of biological effects associated with inflammation disorders.(2) The active site of this enzyme is located at the interface of the three asymmetric monomers, which in turn are formed by four α -helices and are partially occupied by the glutathione (GSH) cofactor.(3) Since many studies proved mPGES-1 overexpression in several inflammatory disorders as well as in different human cancers, this enzyme can be considered as a promising target in cancer and antiinflammatory therapy.(4) Moreover the possibility of overcoming the classical side effects commonly associated with use of traditional anti-inflammatory drugs (NSAIDs), that inhibit the cyclooxygenase pathway, is another important reason that drives the discovery of new and more potent mPGES-1 inhibitors.(5) Basing on the human mPGES-1 X-ray structure we performed a virtual screening on a huge number of synthetically accessible molecules in order to select the best candidates for chemical synthesis. Here we report the identification of a small collection of 2,4 thiazolidindiones as a new potential class of m-PGES1 inhibitors.

References: 1. J. G. Luz, et al. J Med Chem, (2015), 58, 4727. 2. Park, JY.; Pillinger, MH.; Abramson, SB. Clinical Immunology 119, 3 (2006) 229-240. 3. Nakanishia, M.; Gokhaleb, V.; Meuilletc, E.J.; Rosenberg D.W. Biochimie, 92 (2010) 660-664. 4. Chang, H.; Meuillet, E.J.; Future Med Chem, 3 (2011) 1909–1934. 5. Shan He, Cong Li, Ying Liu, and Luhua Lai, J. Med. Chem., 56 (2013) 3296–3309. 6. Li, D.; et al. M. Cryst Growth Des, 14 (2014) 2034-2047.

Computational Study on the Gas-Phase and Aqueous Solution Acidity of Nicotine

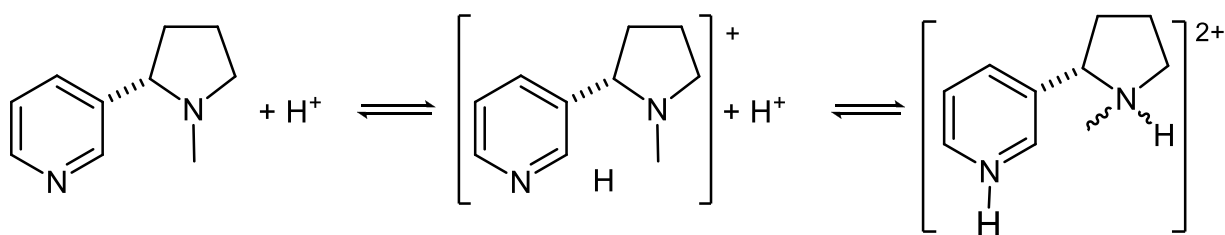
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Dielectric continuum solvation models (1), recently introduced in the routine of computational chemistry, have allowed organic chemists to afford solvation free energies, thus getting a closer insight on the real thermodynamics of chemical reactions in solution. Hydron transfer reactions are by far the most studied due to their importance both in physico-chemical systems and in synthetic applications.

Since, on the other hand, molecules have almost always a notable molecular flexibility, each computational assessment should certainly address an accurate conformational analysis of each species involved in the chemical equilibrium. This rather annoying and troublesome complication has been automated and made simpler to unravel by using the application called RotAnal (Rotational Analysis), still in steady development at our laboratories. RotAnal is a smart front-end program that performs a conformational sampling, pruning, refinement and analysis through an original, multistep procedure, through any of the most widely used quantum computing packages like GaussianTM and FireflyTM, and MPI parallel computing across a PC cluster in Microsoft WindowsTM environments (2).

Alkaloid nicotine has been selected in the present pilot study as a convenient model due both to the simplicity of their structure and phase space and the easy availability of the experimental aqueous sequential ionization pKa's (3).



Calculations performed up to different theoretical levels of theory (Hartree-Fock, Kohn-Sham DFT) both in vacuo and in PCM aqueous solution have provided us with the relative and absolute pKa's. Results show that asserting about hydronation sites of real-chemistry bases grounded mainly upon the empiric rules of introductory organic chemistry should be treated with caution.

A population analysis based on the Natural Bond Orbital (NBO) paradigm (4) has also allowed us to correlate the torsional preferences with the presence of stabilizing interactions between filled and empty orbitals through hyperconjugation effects.

References: 1. B. Mennucci and R. Cammi, *Continuum Solvation Models in Chemical Physics: From Theory to Applications*, Wiley, 2007. 2. M. Ciofalo, RotAnal: una nuova applicazione per lo studio conformazionale di molecole organiche flessibili, Siciliachem – XIV Congresso Nazionale della Divisione Didattica della Società Chimica Italiana, 2005. 3. J. W. Gorrod and P. Jacob III, *Analytical Determination of Nicotine and Related Compounds and Their Metabolites*, Elsevier, 1999. 4. F. Weinhold, *Discovering Chemistry with Natural Bond Orbitals*, Wiley, 2012.

New Mannosylcalix[n]Arenes as Multivalent Ligands for the Inhibition of Hiv/Dc-Sign Interaction

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The fight against human immunodeficiency virus is a big challenge of current times and huge efforts have been made to develop new effective therapies (1). One of the main pathway of infection exploits dendritic cells (DCs) that, used by the virus as Trojan horse, efficiently transfer virions to T-cells, where replication takes place (2). Among receptors on DCs surface, DC-specific ICAM-3 grabbing non-integrin (DC-SIGN) is strongly involved in the process, by interacting with the high-mannose glycans of glycoprotein gp120 present on the virus envelope (3). Therefore, different research groups are focusing their work on the development of glycomimetic compounds that could interfere with gp120/DC-SIGN interaction. Due to the tendency of DC-SIGN to oligomerize on the cell surface (Figure) (3), a multivalent approach seems to be a valuable strategy to design efficient and selective ligands. In this context, we designed and synthesized a small series of mannosylated calixarenes (Figure). The possibility of tuning valency and geometry of the ligating units makes calixarenes very convenient scaffold for generating multivalent ligands (4,5). Preliminary experiments by Surface Plasmon Resonance evidenced the ability of our compounds to bind to DC-SIGN.

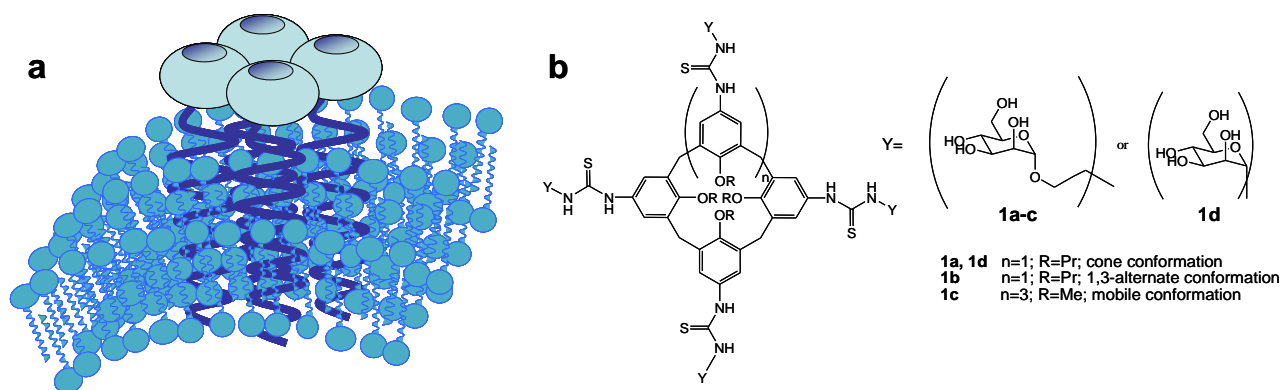


Figure: a) Schematic representation of a DC-SIGN tetramer on the cell surface; b) multivalent mannosylcalix[n]arenes synthesized in this work.

References: 1. Garzino-Demo A.; Gallo R. C. *Curr. Opin. Hematol.* **2003**, *10*, 279-283. 2. Thepaut M.; Guzzi C.; Sutkeviciute I.; Sattin S.; Ribeiro-Viana R.; Varga N.; Chabrol E.; Rojo J.; Bernardi A.; Angulo J.; Nieto P. M.; Fieschi F. *J. Am. Chem. Soc.* **2013**, *135*, 2518-2529. 3. Wu L.; Kewal Ramani V. N. *Nature Rev. Immunol.* **2006**, *6*, 859-868. 4. Sansone F.; Casnati A. *Chem. Soc. Rev.* **2013**, *42*, 4623-4639. 5. Giuliani M.; Morbioli I.; Sansone F.; Casnati A. *Chem. Commun.* **2015**, *51*, 14140-14159.

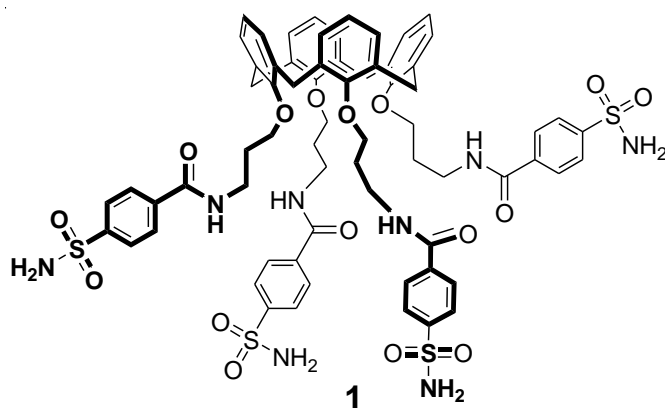
Calixarene-Based Multivalent Inhibitors for Carbonic Anhydrases

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Carbonic anhydrases (CAs) are a group of ubiquitously expressed metalloenzymes (1) involved in numerous physiological and pathological processes, including gluconeogenesis, lipogenesis, ureagenesis, tumour progression and in the growth and virulence of various pathogens. In addition to the established role of CA inhibitors (CAIs) as diuretics and antiglaucoma drugs, it has recently emerged that CAIs could have potential as novel anti-obesity, anticancer and anti-infective drugs (2,3). Recent studies suggest that CA activation may provide a novel therapy for Alzheimer's disease. Moreover, selectivity towards the different CAs isoforms is a valuable and challenging feature that should characterize the action of CAs inhibitors.

Primary sulphonamides, sulphamates and sulphamides act as carbonic anhydrase inhibitors (CAIs) by binding to the catalytic Zn²⁺ ion in the active site of the enzyme and blocking its function (4). We then designed and prepared a small family of new calixarenes functionalized with sulphonamide units (e.g. **1**) to be tested as inhibitor of the CAs activity. Differently to traditional drugs, calixarenes can be functionalized in several ways exposing active units, for instance pharmacophores, in multiple copies and different orientations in space. This feature allows to exploit the so called "multivalency effect" that can result in an affinity towards the biological target significantly higher with respect to analogous monomeric ligands. Usually, multivalent ligands as those based on calixarene scaffolds show the beneficial effects of multivalency in the binding to macromolecules presenting multiple copies of equivalent recognition sites (5). However, recently some attempts have been done to verify this effect in the inhibition of enzymes (6,7). The sulphonamido calixarenes have been tested towards six different CA isoforms (hCAI, hCAII, hCAIX, VchCA β , Can2, MgCA) and compared with two monomeric analogues and acetazolamide, a potent drug in clinical use known as CAs inhibitor. Interestingly, some of our derivatives have shown K_i values in the μ M-nM range. Synthesis of the ligands and inhibition studies will be described in this presentation.



References: 1. Supuran, C. T. *Biochem. J.* **2016**, *473*, 2023–2032. 2. Supuran, C. T. *Nature Rev.* **2008**, *7*, 168-181. 3. Neri, D.; Supuran, C. T. *Nature Rev. Drug Discov.* **2011**, *10*, 767-777. 4. Alterio, V.; Di Fiore, A.; D'Ambrosio, K.; Supuran, C. T.; De Simone, G. *Chem. Rev.* **2012**, *112*, 4421-44683. 5. Sansone, F.; Casnati, A. *Chem. Soc. Rev.* **2013**, *42*, 4623-4639. 6. Rísquez, R. C.; Garcia Fernandez, M. J.; Nierengarten, J. F.; Ortiz-Mellet, C. *Chem. Eur. J.* **2013**, *19*, 16791–16803. 7. Abellán-Flos, M.; Tanç, M.; Supuran, C. T.; Vincent, S. *Org. Biomol. Chem.* **2015**, *13*, 7445-7451.

How the ring size and the side chains affect the solid state assembly of cyclopeptoids.

