University of Trieste
Department of Chemical and Pharmaceutical Sciences

Doctorate in Chemistry

2025

Cycle 41

Research Projects

Positions 1-9: co-financed projects on predetermined topics

Position 10: project on a free topic chosen by the candidate among those described here

Position 11: project funded by Regione FVG with FSE fund on a predetermined topic

Position 12: project funded by EU with ERC starting grant funds on a predetermined topic

University of Trieste
Department of Chemical and Pharmaceutical Sciences

Projects for positions 1-9

Project for position 1 CHEM-07/A

Eco-design of biodegradable polymers by integrating digital tools with chemical and ecological data

Supervisor: Emanuele Carosati
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Background: The transition to sustainable polymers from renewable sources is crucial for reducing environmental impact, especially in sectors where dispersal is inevitable, such as cosmetics, agriculture, and food packaging. Ensuring biodegradability and eco-toxicity compliance is essential to meet stringent eco-design criteria.

The research Project: The project will be developed within the frame of the Be-UP European project (Project number 101178689: *Boosting the Industrial Uptake of Biodegradable polymers for packaging applications by implementing digital tools and advanced techniques to achieve a holistic sustainability goal*). The activity of the PhD candidate will focus on the development of computational fast-predicting models for biodegradability assessment, integrating several predictive tools into a holistic mathematical model for the biodegradation of monomers, oligomers and small molecules applicable as additives in the formulation of plastics for packaging products. The research team at DSCF formally involved in the Be-UP project (Emanuele Carosati, Lucia Gardossi, Fioretta Asaro) will contribute to the integration of multidisciplinary expertise in computational chemistry, biocatalysis, organic chemistry, physical chemistry, molecular modeling, and AI-driven molecule screening. Experimental data will serve as the foundation for refining the models, ensuring alignment with physical, environmental, and technological constraints. A key objective will be the development of an AI-assisted simulation tool, designed to predict degradation behavior under both controlled industrial settings and real-world environments, particularly marine conditions. This tool will incorporate datasets from the scientific literature, experimental biodegradation data, physical-chemical data on samples and environment, to improve predictive accuracy. The resulting on-line platform will allow for a broad accessibility and real-time validation. The integration between computational and experimental data will refine the models throughout the project.

Expected Outcomes: The project aims to deliver a validated computational framework for the rapid biodegradability assessment of oligomers, monomers and small molecules used in plastic formulations. The AI-assisted simulation tool will provide predictive insights into degradation behavior under diverse environmental conditions, supporting the eco-design of sustainable materials.

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Project for position 2 CHEM-05/A

Synthesis of dihydrophenazine based multifunctional polymeric and nanographene systems for optoelectronic and catalytic applications

Supervisor: Jacopo Dosso
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Co-Supervisor: Giacomo Filippini
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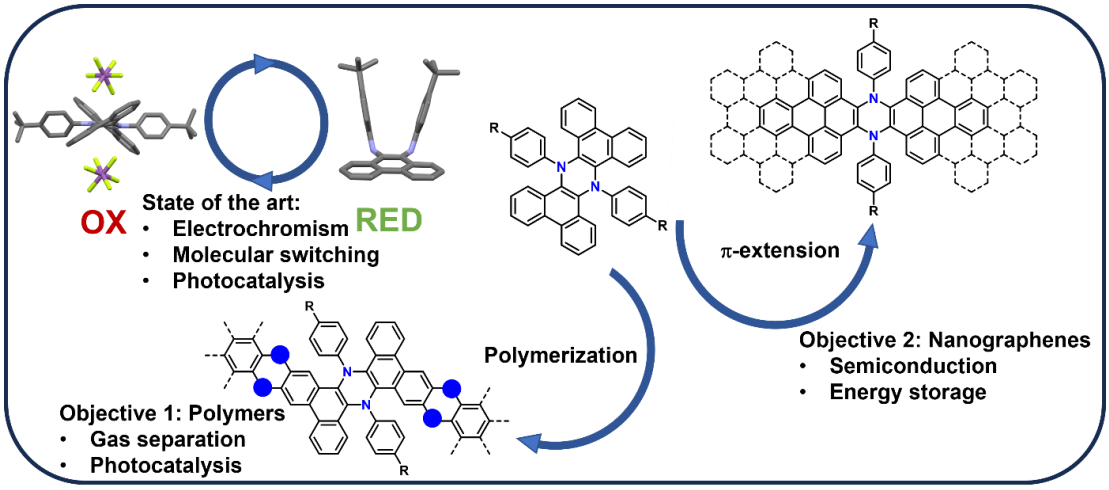
This PhD project aims at the development and implementation of a new generation of smart materials based on a novel class of dihydrophenazine molecular switches presenting an extended aromatic structure. Recent research in the field proved that carefully designed dihydrophenazine systems can be effectively converted to their aromatic dicationic form upon two electron oxidation.[1] Interestingly, this oxidation occurs with a dramatic change in optoelectronic properties and with a marked conformational switching, which is of great applicative potential.[1,2] Also, functionalized derivatives have been successfully exploited in our group as photocatalysts in both the reduced[3] and oxidized form.[4] As such, these molecules are ideal candidates to build novel materials, presenting different properties and behaviours depending on their oxidation state. To reach the desired smart materials, the project revolves around the development of functionalized dihydrophenazine derivatives that can be included in polymers and nanographene systems presenting unprecedented switching capabilities. This aspect is particularly interesting since it could result in a wide range of strategic applications ranging from gas capture/separation, photocatalysis, and semiconduction, producing a new asset in the development of sustainable technologies that can help reduce the impact of human activities on the environment.



