PROJECT N°: 1A

Nano-composite materials and integrated arrays of gas sensors for odorant detection

Supervisor: Prof. Pierluigi Barbieri
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Sensor systems mimicking human olfaction in gaseous mixture detection have relevant industrial, medical and environmental applications (Wilson, 2009), addressing e.g. product or food quality assessment, breath analysis and malodour nuisances characterization (Licen, 2018).

The project aims at manufacturing nano-composite materials to be used as gas sensors, containing both conducting particles and an insulating matrix. Non conductive polymers (Ryan, 2004) or low volatility organic molecules (Gao, 2006) will be considered as insulating matrices, and carbon black, carbon nanotubes (Camilli, 2018), and nano-metal particles as conductive components. Selected and tested materials will be integrated in arrays of chemoresistive sensors for detection of odorant mixtures, core for instrumental odour monitoring systems.

Novel and commercial multisensor systems implementing nano-composite arrays will be characterized for instrumental detection of odorous mixtures, taking into account also low (ppb) odour detection threshold compounds, as sulfur compounds (e.g. hydrogen sulfide, mixtures of mercaptans, tetrahydrothiophene). Case studies in real industrial scenarios will be developed.

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PROJECT N°: 2A

Development of a multisensor platform for agri-food applications

Supervisor: Federico Berti
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The projetc is carried out in cooperation with the group of prof. A. Accardo and A. Boscolo at the Department of Engineering and Architecture of the the University of Trieste. The group has recently developed an integrated multisensor platform capable of simultaneous control of biosensors based on any kind of spectroscopy, fluorimetry and electrochemical detection. On the other hand, our group has developed in the recent years several biomimetic sensing elements, including designed peptides, imprinted nanogels and protein fragments for the detection of small molecules. The sensing elements have been designed to recognize important molecular targets in food control, including coffee phenols (chlorogenic acids, quinides), olive phenols (tyrosol, hydroxytyrosol, oleuropein and derivatives), coffee terpenes (cafestol, 16-O-Methylcafestol), and xanthines (caffeine, theophylline, paraxanthine).
In this project, our experience will be exploited to setup a validation of the multisensor platform. The focus will be on olive oil and olive leaf phenols and coffee xanthines, as they can be detected by either electrochemical or optical/fluorimetric systems if the sensing element bears an embedded optical reporter. Both peptides and imprinted polymers will be considered as recognition elements, they will be designed and synthesized, and mounted inside the multisensor platform. Full validations will be then performed, on real samples.

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PROJECT N°: 3A

Graphene Quantum Dots: bio- and electrochemical applications

Supervisor: Tatiana Da Ros
email: daros@units.it

Graphene is a one-atom thick two-dimensional material and the studies on its excellent conductivity and optical properties boosted the research activities in this field and brought forward novel applications for graphene and its derivatives.[1]
In recent years, very promising derivatives of graphene, i.e. Graphene Quantum Dots (GQDs), have gained significant interest due to the potential for biomedical and electrochemical applications. GQDs are zero-dimensional small fragments of graphene in the size range.[2] Intrinsically, graphene is a zero-energy band-gap material but band-gap can be opened by size reduction and introduction of defects into the graphene moiety, and this leads strong photoluminescence that normally is not present in semi-conducting graphene.[3] So GQDs basically combine the structure of graphene with the quantum confinement and edge effects of QDs and possess unique properties, which are important for the applications in medicine, electronic, photoluminescence, electrochemical and electrochemiluminescence.[4] GQDs generally consist of 1 - 3 layers of graphene flakes with the diameter of less than 20 nm. Their surface groups of GQDs may vary due to the synthetic methodology, and photoluminescence may change depending on the surface functionalization.
The different processes to obtain GQDs may confer different properties to the materials.
GQDs have potential applications in biomedical, optoelectronic, and energy-related fields especially thanks to their properties such as water solubility and luminescence, which make them excellent candidates for bioimaging and drug delivery.
However there is the necessity to find appropriate methodology to tailor the size and the properties of the materials, both by optimizing their preparation and/or their functionalization. In this respect new approaches will be explore and will be devoted to ameliorate the preparation of new GQDs derivatives, especially in combination with other specific dyes to be used for biological purposes and in electrochromic devices.

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PROJECT N°: 4A

O-antigen synthesis in Gram-negative bacteria: the Wzx-Wzy pathway

Supervisor: Dr. Rita De Zorzi
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Exposure of oligo- and poly-saccharides on Gram-negative bacteria cell surface has a key role in bacterial survival and persistence in the environment, through mechanisms such as evasion of host defense, complement deposition and phagocytic killing [1]. One of the main pathways for the production of O-antigen containing LipoPolySaccharides (LPS) in pathogens is the Wzx/Wzy pathway [2] (Figure). Different proteins are involved in the assembly of O-antigen oligosaccharide units, their translocation to the periplasmic space and the polymerization to form the O-antigen [3]. In particular, two integral membrane proteins are involved in the central steps of this pathway: the translocase Wzx and the polymerase Wzy [4]. These two proteins have a very distinctive sequence, different for each bacterial strain, and no homology with human proteins, making them an interesting target for new drugs against antibiotic-resistant bacteria. Inhibitors against Wzx and Wzy proteins would be highly specific and could be used as adjuvants in the antibiotic treatment, improving the intracellular concentration of the drug and therefore its efficacy.

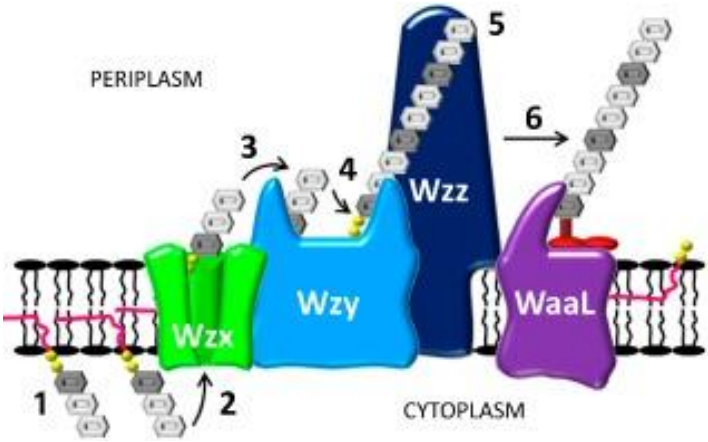

Figure: Schematic representation of the Wzx/Wzy pathway (from ref. [4]).