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The design of novel supramolecular architectures represents an area of growing interest that involves various fields of research such as biochemistry, crystal engineering, material science. Macrocycles are potentially applicable in different areas of nanoscience. A new class of macrocyclic systems is constituted by cyclopeptoids, cyclooligomers of *N*-alkyl glycines. Recently we have highlighted the role of the side chains (1) and of ring size (2) in the solid state assembly and how these strongly affects specific interactions in supramolecular architectures. For example the cyclohexapeptoid containing propargylic side chains shows a layered architecture while the cyclooctapeptoid possesses a tubular structure (figure 1). The combination of propargyl and methoxyethyl side chains in a cyclohexapeptoid provided a tubular solid state assembly, that undergoes a reversible single-crystal-to-single-crystal transformation upon guest release/uptake (figure 2). The transformation is connected to the formation of an unprecedented “CH– π zipper”, which can reversibly open and close, allowing for guest sensing. (3) In this communication the synthesis and solid-state assembly of new cyclooctapeptoids decorated with methoxyethyl and propargyl side chains in different number and position along the peptoid skeleton will be discussed (figure 3).

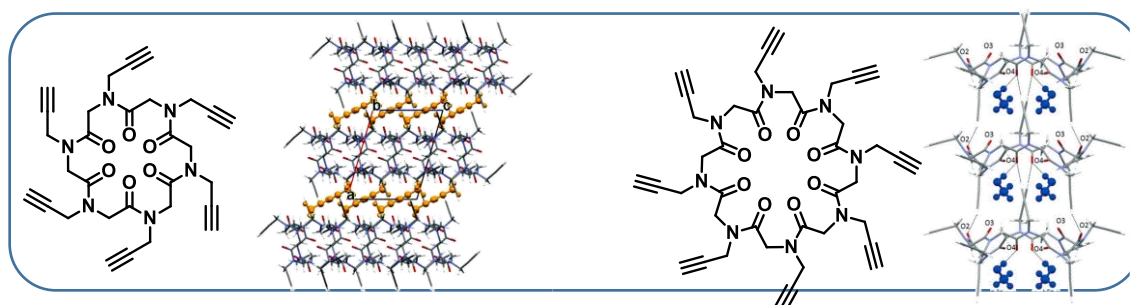


Figure 1. Cyclohexapeptoid: columnar assembly versus Cyclooctapeptoid: tubular structure.

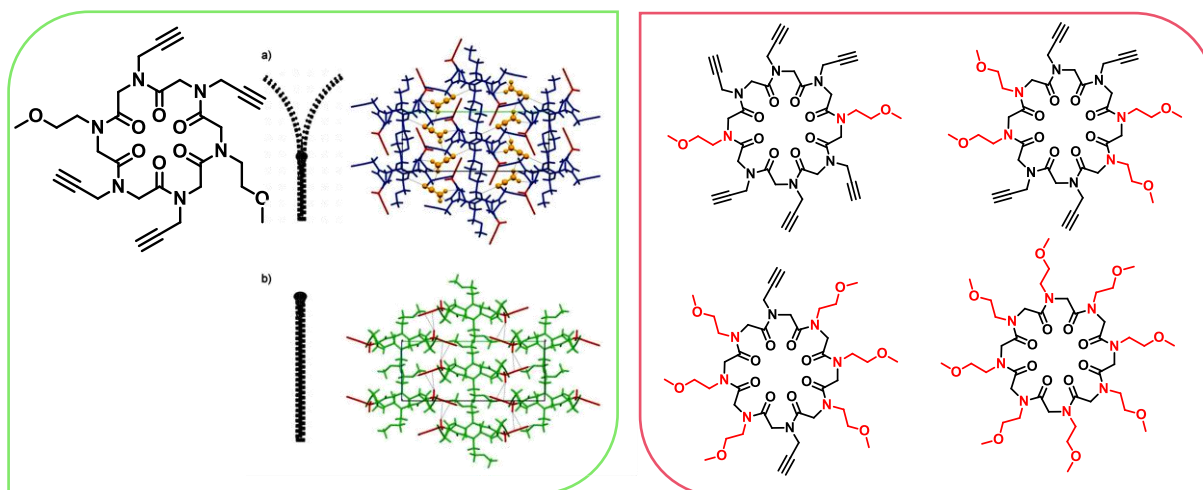


Figure 2. Cyclohexapeptoid: flexible conformation.

Figure 3. Novel Cyclooctapeptoids.

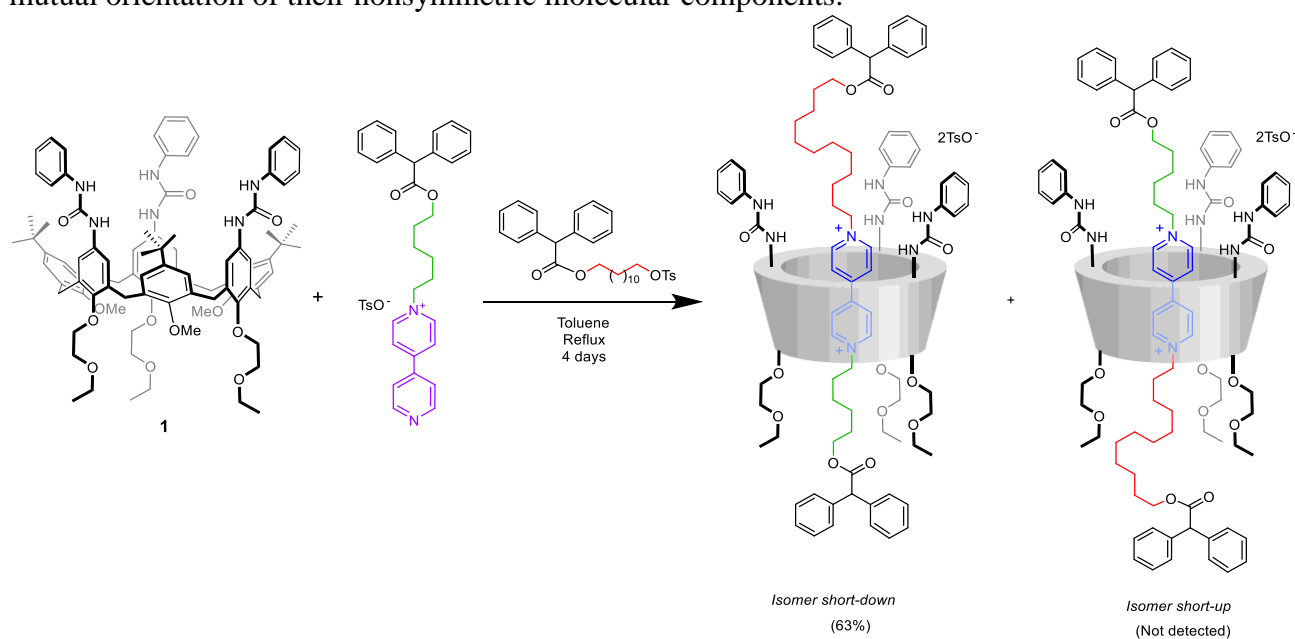
1. C. Tedesco, L. Erra, I. Izzo, F. De Riccardis, *CrystEngComm*, **2014**, *16*, 3667–3687. 2. C. Tedesco, A. Meli, E. Macedi, V. Iuliano, A. G. Ricciardulli, F. De Riccardis, G. B. M. Vaughan, V. J. Smith, L. J. Barbour, I. Izzo, *CrystEngComm*, **2016**, *18*, 8838–8848. 3. A. Meli, E. Macedi, F. De Riccardis, V. J. Smith, L. J. Barbour, I. Izzo, C. Tedesco, *Angew. Chem. Int. Ed.*, **2016**, *55*, 4679–4682.

Efficient Supramolecularly-Assisted Synthesis of Calix[6]Arene-based Oriented Pseudorotaxanes and Rotaxanes

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A substrate can modify its chemical features, up to a change of its reactivity, as a consequence of non-covalent interactions upon inclusion within a molecular host.(1,2) Since the rise of supramolecular chemistry, this phenomenon has stimulated the ingenuity of scientists to emulate the function of enzymes by designing supramolecular systems in which the energetics and selectivity of reactions can be manipulated through programmed host-guest interactions and/or steric confinement. In this paper we investigate how the engulfment of a positively charged pyridinium-based guest inside the π -rich cavity of a tris-(*N*-phenylureido)calix[6]arene host (3) affects its reactivity towards a S_N2 reaction. We found that the alkylation of the complexed substrates leads to the formation of pseudorotaxanes and rotaxanes with faster kinetics and higher yields with respect to the standard procedures exploited so far.(4) 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.



- (1) M. Raynal, P. Ballester, A. Vidal-Ferran and P. W. N. M. van Leeuwen, *Chem. Soc. Rev.*, 2014, **43**, 1660–1733.
 (2) M. Raynal, P. Ballester, A. Vidal-Ferran and P. W. N. M. van Leeuwen, *Chem. Soc. Rev.*, 2014, **43**, 1734–1787.
 (3) A. Arduini, G. Orlandini, A. Secchi, A. Credi, S. Silvi and M. Venturi, in *Calixarenes and Beyond*, eds. P. Neri, J. L. Sessler and M.-X. Wang, Springer International Publishing, Cham, 2016, pp. 761–781.
 (4) G. Orlandini, G. Ragazzon, V. Zanichelli, A. Secchi, S. Silvi, M. Venturi, A. Arduini and A. Credi, *Chem. Commun.*, 2017, **53**, 6172–6174.

Deep Eutectic Solvents as convenient media for the synthesis of gold and platinum nanoparticles

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Deep Eutectic Solvents (DESs) are a new class of solvents which have been developed as alternative to ionic liquids (ILs) to overcome IL toxicity, poor biodegradability and their not environmentally friendly synthesis.⁽¹⁾ Even if DESs share with ILs many physicochemical features such as density, viscosity, low vapor pressure and non flammability, they chemically differ from ILs as they can be obtained also by non ionic species. Indeed DES are formed by simply mixing two components, at least an hydrogen bond donor and a hydrogen bond acceptor, resulting in an eutectic mixture with a melting point lower than those of the pure substances.⁽²⁾ The advantages of DES over ILs are their ease of synthesis, low production costs and the fact that they can be obtained from biodegradable and biocompatible components, fulfilling the green chemistry principles. DESs have been successfully used as alternative media to organic solvents in many fields⁽³⁾ such as gas adsorption, biotransformations, metal processing, organic synthesis, metal nanoparticle synthesis.

Metal nanoparticles (MNPs), in particular those belonging to the noble metal group, such as gold and platinum, are very attractive functional materials due to their peculiar properties that can be potentially useful in a wide range of applications. AuNPs and PtNPs are emerging as important tools in electronics, optics, catalysis, clinical diagnostic and biomedicine.⁽⁴⁾ It is noteworthy that their electric, optical, magnetic and catalytic properties are strongly dependent on size and shape therefore the development of an efficient, eco-sustainable and shape/size controlling synthesis constitutes a very primary challenge.

The present communication describes the synthesis of AuNPs and PtNPs in three different DESs used as the solvent. In the studied DESs, the HBA component was the betaine N,N,N-trimethylglycine and the HBD counterpart was glycolic acid or phenylacetic acid or oxalic acid.⁽⁵⁾ The synthesis was performed in the presence and in the absence of a reducing agent (NaBH₄ or ascorbic acid). The growth and the time-dependent stability of NPs were followed by UV-Vis measurements. Transmission electron microscopy (TEM) was used to determine NP size and shape. TEM micrographs revealed distinct and well separated particles of shape and average size depending on the synthetic protocol and on the particular medium.

1. M. Francisco, A. van den Bruinhorst, M.C. Kroon *Angew. Chem., Int. Ed.* **2013**, 52, 3074-3085
2. A.P. Abbott, D. Boothby, G. Capper, D.L. Davies, R.K. Rasheed *J. Am. Chem. Soc.* **2004**, 126, 9142-9147
3. E.L. Smith, A.P. Abbott, K.S. Ryder *Chem. Rev.* **2014**, 114, 11060-11082
4. Y-C. Yeh, B. Creran, V.M. Rotello *Nanoscale* **2012**, 4, 1871-1880 ; A.L. Stepanov, A.N. Golubev, S.I. Nikitin, Y.N. Osin *Rev. Adv. Mater. Sci.* **2014**, 38, 160-175
5. F. Cardellini, M. Tiecco, R. Germani, G. Cardinali, L. Corte, L. Roscini, N. Spreti *RSC Adv.* **2014**, 4 (99), 55990-56002

Enantioselective phase transfer catalyzed alkylation of phthalide-3-carboxylic esters

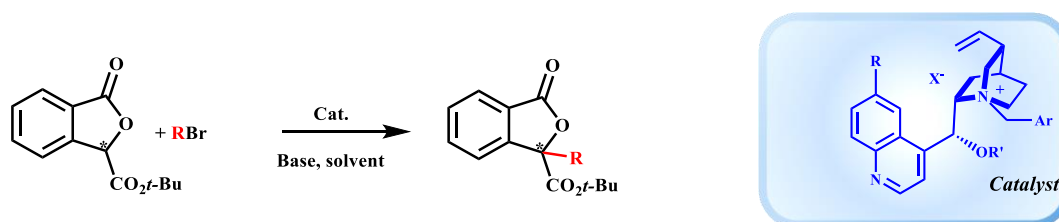
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Isobenzofuran-1(3*H*)-ones, also known as phthalides, are aromatic heterocycles of considerable synthetic interest for organic chemists since they are widely present in many natural products and therapeutically useful agents. More than 180 phthalide compounds have been identified from plants, fungi and bacteria displaying a broad range of pharmacological activities (1).