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(3) Gentile, G.; Bartolomei, B.; Dosso, J.; Demitri, N.; Filippini, G.; Prato, M. *Chem. Commun.* **2023**, *60*, 602–605.
(4) Prato, M.; Dosso, J. *Chem. Commun.* **2025**, *61*, 2584–2587.

Project for position 3 CHEM-07/A

Development of ULK1 and CK1δ kinases inhibitors to study their role in autophagy

Supervisor: Stephanie Federico
Co-supervisor: Paola Storici
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This project focuses on the investigation on two human protein kinases, ULK1 (Unc-51 Like Kinase 1) and Casein Kinase 1 delta (CK1δ), which are often deregulated in various types of cancer and neurodegenerative diseases. Remarkably, both kinases can play complementary roles in regulating autophagy, a catabolic process essential for the degradation and recycling of intracellular components, crucial for cell survival under stress conditions.[1]

The ULK1/ATG13/FIP200 complex initiates autophagy, and ULK1 has emerged as a promising target for its inhibition in mammalian cells.[2] CK1δ has also been linked to autophagy regulation; recent papers reported that CK1δ/ε silencing increases ULK1 expression and enhances autophagic flux, while another that CK1δ positively affects autophagosome formation.[3,4]

The relationship between autophagy and cancer or other neuropathological conditions is tightly regulated and is complicated by the fact that autophagy can have both beneficial and detrimental effects. In order to investigate the diverse roles of ULK1 and CK1δ in this multifaceted process, availability of a pharmacological tool is mandatory. For ULK1, most of reported inhibitors suffer for limitation in cellular potency, selectivity, and/or PK properties, making their development challenging.[5] In the case of CK1δ inhibitors, tools with optimal pharmacological profile to be used to investigate CK1δ effect in autophagy are missing. Therefore, this project aims to identify and develop small-molecule inhibitors targeting ULK1 and CK1δ, investigate their molecular interaction mechanisms, and evaluate their effects on autophagy in cancer cells.

Pregress results have been already obtained in our research teams. A recent screening campaign identified some hit compounds, validated for ULK1 inhibition, while we lately have developed highly potent CK1δ inhibitors which are useful starting points to develop new compounds with the required properties of selectivity, solubility and stability.

This project integrates cutting-edge techniques in medicinal chemistry, biochemistry, and structural biology to develop novel therapeutic tools targeting ULK1 and CK1δ, with potential applications in treating cancers resistant to conventional therapies.

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1. Wang, C., Wang, H., Zhang, D. et al. Phosphorylation of ULK1 affects autophagosome fusion and links chaperone-mediated autophagy to macroautophagy. Nat. Commun. 9, 3492 (2018).
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Project for position 4 CHEM-05/A

Photochemical Valorization of Phenols

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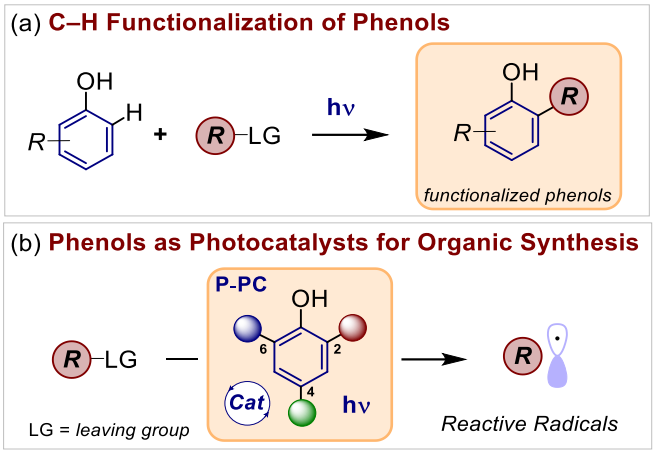
Co-Supervisor: Dr. Jacopo Dosso
email: jacopo.dosso@units.it