Currently, little information is available on the structure and mechanism of action of Wzx and Wzy. In recent years, our group was able to express and purify Wzx and Wzy from *Pseudomonas aeruginosa*, a renowned pathogen very frequent in nosocomial infections and particularly difficult to treat. The PhD student involved in this project will optimize crystallization conditions for Wzx and Wzy proteins, in order to obtain diffraction data and solve the structure of these membrane proteins. When good quality crystals will be available, he/she will collect a complete dataset using Synchrotron Radiation, at Elettra or one of the other European synchrotron sources, solve and refine the 3D crystal structure of the each protein. In parallel, the PhD student will test stability and retention of the secondary structure through complementary techniques, such as Circular Dichroism, Infrared Spectroscopy and UV Raman Resonant Spectroscopy. Using commercially available libraries of glycoside-like compounds, the successful applicant will use Thermal Shift Assays to evaluate possible interactors of Wzx and Wzy proteins, a first step in the quest for protein inhibitors.

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PROJECT N°: 5A

Triterpenes in olive oil and in olive pomace: identification, extraction and use in organic synthesis

Supervisor: Cristina Forzato
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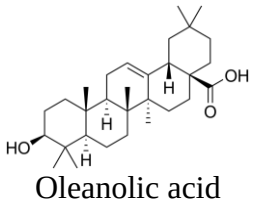
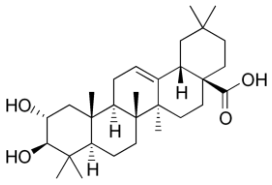
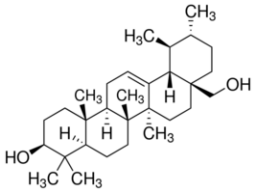
Oleanolic acid, maslinic acid, uvaol and erythrodiol (Fig. 1) are the main triterpenes present in virgin olive oil and it has been scientifically demonstrated that they possess biological activity such as anti-inflammatory, vasodilator, antioxidant and anti-tumor activity.[1] Pomace is very rich in triterpenes (average content 2690 mg / kg) but, according to EU regulations, this cannot be consumed directly but requires a refining process which determines the total removal of all acids triterpenes. Therefore, virgin olive oil can be considered the only source of these compounds. Moreover, from a recent study, which took into consideration 40 different cultivars from the World Database of Olives of Cordoba (Spain),[2] it was found that the triterpene fraction of virgin olive oil can be considered an excellent parameter in the characterization of monovarietal olive oils.
The Region Friuli Venezia Giulia is characterized by the production of extra virgin olive oil of the cultivar Bianchera/Belica which give extra virgin olive oil of excellent quality with a very high content of polyphenols, although the production is not very high since the cultivation area in FVG is about 600 ha. It is important to define a characteristic profile of the local olive oil in order to define its uniqueness.
In this project, to quantify the content of the four triterpenes, samples of local extravirgin olive oil and pomace will be analyzed using both GC as the official method as well as HPLC, which has been already proposed in the literature.
The recovery of triterpenes from pomace will also be evaluated by extraction with supercritical CO_2 characterizing the compounds extracted as potential building blocks or auxiliaries in organic synthesis.
The development of biosensors in order to find a simpler method of analysis and with comparable results will be also considered developing peptides able to work as sensing elements to recognize these compounds.
The extracted triterpenes will be also chemically modified in order to find new anticancer and anti-HIV agents as suggested by A. Parra et al in 2014,[3] who synthetized the acylated triterpenes and evaluated their antiproliferative and antiviral effect.



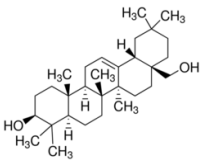
Oleanolic acid



Maslinic acid



Uvaol



Erythrodiol

Fig. 1

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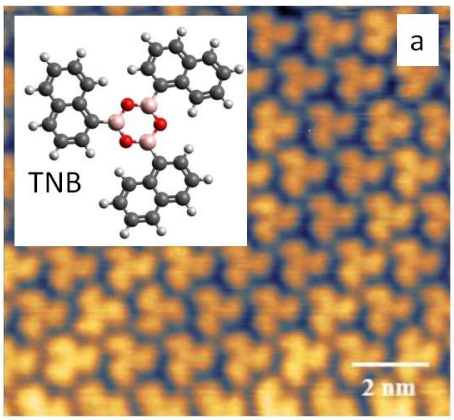
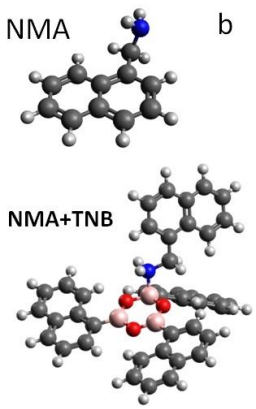
PROJECT N°: 6A

Computational core electron spectroscopies of gas phase molecules and their 2D covalent frameworks on metallic surfaces

Supervisor: Giovanna Fronzoni (DSCF, email: fronzoni@units.it)
Co-supervisor: Daniele Toffoli (DSCF, email: toffoli@units.it)

The focus of the project is the investigation of the adsorption and assembly of medium-sized organic molecules on metallic surfaces. NEXAFS (Near Edge X-ray Absorption Fine Structure) is a powerful tool to investigate the geometry of molecules adsorbed on surfaces [1]. Density Functional Theory (DFT) and its time-dependent generalization (TD-DFT) will be used to accurately simulate core spectroscopies such as XPS and NEXAFS of gas phase molecules and their 2D polymerization products on the surfaces of interest. The computational protocol consists in *i)* an accurate modelling of the surface/adsorbate interface with periodic boundary conditions and plane-wave basis sets (by using solid-state programs such as QUANTUM ESPRESSO [2]) followed by *ii)* the generation of a suitable set of clusters (cut from the periodic structure) from which angularly resolved NEXAFS spectra are calculated with techniques of quantum chemistry and localized basis sets, implemented in the ADF suite [3]. A new method to compute vibrationally resolved NEXAFS spectra of gas phase molecules will be developed within the framework of DFT theory during the three years spanned by the project.
Systems of current interest are boroxine-based 2D structures on metallic surfaces [4]. These 2D COFs (Covalent Organic Frameworks) can selectively host other molecules by shape matching and drive the formation of complex interfaces. The possibility to exploit the chemical affinity between the boroxine group (as a monolayer of trinaphthylboroxine molecules, TNB, Figure 1a) (Lewis acid) and a methylamine-terminated molecule, namely the naphtylmethylamine (NMA, Figure 1b) (Lewis base) will be considered, as an alternative route in the guest-host recognition scheme. These systems will be studied in close collaboration with experimentalists working at the ALOISA beamline of the ELETTRA Synchrotron Lab of Trieste.