Furthermore, they are useful intermediates for the synthesis of biologically active compounds. Significant efforts have been focused on synthesizing functionalized phthalides. In particular, phthalides bearing a quaternary stereocenter at C-3 are important derivatives. Most of the synthetic stereoselective strategies involve the construction of the lactone ring (2), while the stereoselective introduction of a group on C-3 has been much less investigated. Organocatalyzed Mannich reaction, Michael addition and alkylation with Morita-Baylis-Hillman carbonates has been described in literature (3-5), but alkylation under phase transfer catalysis has never reported to date.

Here we describe our preliminary results in the first enantioselective alkylation of phthalide-3-carboxylic esters promoted by cinchona alkaloid-derived and binaphthyl-derived quaternary ammonium salts (Scheme 1).



Scheme 1.

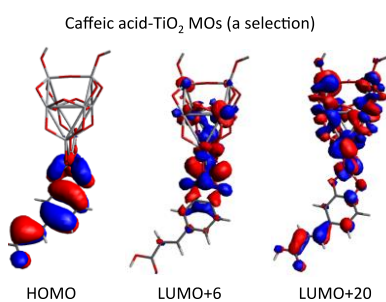
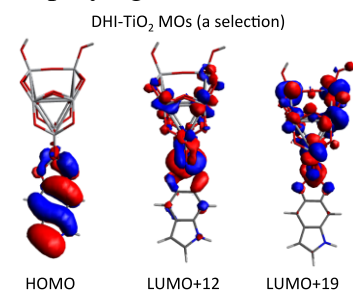
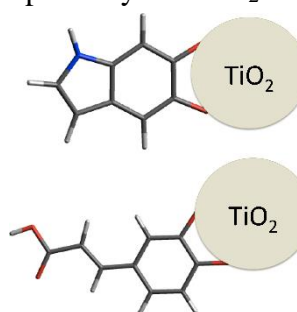
1. Lin, G.; Chan, S. S.-K.; Chung, H.-S.; Li, L. S. In *Studies in Natural Products Chemistry: Bioactive Natural Products*, Vol. 32 (Part L); Atta-ur-Rahman, Ed.; Elsevier, Amsterdam, 2005; pp. 611-669.
2. Karmakar, R.; Pahari, P.; Mal, D. *Chem. Rev.* **2014**, *114*, 6213–6284.
3. Luo, J.; Jiang, C.; Wang, H.; Xu, L.W.; Lu, Y. *Tetrahedron Lett.* **2013**, *54*, 5261–5265.
4. Luo, J.; Wang, H.; Zhong, F.; Kwiatkowski, J.; Xu, L. W.; Lu, Y. *Chem. Commun.* **2012**, *48*, 4707.
5. Zhong, F.; Luo, J.; Chen, G. Y.; Dou, X.; Lu, Y. *J. Am. Chem. Soc.* **2012**, *134*, 10222–10227.

Modeling of 5,6-dihydroxyindole and caffeic acid on TiO₂: direct electron injection in Dye-Sensitized Solar Cells

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Catechol-based sensitizers have been indicated as light-harvesting molecules for Dye-Sensitized Solar Cells (DSSC). Upon binding TiO₂ they exhibit broad photoabsorption dye-to-TiO₂ charge transfer (DTCT) bands, in the longer wavelength region, whose photoexcitation leads to a direct electron injection in the TiO₂ semiconductor (1,2). In order to identify novel sensitizers for DSSC employing such a direct mechanism, we model the electron injection mechanism of 5,6-dihydroxyindole (DHI) and caffeic acid on (TiO₂)₉ using density functional theory (DFT) methods. The calculation of excitation energies at the time-dependent DFT



level show that for both sensitizer/TiO₂ systems it is possible to identify a broad DTCT band along with the absorption of the isolated chromophore. The inspection of the wavefunction plots of the molecular orbitals reveals that the transitions governing the DTCT excitation include the HOMO, localized on the sensitizer, and several unoccupied orbitals whose electron density is mainly localized on the TiO₂ cluster with a non-negligible contribution on the TiO₂-bonding oxygens of the sensitizers. These features indicate a strong electronic coupling for both TiO₂-absorbed sensitizers, which is in favor of a direct mechanism of injection. The strong coupling is also confirmed by a Density of States (DOS) and partial DOS analysis. In conclusion, our results strongly suggest that a direct electron transfer mechanism applies for both DHI and caffeic acid when adsorbed on TiO₂ and used as sensitizers for DSSC.

References:

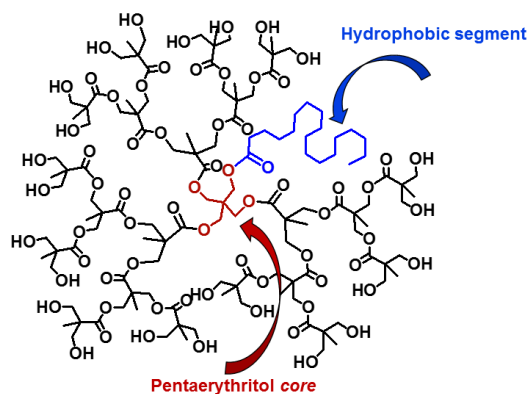
1. Y. Ooyama, M. Kanda, K. Uenaka and J. Ohshita, *ChemPhysChem*, 2015, 16, 3049–3057.
2. R. Sánchez-de-Armas, M.A. San-Miguel, J. Oviedo, J. Fdez. Sanz, *Computational and Theoretical Chemistry*, 2011, 975, 99–105.

Synthesis of a new dendritic anfiphilic polyester with pentaerythritol *core* and a multifunctional periphery for linking amino acids and for using in gene therapy

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Dendrimers are synthetic polymers characterized by tree-like branched symmetric structure, globular shape, low polydispersity and several functions at the periphery which allow further functionalization. Their cavities can accommodate small drugs molecules protecting them from premature degradation, increasing their solubility in biological fluids, decreasing their toxicity and favoring their bioavailability. Dendrimers containing protonable nitrogen atoms can electrostatically bind nucleic acids. These reasons make dendrimers appealing materials for various biomedical applications such as drug or gene delivery non viral carriers, biosensors, bioimaging agents and theranostics. Well known polymeric systems such as *bPEI* or *PAMAM* are among the most investigated synthetic vectors with efficient transfection activity but also affected by high cytotoxicity so chemical modifications are required to reduce these drawbacks and allow a real use in gene therapy. It is known that amino acids (1, 2, 3) or peptides (4) were often used for these purposes and arginine is known to improve *siRNA* cellular uptake (5), efficiency of transfection and to reduce toxicity (6, 7). Hydrophobic segments in the dendrimer structure are also important in the internalization process (3) and may contribute to reduce toxicity caused by high ionic character of vectors. Looking at this background in this communication we report the step-wise protocol and NMR characterization of a new hydrolysable polyester-based dendrimer of third generation built on pentaerythritol as *core* and with a C-18 saturated alkyl chain as hydrophobic segment.



The peripheral 24 OH groups make this anfiphilic dendritic structure fit to the esterification with selected amino acids for obtaining polycationic non viral vectors to use in gene delivery.

References: 1. Navath, R. S.; Menjoge, A. R.; Wang, B.; Romero, R.; Kannan, S.; Kannan, R. M. *Biomacromolecules* **2010**, *11*, 1544-1536. 2. Park, J.; Park, H.; Park, J-S.; Choi, J. S. *Macromol. Res.* **2014**, *22*, 500-508. 3. Wang, F.; Wang, Y.; Wang, H.; Shao, N.; Chen, Y.; Cheng, Y. *Biomaterials* **2014**, *35*, 9187-9198. 4. Lam, S. J.; Sulistio, A.; Ladewig, K.; Wong, E. H. H.; Blencowe, A.; Qiao, G. G. *Austr. J. Chem.* **2014**, *67*, 592-597. 5. Liu, X.; Liu, C.; Zhou, J.; Chen, C.; Qu, F.; Rossi, J. J.; Rocchi, P.; Peng L. *Nanoscale* **2015**, *7*, 3867-3875. 6. Kim, T.; Bai, C. Z.; Nam, K.; Park, J. J. *Control. Release* **2009**, *136*, 132-139. 7. Peng, Q.; Zhu, J.; Yu, Y.; Hoffman, L.; Yang, X. *J. Biomater. Sci. Polym. Ed.* **2015**, *26*, 1163-1177.

Discovery of Potential Small Molecule Modulators of Macrodomain Proteins

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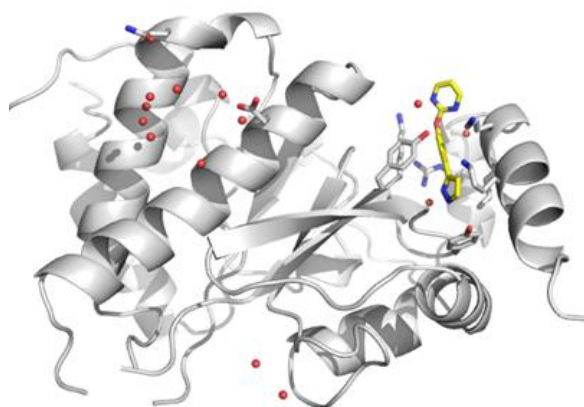
Macrodomains are a family of evolutionarily conserved proteins able to recognize ADP-ribosylation, an important reversible post-translational modification involved in many biological functions, including regulation of chromatin structure, transcription, DNA repair, cell differentiation and proliferation.¹ In humans, there are at least 10 members classified in four groups, however all their functions are not yet fully clarified.

Among these, the MacroD1, MacroD2, and C6orf130 have recently been shown to act as epigenetic erasers as they are able to remove ADP-ribose from mono-ADP-ribosylated substrates.^{2,3}

Despite the exact biological roles of MacroD1 and MacroD2 are not yet known, recent findings suggest that the dysregulation or mutation of macrodomains might be related to several human diseases, including cancer and neurodegeneration. Furthermore, MacroD1 and MacroD2 overexpression is observed in endometrial, gastric and breast carcinoma and is linked to cancer progression and cell invasiveness in tissue cultures.⁴

In this context, macrodomain proteins can be considered strategic targets for the identification of new promising anticancer agents.

Based on these premises, using different drug discovery approaches we evaluated both commercially available fragments and synthetically accessible small molecules in order to identify new chemical entities able to interact with the macrodomain-containing proteins as novel and appealing chemotherapeutics.



References: 1. Li, N.; Chen, *J. Mol. Cells* **2014**, 37, 9-16. 2. Dawei, C. et al. *J. Biol. Chem* **2011**, 286, 13261-13271. 3. Rosental F. et al. *Nat. Struct. Mol. Biol.* **2013**, 20, 502-509. 4. W. Han et al. *Mutation Research* **2011**, 727, 86-103.

Photochemical trifluoromethylation of aromatics by *N*-aryltrifluoromethanesulfonimides

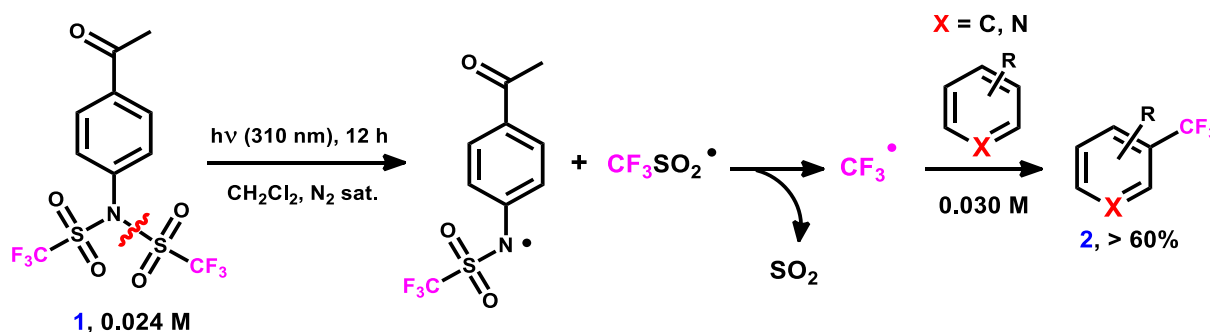
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Fluorine is a very popular element in lead optimization for drug discovery. Indeed, its presence in the structure of drug candidates can improve their metabolic stability, membrane permeability and bioactivity, thus enhancing their pharmacological properties.(1) Among fluorinated drugs, a great number is given by aromatics bearing a trifluoromethyl group (e.g. Fluoxetine, Leflunomide, Nilutamide, etc.). For this reason, much efforts are done to find synthetic ways to incorporate the trifluoromethyl group onto aromatic rings and researchers mainly focus their research on the formation of the Ar-CF₃ bond making use of transition metal catalysis.(2) A greener and more convenient strategy relies on radical trifluoromethylation by photoredox catalysis (3) albeit expensive catalysts and reagents are usually employed.