Phenols are extremely relevant chemical functionalities in natural, synthetic and industrial chemistry. Natural products containing phenols are numerous and include hormones, vitamins, and neurotransmitters.[1] In addition, about ten percent of the top 200 selling pharmaceuticals contains at least a phenol moiety, and several others require the use of phenolic compounds as synthetic intermediate for their production.[2] The importance of phenols is also due to the fact that these chemical entities may be produced from readily available, renewable and inexpensive biomasses, such as lignin.[3] Phenols and their conjugate bases, namely phenolate anions, are electron rich aromatic species which show a strong nucleophilic character.[4] In addition, phenolates are good organic chromophores that may absorb light within the visible region when functionalized with electron withdrawing groups (EWGs).[5] Despite the establishment of the propensity of excited phenolate anions to undergo a photo-induced electron ejection in the 1940s,[6] the mechanism has found limited applications in synthetic organic chemistry to date.[5,7-9] This project intends to design and develop novel photochemical methodologies for either the direct C-H functionalization of phenols or to employ them as catalysts in organic synthesis to photochemically initiate important radical transformations (Figure 1). The optimization of these photochemical processes will be supported by the implementation of mechanistic studies. Lastly, the photochemical efficiency and productivity of the designed approaches will be enhanced under continuous flow conditions.

Figure 1



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Project for position 5 CHEM-05/A

Precise targeting of biological samples for high resolution Cryo-CLEM microscopy using synthetic chemistry

Supervisor: Pierangelo Gobbo
Co-supervisor: Martina Conti
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Background: Cryogenic Correlative Light and Electron Microscopy (Cryo-CLEM) is an advanced imaging technique that combines fluorescence microscopy with electron microscopy to study the ultrastructure of biological samples at high resolution.[1] However, a major challenge in cryo-EM-based approaches for studying cells is to improve their adhesion and localization on standard TEM grids.[2,3] Synthetic chemistry enables advanced labelling strategies to enhance targeting accuracy and improve the reproducibility of the technique.

Project Goal: The project aims to develop a highly versatile methodology to produce nano- and micro-patterns for cell-adhesion on materials for improved control of the Cryo-CLEM imaging on cellular samples. This approach will enable better cell adhesion and precise localization of target cells, ultimately leading to enhanced imaging of their ultrastructures.

Preliminary results and next steps: The student will start by synthesising and characterising the photoactive molecule Sanpah (Fig 1, top), developed by the Gobbo's group to create substrates suitable for the growth of living cells. The student will then develop methods to adhere Sanpah film on the substrate (carbon coated TEM grids, transparent polystyrene, PDMS, glass) by exploiting the phenyl azide moiety. In general, by irradiating Sanpah with 365 nm light in the presence of the substrate, nitrene insertion into different types of bonds is induced.[4] This allows the covalent functionalisation of the substrate with N-hydroxysuccinimide-activated carboxylic acid, present at the other end of the Sanpah molecule, making the substrate reactive towards nucleophiles (namely amines or thiols) and opening up the possibility of covalently binding proteins, including cell membrane proteins and extracellular matrix proteins, to the substrate. As the nitrene insertion reaction is photo-induced, this will allow the creation of nano- and micro-patterns of proteins on the substrate, which are desirable to drive the adhesion of cells to specific areas of a substrate and make the cells much easier to find with microscopes. Based on initial results, the student may explore various directions which include introducing the new substrates into the cryo-CLEM imaging workflow (Fig 1, bottom) using both the state-of-the-art cryo-confocal and cryo-FIB/SEM facilities at the CNR-IOM, and/or functionalising the head of a thermoresponsive polymer chain with a phenyl azide to graft the polymer chin onto a substrate and open a route towards the fabrication of polymer-based substrates for imaging.