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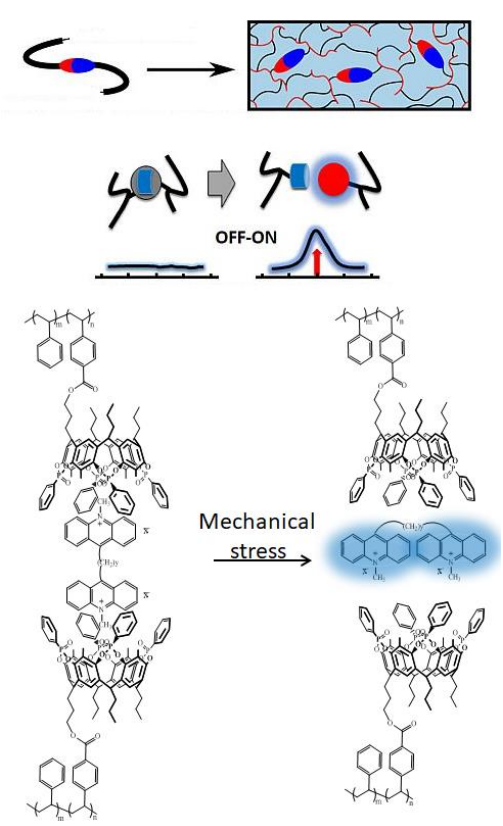
PROJECT N°: 7A

Functional supramolecular polymers for self-diagnostic composites (Supervision: Silvano Geremia, email: sgeremia@units.it)

This financed PRIN-2017 (Progetti di Ricerca di rilevante Interesse Nazionale) project aims at introducing self-diagnostic properties into polymers and carbon fiber reinforced composites. The challenge is to produce fluorescence signals directly linked to the stress-driven breaking of the weak bonds in host-guest complexes, leading to the visualization of emerging mechanical stress in the polymer matrix of the composite. The ultimate goal is to provide enabling technologies to transform polymers into smart materials, to meet the rising demand of safety-related, non-destructive tests in structural composites. Molecular recognition has been chosen as an operating tool in the form of supramolecular cross-linking among complementary host-guest units embedded in the polymeric chains. The guests are selected luminophores, which are quenched in the complex and emitting in the free form. The hosts are calixarenes, cavitands and cucurbiturils, whose molecular recognition properties are well defined and predictable. The implementation of the project requires: specific, resilient and stimuli responsive host-guest systems; their insertion into polymers as weak cross-linking units; a molecular level understanding of number, distribution and connectivity of the host-guest interactions in the polymer matrix; testing protocols for the resulting self-diagnostic properties. The team is composed of 5 Research units: University of Parma (E. Dalcanale), University of Bologna (C. Gualandi), University of Messina (G. Gattuso), University of Pisa (A. Pucci) and University of Trieste (S. Geremia). The structural characterization of number, distribution and density of host-guest crosslinking in self-diagnostic polymers is essential for a precise structural description of the system with predictive value. Small scale oligomers of the desired polymeric systems with narrow molecular weight distribution will be prepared to facilitate the crystallization. The micro-scale crystallization experiments will be performed at Trieste on a small scale (0.1 microliter) to reduce the material demand and to permit many variations of conditions. Crystals of supramolecular polymers have generally small dimensions and the use of synchrotron radiation is mandatory to obtain diffraction data at atomic resolution. In the absence of single crystals, synchrotron powder X-ray diffraction data and Rietveld structure refinements will be used to examine the 3D arrangement. Small-angle X-ray scattering (SAXS) and Wide-angle X-ray scattering (WAXS), collected using Synchrotron radiation, will be used to measure the electrospun nanofibers.



PROJECT N°: 8A

RARE DISEASES AND ORPHAN DRUGS: NEW INHIBITORS OF CERAMIDE GLUCOSILTRANSFERASE FOR THE TREATMENT OF GAUCHER DISEASE

Supervisor: Teresa Gianferrara
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Rare diseases concern more than 30 million throughout Europe and most of them are children. They are a complex and hard to solve public health problem. Since pharmaceutical companies have no or little interest in research and development of new drugs to treat these diseases, definition of orphan drugs is applied.

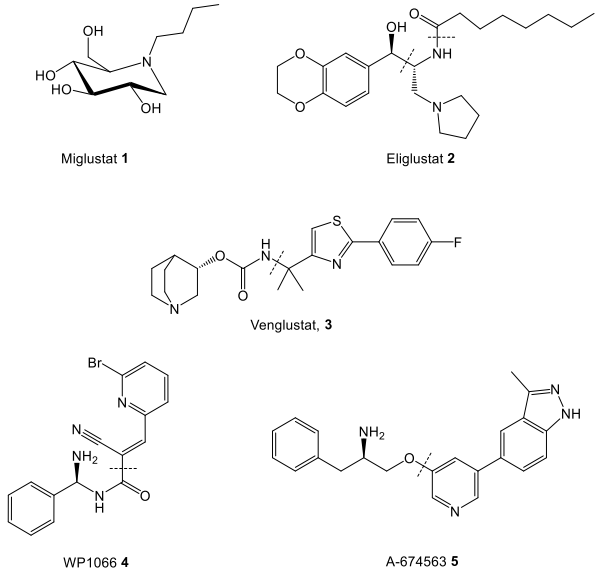

Figure 1: GLCT-1 inhibitors and their potential division into fragments (dotted line).

Aim of this project is to identify new classes of ceramide glucosyltransferase inhibitors (GLCT-1, EC: 2.4.1.80) in the treatment of Gaucher disease (GD). GD is due to the lack of activity of glucocerebrosidase, an enzyme involved in the catabolism of cerebrosides in tissue macrophage cells, which leads to endocellular accumulation of cerebrosides, production of large amounts of chemokines and interference with tissue metabolism and the immune system.[1] GLCT-1 catalyzes the reverse reaction of glucocerebrosidase.