Herein we present a simple and clean photochemical trifluoromethylation of aromatic compounds using cheap *N*-aryltrifluoromethanesulfonimides as trifluoromethylating agents.

As an example, *N*-(4-acetylphenyl)-1,1,1-trifluoro-*N*-[(trifluoromethyl)sulfonyl]methanesulfonamide **1** was irradiated (310 nm) in deaerated dichloromethane in the presence of aromatic and heteroaromatic compounds until total conversion of **1** is reached, giving trifluoromethylated derivatives **2**. A reasonable mechanism for the reaction involves a photoinduced homolysis of a N-S bond in compound **1** to afford a trifluoromethanesulfonyl radical readily prone to release SO₂ thus forming a trifluoromethyl radical.(4) The latter species then reacts with aromatic rings to give eventually compound **2**. Noteworthy, each of the two N-S bond may be sequentially broken during irradiation, thus improving the overall performance of the trifluoromethylation. In selected cases, the reaction can be likewise repeated with similar (or better) results upon sunlight exposition as well as by using a continuous flow apparatus. These protocols may open the ways to “window-ledge” reactions on laboratory scale as well as flow trifluoromethylations of bulk chemicals.



References: 1. C. Alonso, E. Martínez de Marigorta, G. Rubiales, F. Palacios, *Chem. Rev.*, **2015**, *115*, 1847-1935. 2. O. A. Tomashenko, V. V. Grushin, *Chem. Rev.*, **2011**, *111*, 4475-4521. 3. S. Barata-Vallejo, S. M. Bonesi, A. Postigo, *Org. Biomol. Chem.*, **2015**, *13*, 11153-11183. 4. E. Torti, S. Protti, D. Merli, D. Dondi, M. Fagnoni, *Chem. Eur. J.*, **2016**, *22*, 16998-17005.

Expanding the synthetic utility of the electrophilic N-transfer to the sulfur atom

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Recently we developed straightforward strategies for the preparation of NH-sulfoximines.^(1,2,3) Our strategy holds on a direct N-transfer to sulfoxides and a simultaneous NH- and O-transfer to sulfides. With the aim of expanding N-transfer to other sulfur compounds, we investigated the reactions of thiols and sulfinamides to synthesize respectively sulfonimidates and sulfonimidamides. Literature reports that these compounds need a multistep strategy or different starting materials.^(4,5) The new strategy is carried out by using bisacetoxyiodobenzene as oxidant and several N-sources, such as NH₂COONH₄, AcONH₄ and NH₃. This versatile protocol could give access to useful compounds in drug discovery programs.⁽⁶⁾

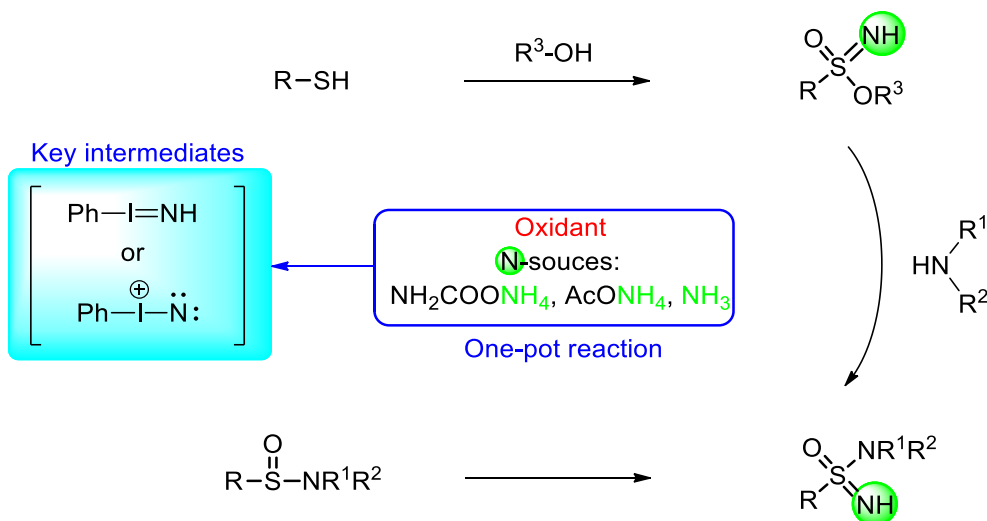


Figure 1. Strategy for synthesis of sulfonimidates and sulfonimidamides by NH-transfer

References:

1. M. Zenzola, R. Doran, L. Degennaro, R. Luisi, J. A. Bull. *Angew. Chem. Int. Ed.* 2016, 55, 7203-7207.
2. A. Tota, M. Zenzola, S. J. Chawner, S. St. John-Campbell, C. Carlucci, G. Romanazzi, L. Degennaro, J. A. Bull, R. Luisi, *Chem. Commun.* 2017, 53, 348-351.
3. M. Zenzola, R. Doran, R. Luisi, J. A. Bull, *J. Org. Chem.*, **2015**, 80 (12), pp 6391-6399.
4. D. Leca, L. Fensterbank, E. Lacote, M. Malacria, *Org. Lett.* 2002, 4 (23), 4093-4095.
5. O. Garcia Macheno, C. Bolm. *Beilstein J. Org. Chem.* 2007, 3 (25).
6. PK. Chinthakindi, T. Naicker, T. Govender, HG. Kruger, PI. Arvidsson, *Angew. Chem. Int. Ed. Engl.* 2017, 56 (15), 4100-4109.

Synthesis of dendrons and dendrimers glycoconjugates for biomedical applications

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Dendrimers are nano-sized macromolecules, featured with a hyperbranched structure displaying a high number of functional groups on its surface, which can be exploited for further derivatisation with different kind of (bio)molecules. Given their peculiar structure and properties, dendrimers have been proposed for a variety of biomedical applications (ⁱ,ⁱⁱ). Interactions between cells and their environments are mediated by protein-carbohydrate recognition processes on cell surface, triggering a wide variety of biological events. In this context, highly branched glycosylated structures may be interesting tools to enhance these recognition events, helping in elucidating the biological role behind carbohydrate as signaling molecules, which mediate aspects of the immune response and of cellular recognition and adhesion (e.g. through their interactions with lectins) or acting as antagonist of important recognition events (i.e. involving viruses or bacteria) (ⁱⁱⁱ). In this work, we present the synthesis of a novel hyperbranched monodisperse linear glycodendrimer, based on 2,2-bis-(hydroxymethyl)-propionic acid (bis-MPA) by convergent metathesis-mediated coupling between the alkene-terminated focal point of bis-MPA dendrons, which terminal ends expose multiple aminoxy groups that has been exploited for glycoconjugation with unprotected sugars. To the best of our knowledge, this is the first example of the use of metathesis for focal point coupling and, as carbohydrates are known to be fundamental biomolecules for cellular signaling, these hyperbranched glycodendrimers may provide good benefit to biomedical and tissue engineering applications, where high density of ligand exposure and spatial topographical presentation are crucial to bring about desired biological effects (^{iv},^v). Dendrimers synthesis started from a bivalent, tetravalent and octavalent dendron monomers with a *core* double bond and Boc-protected aminoxy ends and achieves symmetrical dendrimers, doubling the branching degree of each structure by a single-step metathesis reaction with Hoveyda–Grubbs^{2nd} generation catalyst. Deprotected aminoxy ends of the obtained symmetrical dendrimers were then reacted with maltose, as sample saccharide, yielding glycodendrimers exposing multiple sugar moieties at their ends. These hyperbranched structures are potentially capable of eliciting a biological response in a biomedical context, as the exposed α -glucoside epitopes are known to be fundamental signaling moieties in a variety of biochemical interactions (^{vi},^{vii}).

ⁱ L. Wu, M. Ficker, J. B. Christensen, P.N. Trohopoulos and S. M. Moghimi. *Bioconj. Chem.* **2015**, 26, 1198–1211. DOI: 10.1021/acs.bioconjchem.5b00031

ⁱⁱ A. Mintzer and M. W. Grinstaff. *Chem. Soc. Rev.* **2011**, 40, 173–190. DOI: 10.1039/b901839p

ⁱⁱⁱ X. Dan, W. Liu, T. B. Ng. *Med. Res. Rev.* **2016**, 36(2), 221–47. DOI: 10.1002/med.21363

^{iv} Y. Vida, D. Collado, F. Najera, S. Claros, J. Becerra, J. A. Andrades, E. Perez-Inestrosa, *RSC Adv.*, **2016**, 6(55), 49839–49844. DOI: 10.1039/C6RA06177J

^v Y. M. Chabre and R. Roy. *Chem. Soc. Rev.*, **2013**, 42, 4657–4708. DOI:10.1039/C3CS35483K

^{vi} H. Ghazarian, B. Itoni, S.B. Oppenheimer. *Acta histochem.* **2011**, 113(3), 236–247. DOI:10.1016/j.acthis.2010.02.004

^{vii} J. P. Ribeiro, T. Diercks, J. Jiménez-Barbero, S. André, H.J. Gabius. *Biomol.* **2015**, 5(4), 3177–3192. DOI:10.3390/biom5043177

Studies of Electronic Properties of KuQuinones

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Few years ago we developed a new one-pot synthesis for highly conjugated pentacyclic compounds, called KuQuinones (KuQs) (1). The general synthetic procedure allowed us to prepare a small library of differently substituted KuQ derivatives. These compounds are characterized by a broad absorption spectrum in the visible region and a low reduction potential with respect to simpler quinoid compounds. In particular KuQs show three characteristic reduction processes, while no oxidation processes are observed. Due to these interesting properties, we explored the ability of KuQs to act as sensitive material in photoelectrochemical devices (2,3) obtaining interesting results.

In order to fully characterize active reduced species of KuQs we are currently investigating their nature through spectroelectrochemical measurements and DFT calculations. In this contribution, the preliminary characterization of KuQuinones anions we will be presented.

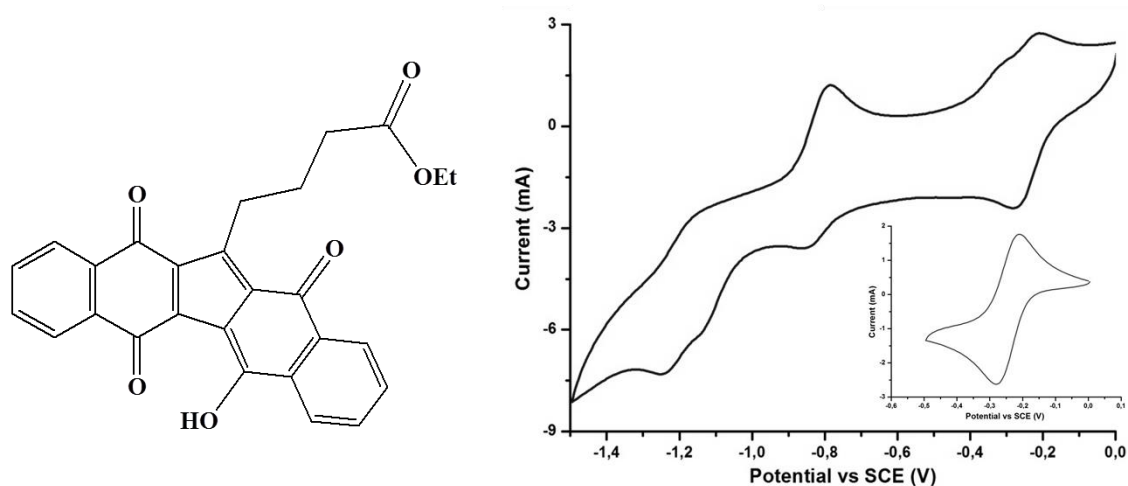


Figure 6 (left) Structure of a KuQ derivate. (right) Cyclic Voltammetry of 1-(3-Ethoxycarbonylpropyl)KuQuinone.