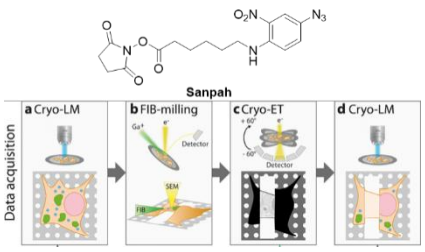

Figure 1. The photoactive molecule Sanpah (top) and the workflow of Cryo-CLEM imaging of a cell on a standard substrate, that will be modified to improve the cell

Student training: The student will be part of a dynamic and interdisciplinary collaboration between the Gobbo Group at the University of Trieste and the Cryo-EM facility at CNR-IOM in Trieste. Through this project, the PhD student will gain hands-on experience in synthetic chemistry, photolithography, and advanced surface characterization techniques (*e.g.*, AFM, indentation). In addition, the student will explore the integration of the new patterned materials they will fabricate into the Cryo-CLEM workflow analysis. This opportunity offers a dynamic research environment, fostering skill development, professional growth, and collaboration across both groups.

References: [**1**] A. Pepe *et al*, *Methods in Cell Biology* (eds. Müller-Reichert, T. & Verkade, P.) vol. 187 175 (Academic Press, 2024). [**2**] S. Jun *et al*, *Protein J* **38**, 609 (2019). [**3**] J. A. Pierson *et al*, *Current Opinion in Structural Biology* **89**, 102934 (2024). [**4**] J. P. Lee *et al*, *Biomaterials* **102**, 268 (2016). [**5**] S. Klein *et al*, *Commun Biol* **4**, 1 (2021).

Project for position 6 CHEM-05/A

Photosynthetic Protocells for Sustainable Urea Synthesis

Supervisor: Pierangelo Gobbo **Co-supervisor:** Federica Battistin
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Background: Protocells are synthetic microcompartmentalised systems that can mimic at least one behaviour of living cells, such as chemical communication, information storage, and ability of growing and dividing.[1] The next challenge of protocell engineering is to develop protocells capable of performing photosynthesis, as this would open up a route towards the next generation of life-like materials capable of harvesting the power of sunlight to produce molecules of interest.

Project Goal: This project aims to develop a synthetic route towards the first photosynthetic protocells capable of CO_2 and N_2 fixation for the light-assisted synthesis of urea. Why urea? Urea is a molecule of wide industrial use and interest, whose production still relies on the highly energivorous Haber-Bosch and Bosch-Meiser processes. The development of protocells capable of producing urea *via* a photocatalytic process would provide an important step towards a greener and sustainable world.

Preliminary results and next steps: To achieve this ambitious goal, the student will begin by learning the techniques developed by the Gobbo group to fabricate and characterise protocells (Figure 1a, b).[2] This will require the student to develop skills in small molecule and polymer synthesis and characterisation, as well as learning optical and electron microscopy techniques. The student will then begin to synthesise and investigate CeO_{2-x} nanorod photocatalysts, which have been reported to successfully convert CO_2 and N_2 to urea.[3] The student will then develop a method to incorporate the photocatalyst into a protocell model, which may include colloidosomes,[4] coacervate microdroplets [5] or polyoxometalate coacervate vesicles,[6] and investigate the capabilities of the resulting photosynthetic protocells. Based on the preliminary results obtained, the student will then be expected to develop the project in a number of directions according to their success and interests. This may include exploring other forms of photocatalysis, assembling the photosynthetic protocells into leaf-like prototissues, and incorporating CO_2-producing proto-organelles (*e.g.*, yeast) into the protocell membrane to provide a high local concentration of substrate (Figure 1c).

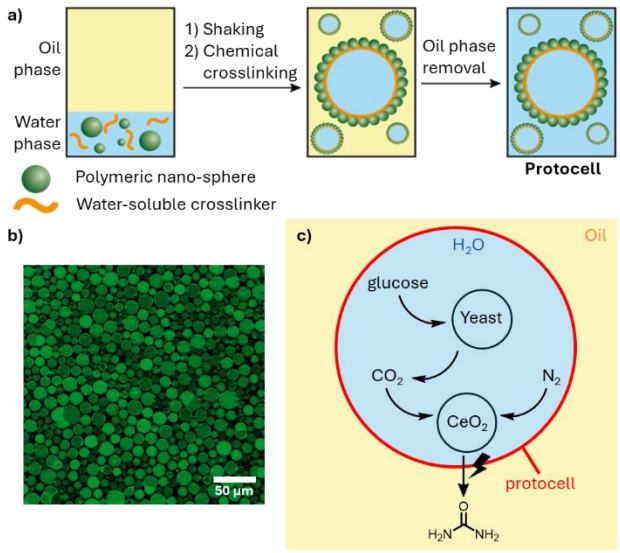

Figure 1. a) Scheme showing the Pickering emulsion technique used to obtain chemically crosslinked protocell membranes in water. b) Microscopy image of protocells. c) Scheme showing compartmentalization of a dual proto-organelle population capable of operating a signaling cascade within individual water in-oil emulsion droplet.