Substrate reduction therapy (SRT) is a therapeutic approach for which two GLCT-1 inhibitors have already been approved: Miglustat (**1**) and Eliglustat (**2**) (Figure 1).[2,3] Eliglustat (**2**) is able to cross the blood brain barrier (BBB), but its accumulation in the brain is limited.[4] Veglustat (**3**) achieves effective concentrations in the CNS and is currently in clinical phase II.[5] Recently two antitumor compounds (**4**, **5**) that act with a mechanism that involve GLCT-1 inhibition have been reported.[6,7] In this project structures **2-5** are the starting point to develop a library of compounds able to overcome BBB and inhibit GLCT-1. The alkyl chains and/or aromatic rings of **2-5** confer the lipophilicity needed to overcome the biological membranes. The approach known as fragment-based lead discovery[8] will be used (Figure 2): each molecule is divided into fragments that will be synthesized and tested in vitro to evaluate the enzymatic activity of GLCT-1. Then they will be appropriately decorated and/or combined together to achieve an inhibition potency of the enzyme greater than the starting molecules. An in silico evaluation will allow to select and synthesize only the derivatives with an optimal pharmacokinetic profile. The selected compounds will be tested on GLCT-1 and the obtained strucure-activity relationship data will allow to optimize the structure obtaining a lead compound.

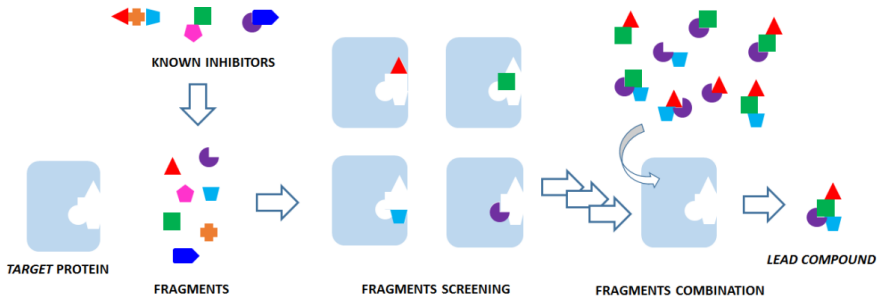

Figure 2: Fragment-based lead discovery approach.

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PROJECT N°: 9A

Novel functional interpretations of Sn^{IV}-porphyrin metal scaffolds.

Supervisor: Prof. Elisabetta Iengo
email: eiengo@units.it

The properties and structural characteristics of Sn^{IV}-porphyrin – planarity, six-coordination, robust binding to oxyanions, tin NMR active nucleous, tunable opto-electronic features (i.e. absorption in the visible region, luminescence, and ease of reduction) – make them intriguing metal scaffolds for the construction of light-responsive supramolecular assemblies or materials, and attracted our interest.[1] We recently survied and established their possible use, in combination with Zn^{II}-porphyin metallacycles and *meso*-pyridyl/benzoic-porphyrins, for the metal-mediated assembling of 3D discrete hollow supramolecular structures, featuring different kinds of (metallo)porphyrin elements.[2] In parallel, we initiated a fruitful investigation on Sn^{IV}-porphyrin/amino acids conjugates as novel biomimetic candidates for photoinduced proton-coupled electron-transfer (PCET).[3,4] for instance, a Sn^{IV}(N-acetyl-L-tyrosinato)$_2$-porphyrin conjugate (**1**) was found to generate a surprisingly long-lived radical pair state, by visible light excitation and in the presence of pyrrolidine (Figure). The single crystal X-ray structure of **1**, determined at the XRD1 ELETTRA synchrotron light source, evidences ordered patterns of intermolecular H-bonds. Notably, reports on the preparation and characterization of tin-porphyrin derivatives featuring chiral aa as axial ligands are extremely limited, and their intriguing use as synthons in the supramolecular realm is yet to come.

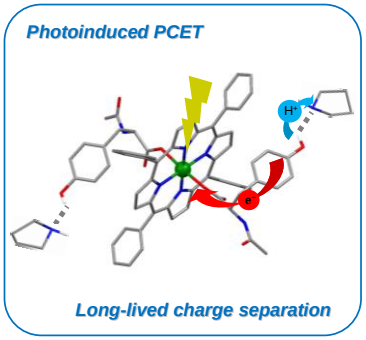

Figure. X-ray structure of **1** (solvent molecules and hydrogens, except for those of the OH groups, are omitted for clarity) and Schematic depiction of the (concerted) PCET process in the presence of pyrrolidine, mediated by H-bonding between the aa -OH residues and the base. Color code: H, white; C, gray; N, blue; O, red; Sn, green.

More in particular, the project will address: i) preparation of tin-porphyrin/amino acids conjugates for the achievement of long-lived charge separation by Proton-Coupled-Electron-Transfer; ii) desing and assembling of multi-porphyrin 3D multiporphyrin containers for molecular recognition. The combinatorial flexibility granted by the metald-mediated approach should promote the obtainment of a common library of Sn^{IV}-porphyrin metal scaffolds. Inorganic, organic and supramolecular synthetic methodologies will be employed alongside a variety of characterization techniques (in solution: ESI-MS spectrometry, multinuclear advanced NMR, UV-vis, emission and CD spectroscopies; in the solid state: single crystal X-ray diffraction by means of the local ELETTRA synchrotron light source). Photochemical and receptor properties of selected assemblies will be addressed by additonal techniques, also in collaboration with other research groups. A six month stay abroad will be strongly recommended, in order to expand and differentiate the PhD fellow skills, research methodologies, as well as working and social environments.

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PROJECT N°: 10A

Dynamic supramolecular systems with *time-control* for smart applications

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Life is composed of supramolecular systems that are dynamic and adaptive to the environment.[1] Living systems evolve over time to allow life processes to occur. In particular, proteins exert the most fascinating roles, being able to control 1) cellular movement (through the cytoskeleton); 2) molecular cargo entry into, and exit out of, cells (through membrane channels and receptors); 3) biochemical pathways for the synthesis of bioactive molecules (through enzymatic cascades), and so on. However, proteins display a structural complexity that risks denaturation, with subsequent loss of function, upon change of experimental conditions.