References:

1. Coletti, A.; Lentini, S.; Conte, V.; Floris, B.; Bortolini, B.; Sforza, F.; Grepioni, F.; Galloni, P. *J. Org. Chem.* **2012**, *77*, 6873-6879.
2. Sabuzi, F.; Armuzza, V.; Conte, V.; Floris, B.; Venanzi, M.; Galloni, P.; Gatto, E. *J. Mater. Chem. C*, **2016**, *4*, 622.
3. Bonomo, M.; Sabuzi, F.; Di Carlo, A.; Conte, V.; Dini, D.; Galloni, P. *New J. Chem.* **2017**, *41*, 2769-2779.

Monomolecular G-quadruplex structures with inversion of polarity sites: new topologies and potentiality

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G-quadruplex structures are secondary conformations of nucleic acids whose constitutive unit is the G-tetrad or G-quartet (1). This building block consists of a square planar arrangement of four guanosines in which each base is associated to the adjacent ones through four hydrogen bonds. Stacking of two or more G-tetrad units can form larger and more stable structures. Soon after they were discovered, these structures were subject to several chemical modifications and conjugation with the aim to promote, stabilize and investigate a particular conformation, improve their properties and encourage the formation of high-order structures (2). Among the sugar-phosphate backbone modifications, the introduction of 3'-3' and/or 5'-5' inversion of polarity sites (IPS) represents an almost “natural” and less heavy chemical structural change, since it involves only naturally occurring deoxyribonucleotides (3). In order to expand the structural variability and the topological repertoire of the G-quadruplex structures by exploiting the presence of IPSs, we designed and synthesized three oligonucleotide sequences, each containing one 3'-3' and two 5'-5' inversion of polarity sites, and four G-runs with a variable number of residues, namely two, three and four (**mTG₂T**, **mTG₃T** and **mTG₄T** with sequence 3'-TG_nT-5'-5'-TG_nT-3'-3'-TG_nT-5'-5'-TG_nT-3' in which n = 2, 3 and 4, respectively). These oligonucleotides have been investigated by circular dichroism, nuclear magnetic resonance spectroscopy and electrophoresis methods, comparing them with their canonical counterparts (TG_nT)₄ (n = 2, 3 and 4). Oligonucleotides **mTG₃T** and **mTG₄T** have been proven to form very stable unprecedented monomolecular parallel G-quadruplex structures, characterized by three side loops containing the inversion of polarity sites. Both G-quadruplexes have shown an all-*syn* G-tetrad, while the other guanosines adopt *anti* glycosidic conformations. All oligonucleotides investigated have shown a noteworthy antiproliferative activity against lung cancer cell line Calu 6 and colorectal cancer cell line HCT-116^{p53^{-/-}}. Interestingly, **mTG₃T** and **mTG₄T** have proven to be mostly resistant to nucleases in a fetal bovine serum assay. The whole of the data suggest the involvement of specific pathways and targets for the biological activity.

References:

1. Neidle, S. and Balasubramanian, S. (2006) *Quadruplex nucleic acids*. RSC Publishing, London.
2. Sagi, J. (2014) G-quadruplexes incorporating modified constituents: a review. *J. Biomol. Struct. Dyn.*, **32**, 477–511.
3. Virgilio, A., Esposito, V., Filosa, R., Mayol, L. and Galeone, A. (2016) The introduction of inversion of polarity sites in DNA G-quadruplex structures: Effects and perspectives. *Mini-Reviews Med. Chem.*, **16**, 509–523.

A Trifunctional Calix[4]arene as Mimic of DNA Topoisomerase I for the Promotion of Phosphoryl Transfer Processes

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The cone-calix[4]arene scaffold has been reported as a convenient platform for the creation, after an appropriate functionalization, of artificial catalysts able to mimic the action phosphodiesterase enzymes (1).

In this poster will be presented the trifunctional calix[4]arene ($1H_3$)²⁺ (2), functionalized at the upper rim two guanidinium units and a phenolic hydroxyl group in order to reproduce the catalytic triad at the active site of human DNA topoisomerase I (3).

The diprotonated form of the catalyst ($1H_2$)⁺ was tested in the cleavage of the DNA model compound bis(p-nitrophenyl) phosphate (BNPP) in 80% DMSO solution, enhancing the p-nitrophenol liberation rate up to 6.5×10^4 -folds respect to the background hydrolysis at pH 9.5.

According to the experimental data, the three active units cooperate to cleave the substrate in a two-step reaction sequence (**Figure 1**) that involves a phosphoryl transfer process from BNPP to the nucleophilic phenolate moiety of ($1H_2$)⁺, followed by the liberation of a second equivalent of p-nitrophenol from the phosphorylated intermediate, assisted by the neighboring guanidine/guanidinium catalytic dyad.

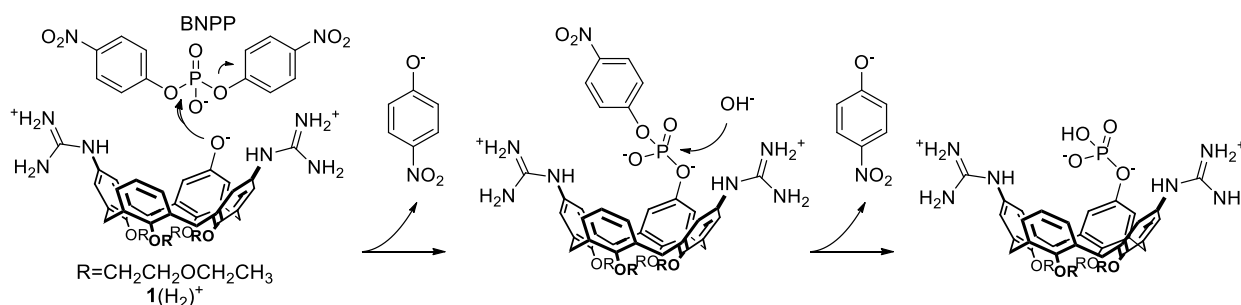


Figure 1: Proposed mechanism for the cleavage of BNPP by ($1H_2$)⁺.

References: 1. M. Giuliani, I. Morbioli, F. Sansone and A. Casnati, *Chem. Commun.* 51 (2015), 14140–14159. 2. R. Salvio, S. Volpi, R. Cacciapaglia, F. Sansone, L. Mandolini, A. Casnati, *J. Org. Chem.* 2016, 81, 9012. 3. M. R. Redinbo, L. Stewart, P. Kuhn, J. J. Champoux, and W. G. J. Hol, *Science* 279 (1998), 1504–1513.

The CeCl₃ Lewis Acid Promoter in the Stereoselective Construction of Carbon-Carbon Double Bonds

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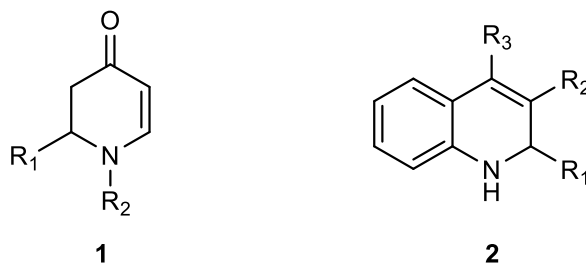
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The presence of a C-C double bond in polyfunctionalized organic molecules is a crucial requirement for the control of its biological activity.(1) The importance of having a site in the molecule that is able to generate geometrical isomerization of a carbon-carbon double bond stimulated the development of new olefination methodologies. In particular, some efforts focused on the ability of Lewis acids to provide a cheap alternative for the synthesis of molecules with C-C double bond in a highly stereoselective fashion.

For several years, we have been investigating CeCl₃ promoted organic reactions. This Lewis acid has been found to efficiently promote carbon-carbon (2) and carbon-heteroatom bond formation reactions.(3) In addition to being green in nature (4), CeCl₃ has been widely used for both inter- and intramolecular reactions for the synthesis of organic molecules with significant biological importance.

Regarding the total synthesis of biologically active small molecules containing a carbon-carbon double bond, we saw the possibility to employ CeCl₃ in the stereoselective construction of 2,3-dihydropyridones **1**,(5) and 1,2-dihydroquinolines **2**.(6)



The additional advantage of using CeCl₃ in a reaction includes its selectivity and tolerance in the presence of other functional groups. For instance, it can be used during the functionalization of molecules at late stage involving complex molecules or undesirable use of protecting groups. Introduction of C-C double bonds, which are known to increase the activity in macrolides against bacterial RNA polymerase, is currently in progress in our laboratory.

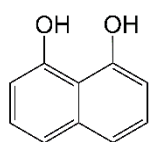
References: **1.** Shen, X.; Nguyen, T. T.; Koh, M. J.; Xu, D.; Speed, A. W.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *541*, 380-385. **2.** Bartoli, G.; Marcolin, M.; Sambri, L.; Marcantoni, E. *Chem. Rev.* **2010**, *110*, 6104-6143. **3.** Properzi, R.; Marcantoni, E. *Chem. Soc. Rev.* **2014**, *43*, 779-791. **4.** Cimarelli, C.; Di Nicola, M.; Diomedi, S.; Giovannini, R.; Hanprecht, D.; Properzi, R.; Sorana, F.; Marcantoni, E. *Org. Biomol. Chem.* **2015**, *13*, 11687-11695. **5.** Bordi, S.; Cimarelli, C.; Lupidi, G.; Marsili, L.; Piermattei, P.; Marcantoni, E. *J. Org. Chem.* **2017**, in preparation. **6.** Cimarelli, C.; Bordi, S.; Piermattei, P.; Pellei, M.; Del Bello, F.; Marcantoni, E. *Tetrahedron* **2017**, submitted.

Oxidative polymerization of hydroxylated naphthalenes: Modeling free radical pathways of polycyclic aromatic hydrocarbons (PAHs) of astrochemical relevance.

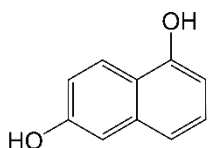
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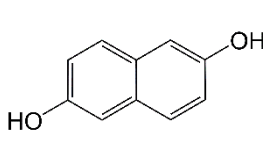
Polycyclic aromatic hydrocarbons (PAHs), which are widely diffused in the interstellar medium (ISM) accounting for more than 20% of the carbon in the universe (1), attract growing interest as possible determinants of infrared emission features seen in different astrophysical environments (2). Dust grain chemistry could be pivotal for PAHs reprocessing, since icy matrixes can trap several astrochemically-relevant CHON-bearing molecules, and mineral catalysis could have played a significant role in prebiotic chemistry (3). Early experiments (4) showed that exposure of naphthalene, the simplest member of PAHs, to ultraviolet radiation in ice under astrophysically-relevant conditions leads to the generation of phenolic and quinone derivatives, allowing specific prediction of the existence and relative abundances of various oxidized naphthalenes in meteorites. The latter can undergo oxidative polymerization reactions via an interplay of competing free radical and quinone coupling pathways (5) accounting for evolution toward structurally diverse organic systems at high levels of complexity. Despite a broad and solid literature on the oxidative polymerization of monocyclic phenolic systems and their derivatives, there are still significant lacunae in the case of hydroxylated derivatives from PAHs. In this paper, we report a combined experimental and theoretical approach aimed at elucidating the mechanisms underlying the oxidative polymerization of 1-naphthol, 2-naphthol, 1,8-dihydroxynaphthalene, 1,6-dihydroxynaphthalene, and 2,6-dihydroxynaphthalene. Preliminarily, the oxidative chemistry of hydroxylated naphthalenes was investigated using an enzymatic system,



1,8-dihydroxynaphthalene



1,6-dihydroxynaphthalene



2,6-dihydroxynaphthalene

peroxidase/hydrogen peroxide, as well as alkaline autoxidation and ammonia-induced solid state polymerization (AISSP) on thin films. The polymers

thus obtained were characterized using mass spectrometry, electron paramagnetic resonance, UV visible spectroscopy and Diffuse Reflectance Infrared Fourier Transform Spectroscopy (DRIFTS). Main oligomeric intermediates were isolated and characterized and the underlying reactivity patterns were rationalized with the aid of DFT calculations. The results revealed marked differences in the oxidation chemistry and mode of coupling of the various derivatives which reflected the number, position and relative disposition of hydroxyl groups on the naphthalene systems. In further experiments, hydroxylated naphthalenes were adsorbed on various Martian soil analogs and exposed to UV radiation or to ammonia vapors (AISSP), and the species thus produced were compared with the reference polymers using various techniques, including mainly DRIFTS. Elucidation of this chemistry provides novel important insights into the mechanisms of processing of PAH in the ISM, a phenomenon of possible relevance to the origin and properties of complex organic matter in environments of astrochemical relevance.