Student training: The student will join a dynamic and interdisciplinary collaboration between the Gobbo Group at the University of Trieste and Enphos S.R.L. This unique environment will provide the student with a comprehensive training experience, covering synthetic chemistry, biotechnology, Python programming, scientific writing, and scientific illustration, along with essential soft skills. The student will join a dynamic research group with important connections with several groups in Europe, Canada, and Japan [7] where a period abroad could be organized.

References: [1] A. Rebasa-Vallverdu, *et al*, *Eur. J. Org. Chem.* **2023**, *26*, e202300529. [**2**] P. Gobbo, *et al.*, *Nature Mater* **2018**, *17*, 1145. **[3]** *S. Yang et al., Angew. Chem. Int. Ed.* **2023**, *62*, e202312076. [**4**] J. H. Park et al, *Eur. J. Org. Chem.* **2022**, e202200968. [**5**] C. Donau, *et al., Nat Commun* **2020,** *11*, 5167. [**6**] P. Gobbo, *et al. Nat Commun.*, **2020**, 11, 41. [**7**] T. Kojima *et al*, *Adv. Sci.* **2025**, 2409066.

Project for position 7 CHEM-03/A

Single-Atom Photocatalysts for hydrogen and Biofuel Production

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The increasing energy demand and the depletion of fossil-fuel reserves, threatening our energy security and the environment, have aroused intense global concern. To mitigate this, the EU aims to become climate-neutral by 2050, by targeting at the next-generation of biofuels from non-land and non-food competing crop wastes. Butanol (BuOH) and hydrogen (H_2), if produced from bio-ethanol, are among the most promising advanced biofuels due to their high energy content, long shelf-life and, in case of BuOH, compatibility with the current engines and fuel distribution infrastructure. However, their production faces challenges due to the low yields and selectivities, even when noble-metal catalysts and harsh reaction conditions are employed. In the framework of the Horizon project GlaS-A-Fuels we envision a holistic approach to transform bio-ethanol to bio-BuOH and to green-H_2 employing recyclable and cooperative single-atom catalysts from earth-abundant elements. The group has already demonstrated the criticality of the single atomic nature of transition metals in heterogeneous catalysis.[1,2] Moreover, engineering of the photoresponsive support (e.g. a semiconductor) is a fundamental demand, because it can affect catalytic activity and selectivity by means of appropriate band matching or affinity with the reagent, as demostrated for graphitic carbon nitride (g-CN) photocatalysts,[3,4] or tailored TiO_2 brookite active in alchol photooxidation.[5] Hence, the dual metal-atom/support cooperativity and stabilization of difficult to achieve reaction intermediates obtained via engineering the coordination sphere and the electronic structure of the catalysts will be a primary objective. [6] To realize this, the concerted effort of five EU partners will integrate key expertise in materials science for solar and thermal energy harvesting, catalysis, laser technologies for tuning light-matter interactions, intelligent process-control systems and advanced theoretical and experimental tools for catalyst function and process understanding. The PhD candidate will therefore have the opportunity to work at the very frontier of material science for catalysis, acquiring knowledge in modern synthesis of materials, advanced characterization and catalysis for sustainability.

References:

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Project for position 8 CHEM-08/A

Development and validation of an artificial biomimetic barrier for skin permeation studies

Supervisor: Massimiliano Pio di Cagno
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Co-supervisor: Greta Camilla Magnano