These shortcomings could be overcome by using instead *minimalistic peptides* made of just a few amino acids that share great chemical diversity just as the building blocks of proteins. Upon design, they can self-organize hierarchically into systems that span from the nano- to the macroscopic scale – thus forming nanostructured materials that we can see by eye.[2] Importantly, they are more robust than proteins, and can mimic enzymatic activity when assembled into a supramolecular structure, similarly to a folded protein with hydrophobic pockets for reactions to occur.[2b] The function can be switched on/off with assembly/disassembly, to give as waste simply water and biodegradable molecules that are environmentally-friendly. These findings open thus the way to smart systems that can change over time, and that could be coupled to others by means of orthogonal chemistry for advanced functions, such as selective chemical separation from a mixture.[3]

Inclusion of amino acids with different functional groups can be exploited for a variety of chemical modifications, such as metal coordination, redox reactions, phosphorylation, and so on, potentially also in a reversible manner. These processes could in fact act as triggers to introduce changes in the system and make it *adaptive* to experimental conditions. This ability, coupled to chemical reactions that yield metastable products, opens the way to the design of complex, multifunctional systems that can evolve over time and adapt to the environment. For instance, fine control over kinetics can yield systems with time-control,[4] *i.e.*, at the desired time they self-organize into a functional material of *controlled lifetime*, and then disassemble into either the starting material (to allow for repetitive cycles), or into a different product (that could even trigger another reaction). In other words, multi-component supramolecular systems will be designed to achieve a *"reaction-clock"* (Fig. 1) to recapitulate fine levels of complexity displayed by elements that compose living systems.

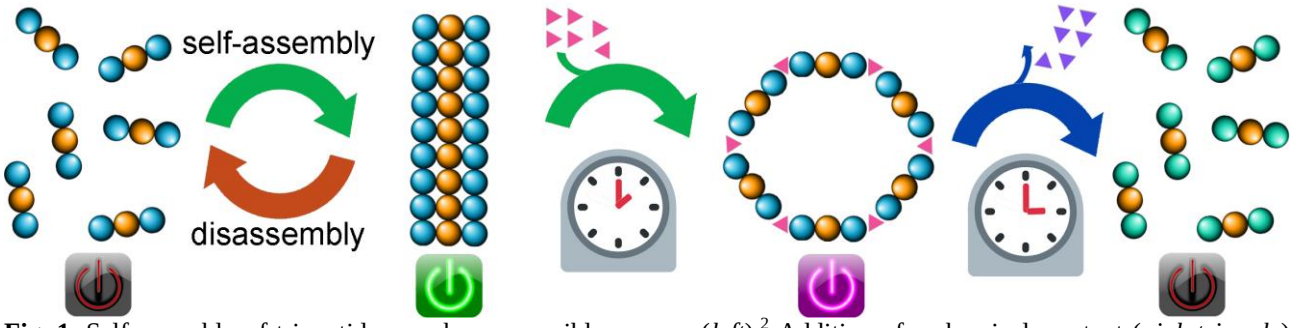

Fig. 1. Self-assembly of tripeptides can be a reversible process (*left*).[2] Addition of a chemical reactant (*pink triangle*) can lead to structural a rearrangement to change the function of the system (*pink switch*). If the latter is a metastable product, its conversion into a final product will switch off the system. Kinetics control the *"reaction-clock"*.

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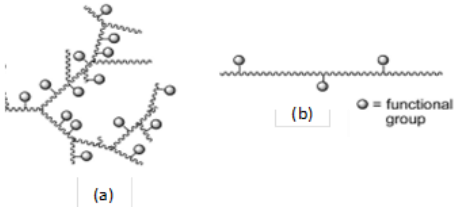
PROJECT N°: 11A

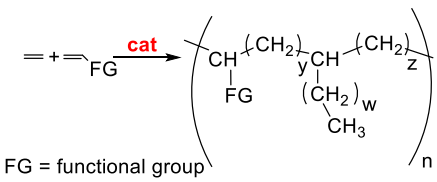
Development of multinuclear Pd complexes as potential catalysts for polymerization reactions

Supervisor: **Prof. Barbara Milani**
email: milaniba@units.it

One of the major unsolved problems in the field of polymer chemistry is represented by the synthesis of **functionalized polyolefins**. Polyolefin materials comprise the large majority of all polymer production by weight.[1] Nevertheless, they suffer of scarce surface properties such as adhesion, dyeability, printability and compatibility. The incorporation of polar functional groups into the polyolefin skeleton will improve such properties, expanding the range of applications, and it has long been the focus of synthetic efforts. Among the different typologies of functionalized polyolefins, two classes are highly desirable (Figure to the right): (a) branched polyolefins having randomly distributed functional groups; (b) linear polyolefins having the polar monomer into the main polymer chain.

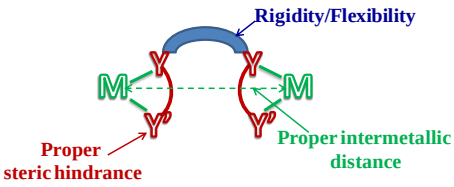


The direct, homogeneously catalyzed, copolymerization of ethylene with polar vinyl monomers is the most powerful tool to obtain these polymeric materials through a sustainable technology (Figure below)**.**[2] However, the catalytic systems reported so far show productivity values thus far below for any industrial exploitation of the reaction. Thus, there is a strong requirement for novel catalysts that lead to an enhancement of catalyst efficiency of two or three orders of magnitude, at the same time, incorporate around 20 % of the polar monomer, and control the macromolecule architecture.[1,2]



Since several years, the group of Prof. Milani has been active in the field of catalysis for polymerization, mainly studying mononuclear Pd(II) complexes with bidentate nitrogen-donor ligands, N-N.[3] The **present research project** deals with the **development of multinuclear homogeneous catalysts** for the target reaction based preferentially on **palladium(II) complexes**.

The research activity of the successful candidate encompasses different steps: ***i.*** the synthesis and characterization of a ***library of polydentate ligands*** featuring two bidentate compartments and tailored according to peculiar features (Figure to the right); ***ii.*** the synthesis and characterization of ***homo- and hetero-dinuclear complexes***; ***iii.*** the detailed study of their ***catalytic behaviour*** in the target copolymerization reaction; ***iv.*** the ***characterization of the produced macromolecules***, mainly by NMR spectroscopy; *v.* ***mechanistic studies*** aimed at unravel the major intermediates involved in the catalytic cycle. The research will be carried out in the frame of several national and international collaborations and some periods in other research groups can be foreseen.