References: 1. Sloan, G. C. *et al. Astrophys. J.* **513**, L65–L68 (1999). 2. Tielens, A. G. G. M. *Annu. Rev. Astron. Astrophys.* **46**, 289–337 (2008). 3. Draine, B. T. *Annu. Rev. Astron. Astrophys.* **41**, 241–289 (2003). 4. Bernstein, M. P., Dworkin, J. P., Sandford, S. A. & Allamandola, L. J. *Meteorit. Planet. Sci.* **36**, 351–358 (2001). 5. Kobayashi, S. & Higashimura, H. *Progress in Polymer Science (Oxford)* **28**, 1015–1048 (2003).

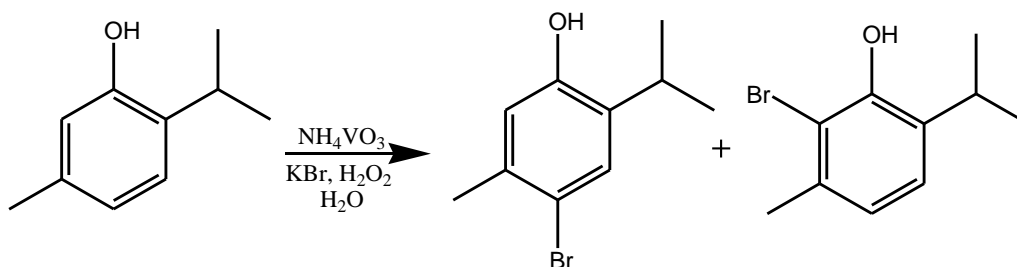
From lab to market: from the mimesis of ν -dependent haloperoxidase activity to the sustainable synthesis of new antimicrobial agents

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Recently, in our laboratories, we have developed a very simple and efficient system for the bromination of thymol, a natural compound extracted from *Thymus vulgaris* essential oils, that is one of the most used active ingredients in many products for personal and home-care. Following the bromination of thymol, 4-bromothymol was obtained as the main product (1).



The most relevant feature of such reaction is that it is carried out in water, in the absence of organic co-solvents and with economic, non-toxic and readily available reagents. These features make this process easily scalable at an industrial level since generally risks related to the scaling-up of laboratory processes are associated with the use of toxic and harmful reagents as well as flammable solvents.

In addition, biological tests have shown that 4-bromothymol has antibacterial and antifungal activity up to 15 times higher than thymol and lower toxicity (2).

Based on these results, we founded BT-InnoVaChem srl, a spin-off of the University of Rome Tor Vergata. The aim of this spin-off is to produce a new and effective antibacterial, antifungal and pesticide agent, i.e. 4-bromothymol, with an efficient, cheap and sustainable approach, in order to introduced it into the market of antimicrobial compounds.

In this communication, the transfer of results obtained in lab into a small business reality will be presented.

(1) Sabuzi, F., Churakova, E., Galloni, P., Wever, R., Hollmann, F., Floris, B., Conte, V., *Eur. J. Inorg. Chem.* **2015**, 3519.

(2) Galloni, P., Conte, V., Sabuzi, F., Thaller, M.C., Migliore, L., Matteucci, G., Italian Patent N. 102016000090701 (pending).

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Arosio Daniela	ORG PO33
Arrigo Rossella	ORG OR49
Arrigoni Federica	ORG PO16
Attolino Emanuele	ORG OR43
Badetti Elena	ORG OR64
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Baker Tom	ORG/INO OR04
Baldino Salvatore	ORG/INO OR03

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Baldoli Clara	ORG OR58
Ballini Roberto	ORG OR47
Balzano Federica	ORG OR13
Banfi Luca*	ORG OR30
	ORG PO04
Baratta Walter*	ORG/INO OR03
Baratta Walter	ORG/INO OR05
Barbero Nadia*	ORG OR24
Barbieri Alessia*	ORG PO05
Barolo Claudia	ORG OR24
Barone Vincenzo	ORG PO104
Barresi Vincenza	ORG OR41
Bartella Lucia*	ORG PO06
Barzon Luisa	ORG PO65
Baschieri Andrea	ORG/INO OR01
Basosi Riccardo	ORG PO94
Basso Andrea	ORG OR30
Battilocchio Claudio	ORG PO49
Battistini Lucia	ORG PO21
Beccalli Egle M.	ORG OR16
Becherini Stefano *	ORG PO07
Becherini Stefano	ORG OR26
Belli Valentina	ORG OR53
Bellina Fabio	ORG OR35
Bellini Marco*	ORG/INO PZ02
	ORG OR15
Belsito Emilia Lucia	ORG PO19
Beltrami Lorena	ORG OR42
Belvisi Laura	ORG PO33
Benedetti Fabio	ORG PO42
Beneduci Amerigo	ORG PO20
Bergamaschi Greta	ORG OR20
Bernardi Anna	ORG OR11
Bernardi Luca	ORG PO93
Bernini Roberta *	ORG PO08
	ORG PO23
Berti Federico	ORG PO42
Bertolini Giorgio *	ORG PZ02
Bertolini Giorgio	ORG OR45
Beverina Luca	ORG OR14
Bianchi Lara	ORG PO71
Bianchini Roberto	ORG PO13
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Bianco Armandodoriano*	ORG PO10
	ORG PO11
Biasolo Alessandra	ORG OR09
Bietti Massimo*	ORG PZ07
Bietti Massimo	ORG PO62

Biffi Stefania	ORG PO56
Bifulco Giuseppe	ORG OR51
	ORG OR52
	ORG PO41
	ORG PO43
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Billod Jean-Marc	ORG OR57
Biscaglia Francesca*	ORG OR09
Bizzarri Claudia	ORG/INO OR01
Bocchinfuso Gianfranco	ORG PO33
Boldrini Chiara Liliana*	ORG OR02
Bonaccorso Carmela	ORG OR41
Bonanni Marco	ORG PO13
Bonasera Aurelio*	ORG OR44
Bonchio Marcella	ORG/INO OR02
Boncompagni Simona	ORG PO92
Bonetti Andrea*	ORG PZ06
Bordi Samuele	ORG PO103
Bortolini Olga*	ORG PO12
Bossi Alberto	ORG PO15
Botta Bruno	ORG OR13
Botta Chiara	ORG PO45
Botticella Ermelinda	ORG PO08
Bourguet-Kondracki Marie-Lise	ORG OR37
Bovicelli Paolo	ORG OR61
Bozzano Andrea	ORG OR30
Bracci Luisa	ORG OR54
Brandolese Arianna	ORG PO12
Bravin Carlo	ORG OR64
Brazzo Paolo	ORG OR14
Broggini Gianluigi	ORG OR16
Brucato John R.	ORG PO104
Brunetti Jenia	ORG OR54
Bruno Giacomo	ORG OR45
Bruno Ines	ORG OR52
	ORG PO77
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	ORG PO96
Brusasca PierNatale	ORG PO50
Bua Silvia	ORG PO89
Buffagni Mirko	ORG OR04
Buiatti Luca	ORG PO42
Bull James A.	ORG PO98
Buscaino Roberto	ORG OR24
Cacciapaglia Roberta	ORG PO102
Cai Hui	ORG OR18
Calamante Massimo	ORG PO37
Calcinelli Fabio	ORG OR31
Calugi Lorenzo*	ORG PO13
Calvio Cinzia	ORG OR65
Campiglia Pietro	ORG OR52
Cantone Vincenza	ORG OR52
	ORG PO43

Capaccio Vito*	ORG PO14
Capaldo Luca	ORG MD03
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Capobianco Amedeo	ORG PO36
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Cappelletti Enrico	ORG OR42
Cappelli Andrea	ORG OR34
Cappellini Daniele	ORG PO50
Cappello Valentina	ORG PO07
Capriati Vito	ORG PO39
	ORG PO74
Carassiti Alessandra	ORG PO11
Cariati Elena	ORG PO45
Carlo Lucarelli	ORG/INO OR04
Carlos Rodríguez del Río	REAXYS-MYCS
Carlucci Claudia	ORG PO27
Carlucci Lucia	ORG PO45
Carraro Davide	ORG PO54
Carraro Mauro *	ORG/INO OR02
Carta Fabrizio	ORG PO89
Cartagenova Daniele	ORG OR30
Caruso Tonino	ORG PO36
Casapullo Agostino	ORG PO66
Caselli Alessandro*	ORG/INO KN01
Caselli Monica	ORG OR04
	ORG OR57
	ORG PO88
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Casnati Alessandro	ORG PO89
	ORG PO102
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Castellano Sabrina	ORG PO43
Cattaneo Cristian	ORG PZ06
Catto Marco	ORG PO74
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Cauteruccio Silvia*	ORG PO15
Cauteruccio Silvia	ORG PO73
Cavani Fabrizio	ORG/INO OR04
Ceccarelli Martina	ORG OR50
Celaj Odeta	ORG PO25
Celesti Consuelo	ORG OR55
Cerichelli Giorgio	ORG OR48
Cerisoli Lucia	ORG PZ06
Cesari Cristiana	ORG/INO OR01
	ORG/INO OR04
Cespugli Marco	ORG OR28
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Chiappe Cinzia	ORG OR26
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	ORG PO64
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Chiarini Marco*	ORG OR48
Chiarotto Isabella	ORG PO22
Chini Maria Giovanna*	ORG PO43

Chini Maria Giovanna	ORG PO41
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Chiummiento Lucia	ORG PO23
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Chiurchiù Elena	ORG OR47
Ciamelli Carlotta	ORG OR19
Ciardiello Fortunato	ORG PO25
Ciaschetti Gianpiero	ORG PO09
Ciccarella Giuseppe	ORG PO20
Ciceri Daniele	ORG PZ06
Cimarelli Cristina	ORG PO103
Cimmino Alessio	ORG PO69
Cingolani Andrea	ORG/INO OR04
Cini Elena	ORG OR56
Ciofalo Maurizio	ORG PO87
Ciogli Alessia	ORG PO75
Cipolla Laura*	ORG PO16
Cipolla Laura	ORG PO99
Cipolla Maria Pia	ORG PO48
Ciresa Cecilia	ORG PO72
Ciufolini Marco A.	ORG PO103
Coe Jotham W.	ORG PO47
Cogliati Beatrice*	ORG PO17
Colella Marco*	ORG PO18
Colella Silvia	ORG OR06
Comandè Alessandra*	ORG PO19
Comandè Alessandra	ORG OR15
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Comes Franchini Mauro	ORG PO56
Consumi Marco	ORG OR08
	ORG OR07
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	ORG PO105
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Corradini Roberto	ORG PO85
Corrente Giuseppina Anna*	ORG PO20
Corsi Massimo	ORG PO13
Costa Barbara	ORG PO16
Costantino Valeria	ORG OR37
Costanzo Paola	ORG PO70
Cozzi Pier Giorgio	ORG OR31
Credi Alberto	ORG PO91
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Crescenzi Orlando	
Crestini Claudia	ORG OR27
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Criscuolo Valeria	ORG PO79
Crisma Marco	ORG PO59
Cruciani Gabriele	ORG OR50
Curti Claudio*	ORG PO21
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D'Abrosca Brigida	ORG OR53
D'Acquarica Ilaria	ORG OR13
Dal Piaz Fabrizio	ORG OR51
Dalcanale Enrico*	ORG MD04
	ORG PO28
D'Alonzo Daniele	ORG PO40