The introduction of drug regulatory approval based on *in vitro* evidence, *i.e.*, biowaivers [1], instead of *in vivo* study can be considered as a first significant step towards the reduction of the number of *in vivo* studies [2] and the implementation of the 3 R's principle (Refine, Reduce and Replace).
In this context, several artificial biomimetic barriers have been introduced. PermeaPad® form Phabioc GmbH is one of the most implemented one both in the University and industrial sector. The PermeaPad® technology was developed at the University of Southern Denmark (Odense, Denmark) in 2013 by Di Cagno and Bauer-Brandl [3]. Originally, the PermeaPad® was manually assembled by depositing phospholipids, *e.g.*, phosphatidylcholine, between two support sheets, *e.g.*, cellulose hydrate, creating a "sandwich" structure. The manufacturing process was later standardized and mechanized. The PermeaPad® barrier is currently laser-cut into small disks, *i.e.*, pads, which are ready-to-use barriers suitable for permeability studies in Franz cells and side-by-side cells. Additionally, PermeaPad® is available in a 96-well plate ready-to-use format. The original PermeaPad® was designed for study the oral absorption of drug. However, a skin-specific version of the PermeaPad® has also been recently introduced [4].
Even though this new skin barrier showed high biomimetic properties towards both pig and human skin, the manufacturing procedure of this type of barrier remains challenging, particularly in terms of scalability and automatization of the production.
Building on the already existing knowhow on such barriers, the goal of this Ph.D. project is to develop a new biomimetic artificial barrier designed for skin studies, with improved manufacturability features.
Specifically, in this project the PhD student will:

1) Screen different production batches (manufactured by Phabioc GmbH) in order to determine the most biomimetic type;
2) Perform stabiliy study to assess the durability and reliability of such barriers;
3) Test different semisolid formulations on the most promising barrier developed;
4) Compare the biomimetic properties of the artificial barrie with *ex-vivo* barrier (pig and human skin);

If the time allows, alternative types of biomimetic barriers for non-human application could also be attepted and explored. As scientific outcome, a minimum of three article in peer-reviewed journal can been forseen for such project.

References:

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[2] Amidon, G.L.; Lennernäs, H.; Shah, V.P.; Crison, J.R. A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of in Vitro Drug Product Dissolution and in Vivo Bioavailability. Pharm. Res. **1995**, 12, 413–420.
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Project for position 9 CHEM-04/A

Luminescent solar concentrators based on carbon dots

Supervisor: Federico Rosei
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In recent years, harnessing solar energy to reduce building energy consumption has become a hot research topic. Building Integrated Photovoltaic (BIPV) technology, which integrates photoconversion panels into buildings, has been identified as one of the most promising solutions. Among the various complementary technologies/alternatives to PV cells, luminescent solar concentrators (LSCs) have gained significant attention. LSC are optically active semi-transparent slabs, which can absorb and re-emit part of solar radiation. The emitted light is collected toward the borders of the slab, where it is photoconverted through thin standard PV cells. The key to maximizing light energy conversion efficiency in LSC devices lies in the careful selection of luminescent emitters. Several types of emitters, including fluorescent dyes, semiconductor quantum dots, and metal ligands, have been explored. The most critical issue is the significant energy loss due to reabsorption, which arises from the overlap between the absorption and emission spectra of luminescent materials. To address these challenges, carbon dots (CDs) emerged as a new type of luminophores for LSCs. CDs are attractive for LSC integration due to their tunable excitation and emission properties, broad absorption spectrum, eco-friendliness, large Stokes shift, low cost, good photostability, and high photoluminescence quantum yields (PLQYs). In this thesis, we want to develop doped CDs to tune their optoelectronic properties and maximize LSC photoconversion efficiency. The proposed research includes synthesis, structural and optoelectronic characterization of CDs, their integration in LSCs and functional characterization of LSC devices.

University of Trieste
Department of Chemical and Pharmaceutical Sciences

Projects for position 10

Project 1 for position 10 CHEM-03/A

Homogeneous catalysts for the synthesis of sustainable polyolefin-like materials

Supervisor: **Prof.ssa Barbara Milani**
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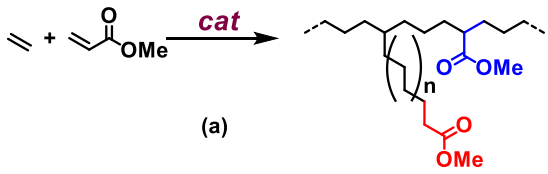
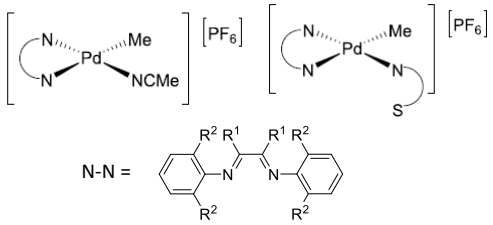
Polyolefins are the most widely applied synthetic plastics and nowadays the demand for plastic materials is ever increasing.[1] The chemical inertness of C-C bond makes polyolefins recalcytrant to degradation.[2] To achieve a sustainable plastic economy, chemical recycling processes need to be established and the introduction of polar functional groups into the polyethylene chain might represent predetermined breaking points,[1] leading to **sustainable polyolefin-like materials** (***SPO***).[3] One approach to obtain these ***SPO*** is based on the direct, controlled, homogeneously catalysed copolymerization of ethene with polar vinyl monomers, such esters, ethers or carbonyls.[3]