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PROJECT N°: 12A

DEVELOPMENT OF SUSTAINABLE CATALYTIC PROCEDURES FOR THE SELECTIVE SYNTHESIS OF NOVEL ORGANOFLUORO COMPOUNDS

Supervisor: Prof. Patrizia Nitti
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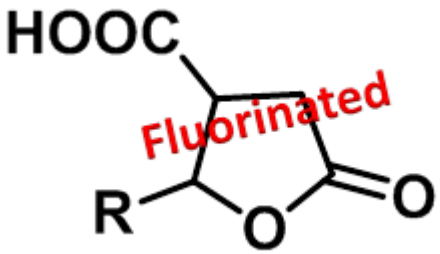
According to the Twelve Principles of Green Chemistry, the design of sustainable protocols for organic synthesis is best accomplished by use of catalytic procedures, using either enzymatic or transition metal-based catalysts. As a consequence, in the last decade much effort has been employed in the development of highly active and selective catalysts which promote reactions of interest in the synthesis of target molecules.
Paraconic acids are a class of natural highly functionalized γ-lactones, bearing a carboxylic group at C-beta. Their enantioselective synthesis therefore represents an intriguing challenge for the organic chemist.[1] Natural paraconic acids having a methylene at C-alpha are typically biologically active[2] as they can act as alkylating agents in Michael type addition reactions.
Organofluorine compounds are widely used in various areas of chemistry, including agrochemistry, materials science, and medicinal chemistry. It is well known that the presence of **fluorine atoms** or **fluorine-containing motifs** in organic molecules alters their physical and chemical properties, such as their electronic nature, conformation, lipophilicity, and stability, and it can also affect their metabolism. In a medicinal chemistry context, the improved binding affinities and biological activities of **fluorinated compounds** have prompted organic chemists to develop new synthetic strategies for the selective incorporation of **fluorine** into organic compounds.

The project is focussed on the synthesis of **fluorinated gamma-lactones**, in enantiomerically enriched form. For this purpose, in the crucial steps of the synthesis (*e.g.* fluorination reactions, selective reduction of carbonyl group[3]) catalytic strategies including transition-metal catalyzed reactions and enzymatic resolution procedures will be developed.



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PROJECT N°: 13A

A new era in the treatment of Schistosomiasis in pediatric patients: new crystalline forms, solid solutions and supersaturated systems of Praziquantel

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Praziquantel (PZQ) is the most used anthelmintic drug for the treatment of Schistosomiasis, a disease that causes almost 10,000 deaths a year. This drug is characterized by a low water solubility and bioavailability. Therefore both high dosage (40 mg/Kg) and large tablets are needed to be effective. That, combined with the disgusting taste of the drug, results in a difficult compliance and adherence to the therapy, especially in pediatric patients. Since children are the main target of treatment, given that Schistosomiasis causes serious damage to vital organs in the pediatric population, improving oral absorption of the PZQ would be desirable to reduce the high therapeutic doses, as well as performing an adequate taste masking, so as to encourage adherence to therapy. The project is based on three alternative approaches to be developed through the use of a *solvent-free* technique such as the mechanochemical activation in vibrational mills and cryomills, exploiting the remarkable PZQ tendency to new solid forms, as documented in the last 5 years of researches (see aforementioned bibliography). First of all, the aim is to continue the search for new anhydrous/hydrate PZQ polymorphs, with improved biopharmaceutical performance and antihelmintic activity. Then, super-saturated systems and solid solutions with suitable GRAS excipients will be investigated, to guarantee an increased in vivo absorption and at the same time a pleasant taste. A single process will therefore be used in order to obtain systems with different solid states, thanks to the know-how of mechanochemical activation and the in-depth-knowledge of solid forms' formation mechanisms by the research group and wide cooperation network. The multidisciplinary approach for evaluating the systems will allow a modern holistic view of functional materials not limited to the molecule or the process while including the formation mechanism, the physico-chemical and biopharmaceutical characterization, the (*in vitro and in vivo*) bioactivity and pharmacokinetic analyses. This will allow the student to interact with experienced researchers from different research fields (not only chemical) gaining a very broad knowledge over the three years' period. The collaboration network across Europe involved in this project is wide and in continuous growth, enclosing researchers from Elettra-Sincrotrone, University of Bologna, Turin, Padua, Leicester, Cambridge, McGill University-Montreal, Swiss Tropical and Public Health Institute of Basel, University of Aix-Marseille, Lisbon, Zagreb, Limerick and Granada. This Ph.D. project will combine several hot topics in the current chemical and pharmaceutical research, namely, pediatric formulations, neglected tropical diseases, crystal engineering, mechanochemistry, poor bioavailability issues while presenting a new approach to the development of functional materials and suitable formulations for praziquantel.

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PROJECT N°: 14A

Design, synthesis and application of Carbon Nanodots

Supervisor: Prof. Maurizio Prato
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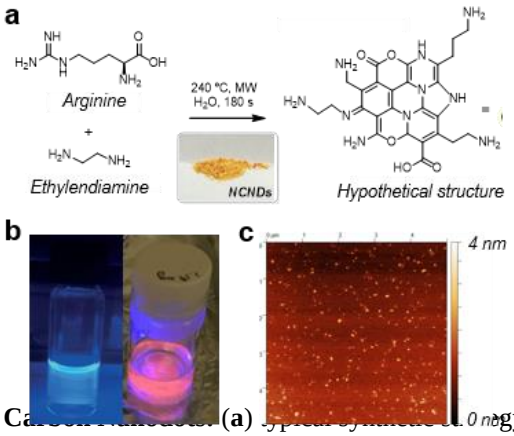
This project is focused on Carbon Nanodots, the latest member of the carbon nanomaterials family. Applications include photo- and electro-catalysis, drug delivery and contrast agents.

Carbon Nanodots are carbon-based quasi-spherical nanoparticles with size below 10 nanometres. In contrast with other carbon-based nanomaterials they show good water solubility and are fluorescent; moreover, they have low toxicity. These features make them suitable for both technological and biological applications.



Carbon Nanodots (**a**) typical synthetic strategy; (**b**) blue and red-emitting carbon nanodots; (**c**) AFM image of the studied material.

Our group is particularly interested in the chemistry of carbon nanodots, from the investigation and engineering of their properties, up to their application. Examples are the study of core and surface properties (including electrochemical and chiral properties), the engineering of fluorescence, and the use of carbon nanodots in light-emitting devices, as organo- and photo-catalysis, and as drug carriers.[1]

The synthesis of this material is typically performed with a simple and inexpensive microwave reaction.[2] In this process, different organic precursors are chosen (e.g. amino acids, small aromatic and aliphatic molecules) to tailor the properties of the target material.