D'Amato Assunta*	ORG PO26
D'Andrea Felicia	ORG PO07
D'Anna Francesca *	ORG PO22
D'Anna Francesca	ORG OR49
D'Auria Maria Valeria	ORG OR22
De Angelis Sonia*	ORG PO27
De Bonis Angela	ORG PO24
De Combarieu Eric	ORG PZ06
De Fenza Maria*	ORG PO28
De Fenza Maria	ORG PO40
De Luca Giuseppina	ORG PO06
De Luca Lidia	ORG PO44
De Marco Luisa	ORG PO48
De Marino Simona*	ORG PO29
De Marino Simona	ORG OR22
De Matteo Marilena	ORG PO50
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De Nino Antonio*	ORG OR62
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De Nino Antonio	ORG PO57
	ORG PO70
	ORG OR60
De Riccardis Francesco	ORG PO26
	ORG PO30
	ORG PO90
	ORG PO93
De Rosa Margherita*	ORG OR59
De Rosa Margherita	ORG PO36
	ORG PO53
De Sanctis Gaia	ORG OR19
De Simone Nicola Alessandro*	ORG PO30
De Tommasi Nunziatina	ORG OR51
De Vita Simona*	ORG PO41
De Zotti Marta*	ORG PO32
De Zotti Marta*	ORG PO33
Deagostino Annamaria*	ORG PO34
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Degennaro Leonardo	ORG PO27
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Deichtmann Walter	ORG OR45
del Gaudio Federica*	ORG PO35
del Gaudio Federica	ORG OR51
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	ORG PO26
Della Sala Giorgio	ORG PO30
	ORG PO93
Della Sala Paolo *	ORG PO36
Dell'Aera Marzia	ORG PO39
Delso Ignacio	ORG PO57
Denis William	ORG PO54
Dentoni Litta Antonella	ORG OR60
Dessi Alessio*	ORG PO37
d'Ettore Alessio	ORG PO94
Di Bari Lorenzo	ORG OR03
Di Carmine Graziano	ORG PO12
Di Cecco Mirella	ORG PO09
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Di Donna Leonardo	ORG PO06
Di Fabio Giovanni*	ORG PO38
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Di Gioia Maria Luisa*	ORG OR40
Di Gioia Maria Luisa	ORG PO03
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Di Marino Cinzia	ORG PO83
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Di Pietro Federica	ORG OR61
Di Stefano Stefano	ORG PO05
Dilauro Giuseppe*	ORG PO39
Dintcheva Nadka Tzankova	ORG OR49
d'Ischia Marco	ORG OR25
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Doria Filippo*	ORG OR20
D'Orsi Rosarita*	ORG PO23
D'Orsi Rosarita*	ORG PO24
Dova Davide	ORG OR58
Drioli Sara	ORG PO42
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Ebrahimi Majdar Reza	ORG OR27
Ertl Martin	ORG PO31
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Esposito Anna*	ORG PO40
Esposito Roberta	ORG PO66
Esposito Veronica	ORG PO101
Esposito Veronica*	ORG OR39
Ettorre Valeria	ORG PO92
Evidente Antonio	ORG PO69
Facchini Fabio A.	ORG OR57
Fadeyi Olugbeminiyi O.	ORG PO47
Fagnoni Maurizio	ORG MD03
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Fagnoni Maurizio*	ORG PO31
Falciani Chiara	ORG OR54
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Farinola Gianluca Maria	ORG PO55
Fazzi Daniele	ORG OR01
Felluga Fulvia*	ORG PO42
Feroci Marta	ORG PO22
Ferrante Luca	ORG PO50
Ferrigato Aurelia	ORG OR42
Festa Carmen	ORG PO29
	ORG PO66
Festa Carmen*	ORG OR22
Fiammengo Roberto*	ORG OR18
Fieschi Franck	ORG OR11
Fieschi Franck	ORG PO88
Figliolia Rosario	ORG/INO OR03
Figliolia Rosario*	ORG/INO OR05
Filatov Michael	ORG OR34

Filippi Jonathan	ORG/INO PZ02
Fiorani Giulia*	ORG PZ04
Fiorentino Antonio	ORG OR53
	ORG PO25
Fiorucci Stefano	ORG OR22
	ORG PO29
Floresta Giuseppe	ORG OR59
Floris Barbara	ORG OR07
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Folliero Maria G.	ORG/INO PZ02
Fontana Antonella	ORG PO92
Formaggio Fernando	ORG PO33
Forni Alessandra	ORG PO45
Forte Giovanni	ORG OR51
Fortuna Cosimo Gianluca*	ORG OR41
Fortunati Elena	ORG PO08
Franza Gabriele	ORG OR65
Franzini Roberta	ORG OR58
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Fredrich Sebastian	ORG OR44
Frezza Claudio	ORG PO10
Frezza Claudio*	ORG PO11
Funicello Maria	ORG PO23
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Fusi Stefania	ORG OR34
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Gabriele Bartolo*	ORG OR17
Gabrielli Luca	ORG PO84
Gabrielli Serena *	ORG OR47
Gaeta Carmine	ORG OR59
	ORG PO30
	ORG PO36
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Galeone Aldo	ORG OR39
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Galloni Pierluca*	ORG OR07
Galloni Pierluca	ORG PO100
	ORG PO105
Gambini Andrea	ORG PZ06
Garbarino Silvia	ORG MD03
García Mancheño Olga	ORG PO46
Gardossi Lucia	ORG OR28
Gaspa Silvia*	ORG PO44
Gasparrini Francesco	ORG PO75
Gatto Emauela	ORG OR07
Gazzero Patrizia	ORG OR51
Gazzola Silvia	ORG OR16
Gemmi Mauro	ORG PO07
Gennari Cesare	ORG PO33
Geremia Silvano	ORG PO53
Germani Raimondo	ORG OR46
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Ghirga Francesca*	ORG OR13
Giannini Clelia*	ORG PO45
Giannini Giuseppe	ORG OR56

Giboulot Steven	ORG/INO OR05
Gigli Giuseppe	ORG PO48
Gini Andrea*	ORG PO46
Giofrè Salvatore Vincenzo	ORG PO58
Giofrè Salvatore Vincenzo*	ORG OR55
Giordano Assunta	ORG OR51
	ORG PO43
Giorgi Simone*	ORG PO47
Giovannini Pier Paolo	ORG PO12
Giovenzana Giovanni Battista	ORG OR42
Glarner Thomas	ORG OR45
Gobbo Marina	ORG OR09
Godineau Edouard	ORG PO49
Goracci Laura*	ORG OR50
Grande Vincenzo	ORG OR20
Gravante Raffaele	ORG PO38
Graziani Vittoria	ORG PO25
Graziani Vittoria*	ORG OR53
Grisorio Roberto*	ORG OR06
Grisorio Roberto*	ORG PO48
Griva Sirio	ORG PO04
Groben René	ORG OR37
Grützmaker Hansjörg	ORG/INO PZ02
Gschwind Ruth M.	ORG OR32
Gualandi Andrea*	ORG OR31
Guaragna Annalisa	ORG PO28
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Guarneri Alice*	ORG OR28
Guazzelli Lorenzo	ORG PO64
Guazzelli Lorenzo*	ORG OR26
Guazzelli Nicola	ORG OR35
Guglielmero Luca	ORG PO64
Guizzardi Roberto	ORG PO16
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Hasanu Elena	ORG PO07
Hecht Stefan	ORG OR44
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Hiremathad Asha	ORG PO74
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Hussain Rohanah	ORG PO32
Iacobellis Rosabianca	ORG PO48
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Ingallina Cinzia	ORG OR13
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Innocenti Riccardo*	ORG PO51
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Izzo Irene	ORG OR60
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Jozeliunaite Augustina	ORG OR01
Kleij Arjan W.	ORG PZ04
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Koerberle Andreas	ORG OR52
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Korom Saša	ORG OR10
Kunz Horst	ORG OR18
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La Manna Pellegrino	ORG OR59
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La Rocca M. Vincenzo	ORG OR16
Laghezza Antonio	ORG PO74
Lambruschini Chiara	ORG OR30
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Lange Heiko*	ORG OR27
Lanzalunga Osvaldo	ORG PO05
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Lattanzi Alessandra	ORG PO63
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Lauro Gianluigi	ORG PO96
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Lautz Christian	ORG OR45
Leggio Antonella	ORG PO19
Leggio Antonella*	ORG OR15
Lenci Elena*	ORG OR36
Léonard Jérémie	ORG OR34
Leone Gabriella	ORG PO55
Leonelli Francesca*	ORG OR38
Lessi Marco*	ORG OR35
Ley Steven V.	ORG PO49
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Licini Giulia	ORG OR64
Licini Giulia*	ORG PO54
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Liguori Angelo	ORG PO19
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Limongelli Vittorio	ORG PO29
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Linaldeddu B.T.	ORG PO02
Lissia Margherita	ORG OR06
Listorti Andrea	ORG PO48
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Liu Jia	ORG OR18
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Lo Presti Marco*	ORG PO55
Locatelli Erica*	ORG PO56
Loiodice Fulvio	ORG PO74
Lombardo Marco	ORG PZ06
Lotteria Simone	ORG OR28
Lu Menji	ORG OR18
Lucenti Elena	ORG PO45
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Lupidi Gabriele	ORG PO47
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Maddau Laura	ORG PO69
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Maggi Filippo	ORG PO10
Magini Andrea	ORG PO88
Magli Sofia	ORG PO16
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Maglione Maria Grazia	ORG PO79
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Magnani Agnese	ORG OR08
Maione Francesco	ORG PO41
Maiorana Stefano	ORG PO50
	ORG OR62
Maiuolo Loredana	ORG PO03
	ORG PO70
Maiuolo Loredana*	ORG PO57
Malacarne Marco	ORG PO80
Manca Michele	ORG PO48
Mancin Fabrizio	ORG PO65
Mancin Fabrizio	ORG PO84
Mancinelli Michele	ORG PO78
Mancuso Raffaella	ORG OR17
Mancuso Raffaella*	ORG PO58
Mandolini Luigi	ORG PO102
Manetti Fabrizio	ORG OR56
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Manfredi Norberto	ORG PO73
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Manicardi Alex	ORG PO85
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Marchesi Andrea	ORG PO99
Marchionni Andrea	ORG/INO PZ02
Marianetti Giulia	ORG OR35
Marini Bettolo Rinaldo	ORG OR38
Marino Maria Leda	ORG PO93
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Marsico Giulia*	ORG PO60
Marsico Giulia*	ORG PO61
Marteinsson Viggo Thor	ORG OR37
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Martino Elisa	ORG OR30
Martin-Santamaria Sonsoles	ORG OR57
Marullo Salvatore	ORG PO22

Marullo Salvatore*	ORG OR49
Mascolo Nicola	ORG PO41
Masi Marco	ORG PO69
Massi Alessandro	ORG PO12
Matteucci Elia	ORG OR31
Matteucci Elia	ORG/INO OR01
Mattiello Sara	ORG OR14
Maurizio Taddei*	ORG MD02
	ORG OR39
Mayol Luciano	ORG PO101
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Mazzanti Andrea	ORG PO78
Mazzarella Daniele	ORG OR31
Mazzoni Rita	ORG/INO OR01
Mazzoni Rita*	ORG/INO OR04
Mazzotti Fabio	ORG PO06
Medve Laura*	ORG OR11
Mella Massimo	ORG/INO OR04
Mella Massimo*	ORG OR16
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Menchi Gloria	ORG PO51
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Meneghetti Moreno	ORG OR09
Mengozzi Luca	ORG OR31
Menichetti Stefano	ORG OR54
Meninno Sara*	ORG PO63
Menta Sergio	ORG PO75
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Merino Pedro	ORG PO57
	ORG OR26
Mezzetta Andrea	ORG OR26
Mezzetta Andrea*	ORG PO64
Miceli Claudia	ORG PO54
Micheli Corinna	ORG PO07
Micheli Laura	ORG OR07
Migneco Luisa Maria	ORG OR38
Milano Francesco	ORG PO55
Milite Ciro	ORG PO43
Miller Hamish A.	ORG/INO PZ02
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Minarini Carla	ORG PO79
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Monaco Ilaria	ORG PO56
	ORG OR30
Moni Lisa	ORG PO04
Montagna Giuseppe	ORG PO16
Monti Filippo	ORG OR31
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Monti Maria Chiara	ORG PO66
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Morbioli Ilaria	ORG PO88
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Mordini Alessandro	ORG PO37
Morelli Carlo*	ORG OR65
Moretto Alessandro	ORG PO59
Morgillo Floriana	ORG PO25
Morillas Becerril Lucia*	ORG PO65
Morretta Elva*	ORG PO66
Mucchi Adele	ORG OR04
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Mussini Patrizia R.	ORG PO73

Musumarra Giuseppe *	ORG PO67
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Naletova Irina	ORG OR41
Napoli Anna	ORG PO06
Napolitano Alessandra	ORG PO104
Nardi Monica	ORG OR40
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Nardi Monica*	ORG PO68
Nativi Cristina	ORG OR08
Navazio Federica	ORG PO103
Nedden Hans Günter	ORG/INO OR03
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Nejrotti Stefano	ORG OR12
Neri Placido	ORG OR59
	ORG PO30
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	ORG PO53
Nicoletti Marcello	ORG PO10
Nocera Paola *	ORG PO69
Nola Marta	ORG OR30
Noto Renato	ORG OR49
Noto Renato	ORG PO22
Nuhant Philippe	ORG PO47
Oberhauser Werner	ORG/INO PZ02
Oliverio Manuela	ORG OR40
	ORG PO68
Olivito Fabrizio*	ORG PO70
Olivo Giorgio	ORG PO05
Olivucci Massimo	ORG OR34
Oneto Marzia	ORG OR61
Operamolla Alessandra*	ORG OR05
Orentas Edvinas	ORG OR01
Orlandi Marco	ORG OR29
Orlandini Guido	ORG PO91
Ortega Martínéz Aitor	ORG OR31
Ounigbo Louis	ORG PO81
Pacifico Severina	ORG OR53
Pagano Angela	ORG PO23
Pagano Angela*	ORG PO71
Pagliari Míaria V.	ORG/INO PZ02
Painelli Anna	ORG PO17
Paiotta Alice	ORG PO52
Pallavicini Luca	ORG PO50
Palleschi Antonio	ORG PO33
Palleschi Giuseppe	ORG OR07
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Palmioli Alessandro*	ORG PO72
Palmioli Alessandro*	ORG PO14
Palombi Laura	ORG PO08
Pannucci Elisa	ORG PO08
Paolino Marco*	ORG OR34
Paonessa Rosina	ORG OR40
Papaianni Valentina	ORG PO19