Prof. Milani has a consolidate experience in the homogeneously catalysed copolymerization of ethene with acrylic esters to obtain **functionalized polyolefins** (Fig. a). The best performing catalysts so far are based on Pd(II) complexes with alfa-diimine ligands (Fig. b). Particular attention was addressed to the control of the factors affecting the macromolecule microstructure, to drive the insertion of the polar monomer into the polyolefin main chain.[4]

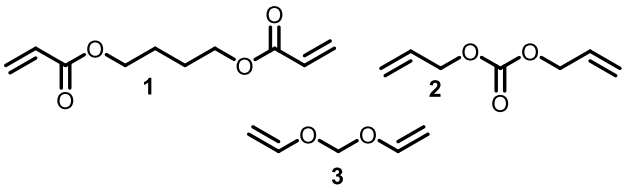


(a)



(b)

The aim of the present research project consists in the development of homogeneous catalysts able to copolymerize ethene with difunctional polar vinyl monomers, such as those reported in figure c.



(c)

To the best of my knowledge only the copolymerization of ethene with comonomer **1** has been reported.[5] Thus, this study represents a challenging approach to the synthesis of polymers potentially tailored for degradation.

The research activity of the **successful candidate** encompasses different steps: ***i.*** synthesis and characterization of proper alfa-diimine ligands; ***ii.*** synthesis and characterization of the relevant Pd(II) and Ni(II) complexes to be used as precatalysts; ***iii.*** study of their catalytic behavior in the target copolymerization reaction; ***iv.*** characterization of the produced macromolecules; ***v.*** mechanistic investigations; ***vi.*** investigation of the degradation process.

Prof. Milani is an internationally recognized expert in the field of the research project and the research activity will be carried out in the frame of several national and international collaborations and some periods in other research groups or in Industry can be foreseen.

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Project 2 for position 10 CHEM-05/A

Artificial Ionophores

Supervisor: Prof. Paolo Tecilla
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Artificial ionophores are synthetic molecules able to promote the transport of ions and/or polar molecules across a biological membrane thus mimicking the action of natural occurring ion channels and carriers. The interest in this research is twofold: on one hand to get insight on the molecular basis of recognition and transport, and on the other hand to get control of the biomedical relevant processes. For example, several genetic diseases, the most known being cystic fibrosis, involve chloride channel impairments and current therapeutic leads comprise artificial ionophores able to restore the chloride transport process [1].

Ion transport across phospholipid membrane is a typical supramolecular function involving dynamic recognition of the substrate during the whole translocation process. Therefore, the design of artificial ionophores requires a careful balance of several factors from binding affinity to lipophilicity. We have been involved for some time in the design of artificial ionophores developing amphipathic molecules based on steroid, calixarene, porphyrin and other organic scaffolds [2]. More recently we have started a research program aimed to investigate the ability of metal complexes, in particular Pd(II) complexes, to act as molecular carrier of chloride and other biological relevant anions [3]. Within the project the candidate will identify and synthesize new ionophores and will study their ionophoric activity on model membranes with particular regard to the definition of the structure/activity correlation in order to investigate the mechanism of action and optimize the carrier efficiency. The best found ionophores will be tested for biological activity in a collaborative work.