The PhD student will develop both synthetic and instrumental skills. The synthesis of small molecules, as well as carbon nanodots will be performed. The obtained materials will be analysed with state-of-the-art spectroscopic methods, including nuclear magnetic resonance (NMR), optical spectroscopies, atomic force microscopy (AFM), transition electron microscopy (TEM) and infrared spectroscopy (IR). Our group has also a strong track record of fruitful collaborations, that involve also the use of X-ray facilities at the synchrotron (Trieste) or at CIC biomaGUNE (San Sebastian, Spain). For the optimal development of collaborative projects, it is likely for PhD students to perform a research stay abroad.

Currently, seven members of the group are involved in this frontier research line, thus creating a lively and stimulating environment for the professional development of new members. Our group is committed to interdisciplinarity and the student will be exposed also to other fields related to carbon nanomaterials, that represent the group core expertise.

Typically, the PhD work starts from a project that is ongoing in the group. Then, the individual interests and attitudes of the student come into play and shape the development of his path into research.

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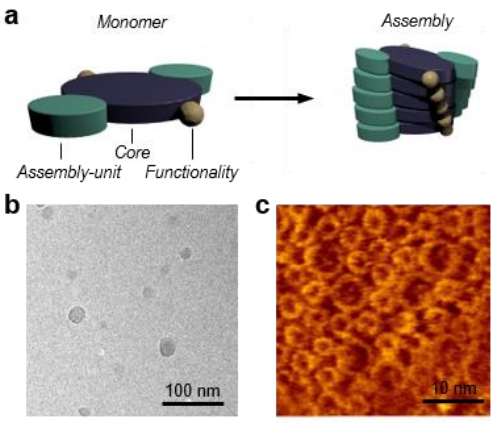
PROJECT N°: 15A

Nonequilibrium supramolecular synthesis

Supervisor: Dr. Giulio Ragazzon
Co-supervisor: Prof. Maurizio Prato
email: gragazzon@units.it

This project is focused on the design, synthesis and assembly of nonequilibrium supramolecular systems. Soft materials for catalysis and energy conversion are envisioned as applications.

Self-assembly processes are typically governed by thermodynamic equilibrium. A current challenge is to go beyond equilibrium, thus being able to obtain self-assembled structures that are not dictated by equilibrium constraints.[1,2] Two possible strategies are the multistep assembly of complex structures[1], and the exploitation of an energy source to drive unfavourable processes, as occurring in natural systems.[2] Our group is approaching this research field, combining the expertise of Dr. Ragazzon in nonequilibrium systems[2,3] with the excellent background in organic synthesis and self-assembly of Prof. Prato[4].



Self-assembled structures: (**a**) assembly reaction of a functional monomer; electron microscopy images of (**b**) nonequilibrium catalytic vesicles[3] and (**c**) hierarchically organized perylene bisimides[4].

The project includes the design and synthesis of novel self-assembling building blocks. In these monomers, suitably designed functional groups provide room for further hierarchical assembly, or the capability to assembly in response to an energy supply.

The student is expected to become proficient both in synthesis and analytical methods. The obtained structures will be analysed with state-of-the-art spectroscopic methods, including nuclear magnetic resonance (NMR), optical spectroscopies, atomic force microscopy (AFM), transition electron microscopy (TEM) and infrared spectroscopy (IR). Our group has also a strong track record of fruitful collaborations, that involve the use of X-ray facilities at the synchrotron (Trieste) or at CIC biomaGUNE (San Sebastian, Spain). For the optimal development of collaborative projects, it is likely for PhD students to perform a research stay abroad.

The student will be fully integrated in the group of Prof. Prato, thus experiencing a lively and stimulating environment for the professional development of new members. Our group is committed to interdisciplinarity and the student will be exposed to other fields related to carbon nanomaterials, that represent the group core expertise.

Typically, the PhD work starts from a project that is ongoing in the group. Then, the individual interests and attitudes of the student come into play and shape the development of his path into research.

References:

[1] "The construction of supramolecular systems", G. Vantomme, E. W. Meijer, *Science* **2019** 363, 1396-1397;
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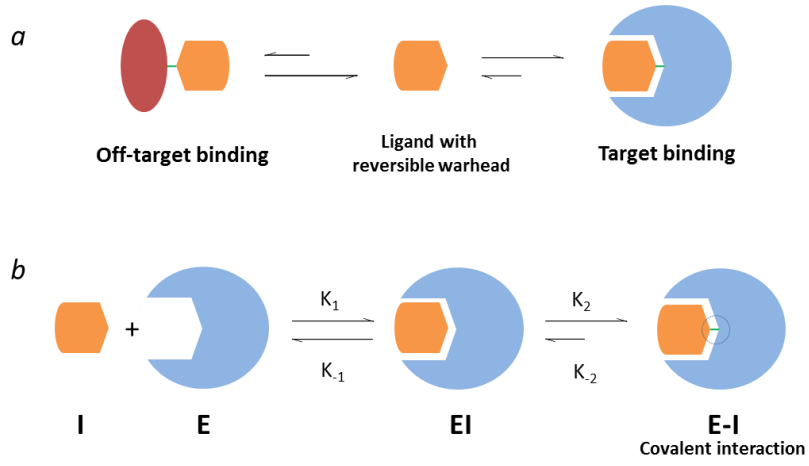
PROJECT N°: 16A

Covalent reversible kinase inhibitors as potential neuroprotective agents in neurodegenerative diseases

Supervisor: Prof. Giampiero SPALLUTO
email: spalluto@units.it

Targeting protein kinases with small inhibitors is one of the most challenging fields in pharmacology and drug discovery. Among the different types of kinase inhibitors, covalent inhibitors that bind to the ATP-binding site, prevent the interaction of ATP with the kinase and are characterized by a long half-life, thus maximizing the effectiveness of the inhibition while reducing the exposure to the drug.[1] The potential toxicity and off-target activity (reactivity towards proteins, DNA and glutathione) could be overcome by developing covalent kinase inhibitors with well-balanced molecular recognition and able to interact reversibly with the target (figure, panel A).[2] The targeted covalent reversible inhibitors recently described in literature show common features, in particular a heterocyclic core structure (driving portion), generally resembling that of reversible ATP-competitive inhibitors, carrying at a proper position an electrophilic "warhead", such as Michael acceptors, epoxides or acetylenes, that covalently interact with a specific cysteine, serine, threonine or lysine residue in the target protein (figure, panel b).[2] In this project, three specific kinases will be targeted: the serine/threonine kinases CK-1δ (casein kinase 1 delta) and GSK-3β (glycogen kinase 3 beta) and the non-receptor tyrosine kinase FYN. These proteins are involved in neuroinflammatory processes which prompt us to investigate them in view of searching new strategies for the treatment of neurodegenerative diseases.[3]