Parenti Francesca	ORG OR04
Parisi Giovanna	ORG PO18
Parisi Maria Laura	ORG PO94
Parisotto Stefano	ORG PO34
Paternò Alessio	ORG PO67
Pavone Michele	ORG OR25
Pelliccioli Valentina*	ORG PO73
Peluso Andrea	ORG PO36
Pennetta Chiara*	ORG OR21
Perego Luca A.	ORG OR35
Peri Francesco	ORG OR57
Perna Filippo Maria	ORG PO39
	ORG PO74
Perticarari Sofia	ORG PO78
Peterlongo Federico	ORG PZ06
Petricci Elena*	ORG OR56
Petrillo Giovanni	ORG PO71
Pett Christian	ORG OR18
Pezzella Alessandro	ORG OR25
	ORG PO79
Pezzetta Cristofer	ORG OR35
Piantini Sara*	ORG OR54
Piarulli Umberto	ORG PO33
Piccolella Simona	ORG OR53
Piemontese Luca*	ORG PO74
Pierini Marco*	ORG PO75
Piermattei Pamela*	ORG PO103
Pighini Andrea	ORG PO50
Pignataro Barbara A.	ORG PO61
Pignataro Luca	ORG PO33
Pinoli Monica	ORG PO33
Pirota Valentina	ORG OR20
Pirovano Valentina	ORG PO01
Pirovano Valentina*	ORG/INO PZ01
Pizzolante Valeria	ORG PO89
Pomelli Christian Silvio	ORG PO64
Pomelli Christian Silvio*	ORG PO76
Pontisso Patrizia	ORG OR09
Porkolab Vanessa	ORG PO88
Potenti Simone	ORG PO104
Potenza Marianna*	ORG PO77
Potenza Nicoletta	ORG OR53
Prandi Adolfo	ORG PO50
Prandi Cristina*	ORG OR12
Prati Luca*	ORG PO78
Previtali Andrea	ORG PO45
Primitivo Ludovica	ORG OR61
Procopio Antonio	ORG OR40
	ORG PO68
	ORG PO70
Prontera Carmela Tania	ORG OR25
Prontera Carmela Tania*	ORG PO79
	ORG MD03
Protti Stefano	ORG PO81
	ORG PO97
Protti Stefano*	ORG PO80
Pucci Andrea	ORG OR35

Puzzo Francesco	ORG/INO OR04
Quaglio Deborah	ORG OR13
Quarta Santina	ORG OR09
Ragazzon Giulio	ORG PO91
Ragni Roberta	ORG PO55
Ragno Daniele	ORG PO12
Randazzo Pietro	ORG PO50
Raniolo Sofia	ORG PO33
Rassu Gloria	ORG PO21
Ravelli Davide	ORG PO31
Ravelli Davide*	ORG MD03
Raviola Carlotta*	ORG PO81
Razzetti Gabriele	ORG OR43
Reginato Gianna	ORG PO37
	ORG PO94
Regini Giorgia	ORG PO42
Reichardt Niels	ORG OR11
Renzi Polyssena*	ORG OR32
Rescifina Antonio	ORG OR59
Rescigno Donatella	ORG PO43
Riccio Raffaele*	ORG MD01
Riccio Raffaele	ORG OR51
	ORG OR52
	ORG PO35
	ORG PO43
	ORG PO66
	ORG PO77
	ORG PO86
	ORG PO96
Richichi Barbara	ORG OR08
Richter Sara	ORG OR20
Righetto Stefania	ORG PO45
Righi Giuliana	ORG OR61
Risi Caterina*	ORG PO82
Riva Renata	ORG OR30
	ORG PO04
Rizzo Aurora	ORG PO48
Rizzo Carla	ORG OR49
	ORG PO22
Rodríguez Douton María Jesús	ORG PO76
Romagnuolo Fabio	ORG OR65
Romanucci Valeria	ORG PO38
Romanucci Valeria*	ORG PO83
Romeo Roberto	ORG OR55
	ORG PO58
Rontogianni Matina	ORG PO35
Rooney Myles	ORG OR14
Roose Bart	ORG OR06
Rosa-Gastaldo Daniele*	ORG PO84
Rossella Francesco	ORG PO76
Rossi Alessio	ORG OR36
Rossi Elisabetta	ORG/INO PZ01
	ORG PO01
Rossi Federico Vittorio	ORG PO47
	ORG OR63
Rozzi Andrea	ORG OR10
Rozzi Andrea*	ORG PO85

Russo Alessandra	ORG PO77
	ORG PO96
Russo Alessandra*	ORG PO86
Russo Annapina	ORG OR39
	ORG PO101
Russo Beatrice	ORG OR62
	ORG PO57
Russo Giulia	ORG OR39
	ORG PO101
Sabuzi Federica	ORG OR07
	ORG PO100
	ORG PO105
Sacco Elena	ORG OR19
Sach Neal W.	ORG PO47
Saiano Filippo*	ORG PO87
Salamone Michela	ORG PZ07
	ORG PO62
Salanti Anika	ORG OR29
Salerno Gianluca*	ORG OR08
Salvio Riccardo	ORG PO102
Sambri Letizia	ORG OR31
Sambri Letizia*	ORG/INO OR01
Sampaolesi Susanna	ORG OR47
Sampaolesi Susanna*	ORG OR63
Sansone Francesco	ORG PO102
Sansone Francesco*	ORG OR57
Sansone Francesco*	ORG PO88
Sansone Francesco*	ORG PO89
Santagata Antonio	ORG PO24
Santi Luca	ORG PO08
Santini Roberta	ORG OR56
Santos Maria Amélia	ORG PO74
Sanzone Alessandro	ORG OR14
Sappino Carla*	ORG OR61
Sartini Stefania	ORG PO76
Sartorel Andrea	ORG OR07
Sartori Andrea	ORG PO21
Sassi Mauro*	ORG OR14
Satriano Cristina	ORG OR41
Sbravati Davide	ORG PO89
Scafato Patrizia	ORG PO60
	ORG PO61
Scalabrin Matteo	ORG OR20
Scandiuizzi Cristina	ORG PO50
Schettini Rosaria	ORG OR60
	ORG PO30
Schettini Rosaria*	ORG PO90
Scire Salvatore	ORG PO67
Scognamiglio Monica	ORG OR53
Secchi Andrea	ORG PO17
Secchi Andrea*	ORG PO91
Sepe Valentina	ORG PO29
Serafini Mauro	ORG PO10
	ORG PO11
Seravalli Luca	ORG PO17
Serna Sonia	ORG OR11
Serrilli Anna Maria	ORG PO09

Sestito Stefania E	ORG OR57
Sforazzini Giuseppe*	ORG OR01
Siani Gabriella*	ORG PO92
Sicignano Marina	ORG OR60
Sicignano Marina*	ORG PO93
Siligardi Giuliano	ORG PO32
Silvi Serena	ORG PO91
Sindona Giovanni	ORG OR40
	ORG PO06
	ORG PO68
Sini Loredana	ORG OR42
Sinicropi Adalgisa*	ORG PO94
Snoeck Robert	ORG PO28
Snoeck Robert	ORG PO40
Solfrizzo Michele	ORG PO74
Soriente Annunziata	ORG OR59
	ORG PO53
Speranza Giovanna	ORG OR65
Spinelli Michela	ORG OR19
Squarcina Andrea	ORG/INO OR02
St. John Campbell Sahra	ORG PO98
Stecca Barbara	ORG OR56
Stecker Kelly	ORG PO35
Stefano Caporali	ORG PO76
Stella Lorenzo	ORG PO32
	ORG PO33
Suber Lorenza	ORG OR61
Sunseri Francesco	ORG PO58
Superchi Stefano	ORG PO60
	ORG PO61
Supuran Claudiu T.	ORG PO89
Suranna Gian Paolo	ORG OR06
Suranna Gian Paolo	ORG PO48
Taddei Maurizio	ORG PO82
	ORG PO94
Tagliabue Andrea	ORG/INO OR04
Talarico Giovanni	ORG PO40
Tallarida Matteo Antonio	ORG PO03
	ORG PO57
Talotta Carmen	ORG OR59
	ORG PO30
	ORG PO36
	ORG PO53
Taptue Gaby Brice	ORG OR23
Taptue Gaby Brice*	ORG PO95
Tassini Paolo	ORG OR25
	ORG PO79
Tavani Cinzia	ORG PO71
Tedesco Consiglia	ORG PO90
Teghil Roberto	ORG PO24
Terracciano Stefania	ORG OR52
	ORG PO77
	ORG PO86
Terracciano Stefania*	ORG PO96
Terreno Enzo	ORG PO56
Teta Roberta*	ORG OR37
Thiel Walter	ORG OR01

Tiecco Matteo	ORG PO92
Tiecco Matteo*	ORG OR46
Tisi Renata	ORG OR19
Tomás Daniel	ORG PO74
Toniolo Claudio	ORG PO59
Torre Luigi	ORG PO08
Torti Edoardo*	ORG PO97
Tortorella Paolo	ORG OR52
Tota Arianna	ORG PO27
Tota Arianna*	ORG PO98
Trabocchi Andrea	ORG OR36
	ORG PO51
Tramutola Francesco	ORG PO23
Trevisan Marta	ORG PO65
Troiani Teresa	ORG OR53
Trotta Massimo	ORG PO55
Turato Cristian	ORG OR09
Uccello-Barretta Gloria	ORG OR13
Ugo Renato	ORG PO50
Uygur Mustaga	ORG PO46
Vaccaro Maria Carmela	ORG PO77
	ORG PO86
Vacchini Mattia	ORG PO16
Vacchini Mattia*	ORG PO99
Valderrey Virginia	ORG OR44
Valentini Francesca	ORG OR07
Valentini Francesca*	ORG PO100
Vanossi Davide	ORG OR04
Varra Michela	ORG OR39
Vassallo Antonio	ORG PO77
Venditti Alessandro	ORG PO11
Venditti Alessandro*	ORG PO09
Venditti Alessandro*	ORG PO10
Venturi Margherita	ORG PO91
Verdolino Vincenzo	ORG OR10
Vergara Daniele	ORG OR35
Verona Massimiliano Donato	ORG OR10
	ORG OR58
Villani Claudio	ORG PO75
	ORG OR09
Villano Gianmarco	ORG OR09
Virgilio Antonella	ORG OR39
Virgilio Antonella*	ORG PO101
Viscardi Guido	ORG OR24
Visentin Sonja	ORG OR24
Vita Francesca	ORG OR28
Vitale Paola	ORG PO39
Vitali Forconesi Gabriella	ORG OR30
Vivès Corinne	ORG OR11
Vizza Francesco	ORG/INO PZ02
Vladiskovic Chiara	ORG OR43
Volonterio Alessandro	ORG OR21
Volpe Chiara	ORG PO63
Volpe Raffaele	ORG PO26
Volpi Stefano*	ORG PO102
Wagner Björn	ORG OR50
Wang Anna	ORG PO49

Werz Oliver	ORG OR52
	ORG PO43
Westerlind Ulrika	ORG OR18
Williams Charlotte K.	ORG PZ04
Zambon Alfonso*	ORG OR04
Zampella Angela	ORG OR22
	ORG PO29
Zampella Giuseppe	ORG PO16
Zanardi Franca	ORG PO21
Zanardi Franca*	ORG PZ01
Zanella Simone	ORG PO33
Zani Lorenzo	ORG PO37
	ORG PO94
Zani Lorenzo*	ORG/INO KN02

Zanichelli Valeria	ORG PO91
Zanin Davide	ORG PO50
Zanotti Valerio	ORG/INO OR04
Zanotti-Gerosa Antonio	ORG/INO OR03
	ORG/INO OR05
Zappacosta Romina	ORG PO92
Zardi Paolo	ORG PO54
Zarrelli Armando	ORG PO38
	ORG PO83
Zoia Luca*	ORG OR29
Zonta Cristiano	ORG PO54
Zonta Cristiano*	ORG OR64
Zonzin Martina	ORG/INO OR02