The project will involve the initial rational design of the potential covalent reversible inhibitors for the three kinases by identification of: 1. nucleophile target residues on the proteins' ATP binding sites; 2. driving portions; 3. electrophilic warheads. Following, potential covalent inhibitors will be synthesized and characterized. Characterization of a protein-ligand covalent interaction requires specific biochemical protocols. In order to achieve these data, CK-1δ, GSK-3β and FYN will be produced and purified. In addition, investigation of the specific pattern of inhibitor-kinase interactions, requires the 3D structure of this complex which will be obtained by co-crystalization methods. This work will be performed in collaboration with Dr. Paola Storici (Elettra Sincrotrone Trieste). This work-flow will allow to immediately highlight optimal modifications to be performed on the ligand structure (structure-based design), leading to high potent inhibitors in a short time. Selected covalent inhibitors will be then tested in vitro models of neuroinflammation and/or neurodegenerative diseases in order to validate their potential for the treatment of these conditions.

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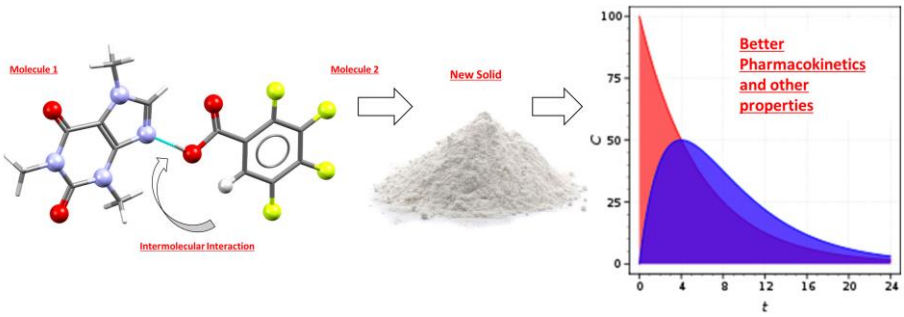
PROJECT N°: 17A

Probing the formation and stability of multicomponent solids in the presence of common pharmaceutical excipients

Supervisor: Prof Dario Voinovich
email: vojnovic@units.it

Cocrystallization technology that is the formation of **crystalline single-phase materials** containing a stoichiometric ratio of **two or more molecules**, has gained popularity due to its potential for improving properties of drugs and providing a versatile opportunity to synthesize organic solids by design, using **supramolecular synthon approach**. Indeed, several examples of cocrystal strategy have been already showed to bring significant advancements from an early development option (support preclinical studies) to marketed drug products. For example, **Entresto (valsartan−sacubitril)** by Novartis and **Suglat** (iproglifozin−L-proline) by Astellas Pharma represent two **multi-million cocrystal** products that have singificantly contributed to the development of better pharmaceutical treatments. Additionally, an ertugliflozin−L-pyroglutamic acid cocrystal formulation by Pfizer is under late stage development.[1]



In order to develop a cocrystal into a pharmaceutical dosage form such as tablets, however, it is necessary **understanding** cocrystal **stability** under several conditions. Noteworthy, a specific cocrystal system needs also to be characterized in the presence of **excipients or additives**, and during various processing steps in the manufacture of solid dosage form where significant mechanical stress is usually involved. **The formulation pathway** of a pharmaceutical cocrystal is therefore **complex**, and the effect of process-induced stress should be considered simultaneously along with the effect of particular polymeric excipients. In this context, recently a new technique namely **polymer-assisted grinding (POLAG)**[2] was developed for understanding the stability of hydrates.[3]

This PhD project focuses on the **fundamental understanding** of solid state cocrystallization and dissociation through competitive hydrogen bonding of important cocrystal systems. A **unique combination of expertise** in crystal engineering and advanced solid state characterization techniques will be used, that are facilitated through a series of **national and International collaborations**. Specifically, the PhD student will have the opportunity to work with collaborators from the University College London[4] (UK), and University of Insubria[5]. **The objective is to progress towards the deep understanding** of cocrystal formation/dissociation in the solid state, and at the same time **exploring new pathways for better medicines** and methods of drug delivery; changes to products, **new technologies** and applications **for the pharmaceutical and materials sectors**. This project, at the borderline of materials science offers a unique integration of approaches that can help **drawing general guidelines** for the selection of **suitable excipients during the industrial formulation of cocrystals**.

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PROJECT N°: 18A

Synthesis of new σR and GluN2b modulators as neuroprotective agents

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Sigma receptor (σR) are a class of non-opiod receptor that binds diverse classes of psychotropic drugs and are subdivided into two subtypes named sigma-1 (σ1R) and sigma-2 (σ2R). These receptors are widely distributed and both subtypes are involved in several pathologies. The σ1Rs are involved in neuroprotective and antiamnesic activity [1], modulation of opioid analgesia [2] and drug addiction [3]. Similarly, σ1 antagonists seem to be effective against the negative manifestations of schizophrenia, without producing extrapyramidal side effects [4,5]. The σ2R subtype has been recently purified and identified as transmembrane protein-97 (TMEM97) [6] and are overexpressed in many tumours. On the other hand, the N-methyl-D-aspartate receptors (NMDARs) are glutamate-responsive ion-channel receptors and likewise, for σRs, the NMDARs play key roles in synaptic transmission, synaptic plasticity, neuronal development, learning, memory and other physiological and pathological processes [7, 8]. Hence, antagonists of NMDAR (and, in particular, of the GluN2 subunits) are of interest as potential neuroprotective drugs to treat several CNS disorders. After several years of dealing with σR ligands, our aim is to discovery new chemical entities gifted with a pan-affinity towards σ1/GluN2b receptors acting as antagonists in order to develop new neuroprotective drugs useful for several neurodegenerative disorders aforementioned. Furthermore, the crystallographic structures of both receptors, σ1 and GluN2b are known, therefore our intention is to develop a new pharmacophore model for the GluN2b subunit, being its known ligands (i.e. infeprodil) gifted with low selectivity for this receptor. Finally, a recent *in vivo* mechanical allodynia assay developed by our coworkers [9], will be used to define the antagonism profile of the new synthesized compounds.

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