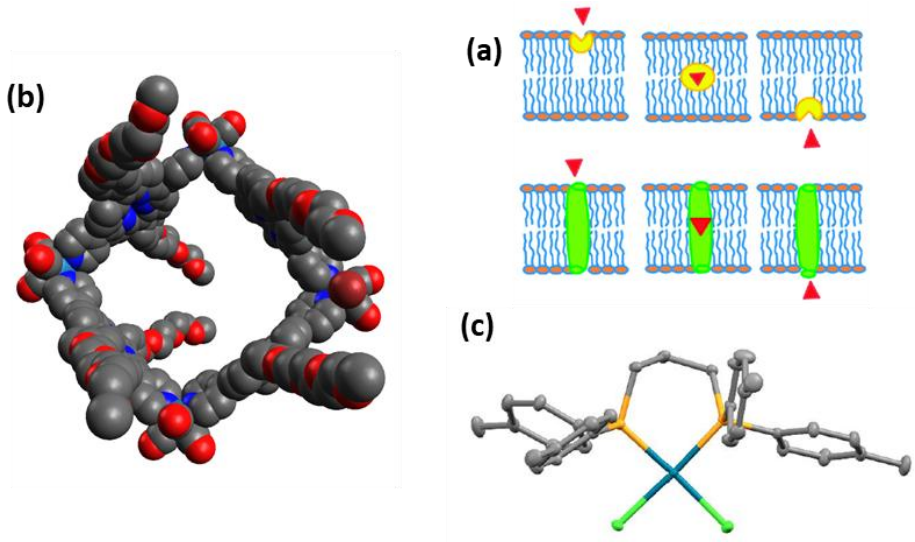

Figure: (a) schematic representation of a carrier (top) and a channel ionophore (bottom); (b) a channel forming porphyrin metallacycle; (c) a Pd(II)-diphosphine complex acting as a carrier for chloride.

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Project 3 for position 10 CHEM-04/A

Nanostructured transition metal phosphates (TMPs) for electrochemical hydrogen production

Supervisor: Federico Rosei
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In recent years, transition metal phosphates (TMPs) have gained widespread attention due to their unique structural characteristics and catalytic behavior in several applications, including hydrogen production through water splitting. The intrinsic surface wettability and flexible coordination features of the phosphate groups make TMPs exceptional candidates for effective redox reactions on the catalyst-electrolyte interface. The proposed research aims to study some of the most promising TMPs (among which, for instance, Mn-based TMP) as catalysts for the oxygen evolution reaction (OER) process, which is the rate determining step in electrocatalytic hydrogen production. A series of TMPs have already been investigated, like cobalt metaphosphate ($Co_2P_4O_{12}$), iron metaphosphate ($Fe_2P_4O_{12}$), and nickel metaphosphate ($Ni_2P_4O_{12}$), while the Mn-based counterpart remains unexplored in the literature and highly promising. The proposed research will focus on the preparation through chemical routes of a series of TMPs, their complete structural and morphological characterization through advanced characterization tools (electron microscopy, optical spectroscopies, scanning probe microscopies, etc.), and their integration into an electrochemical system. *Operando* and *in-situ* characterizations are planned using synchrotron radiation and Raman/Ft-IR spectroscopies to unveil the structural evolution of the catalysts and the surface processes determining the efficiency of water oxidation.

Project 4 for position 10 CHEM-08/A

Development and Characterization of Pharmaceutical Ternary Cocrystals

Supervisor: Beatrice Perissutti
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Pharmaceutical cocrystals represent an innovative strategy to modulate the physicochemical properties of active pharmaceutical ingredients (APIs), particularly solubility and bioavailability. While binary cocrystals have been extensively studied, the introduction of a third component in ternary cocrystals offers new opportunities to optimize (biopharmaceutical, pharmacological, stability, patent-related, etc…) drug properties[1], justifying the ambitious challenge of incorporating more than two components into a single crystalline phase. This project aims to develop and characterize ternary cocrystals comprising at least two poorly soluble APIs and a third component (selected among Generally Recognized As Safe molecules). The objective is to understand the relationships between composition, structure, biopharmaceutical performance, and stability in solution and in the solid state.

After a rational selection of APIs and coformers based on computational simulations, molecular compatibility analysis, and crystallographic databases, the ternary cocrystals will be mechanosynthesized using neat and liquid-assisted grinding under selected conditions. Unlike other projects, the selection of coformers will be strictly linked to mechanosynthesis, as it will be exclusively validated through mechanochemical methods. The mechanochemical synthesis, which is a highly sustainable process, will be conducted either starting from individual coformers and by combining different building blocks (i.e. preformed binary solids) (Figure 1).

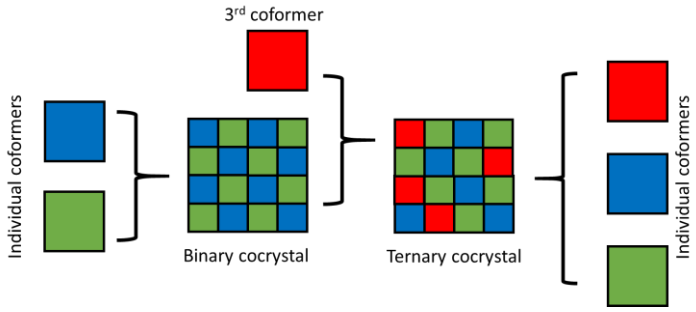

Figure 1. Schematic representation of the mechanosynthesis strategies employed for constructing ternary cocrystals

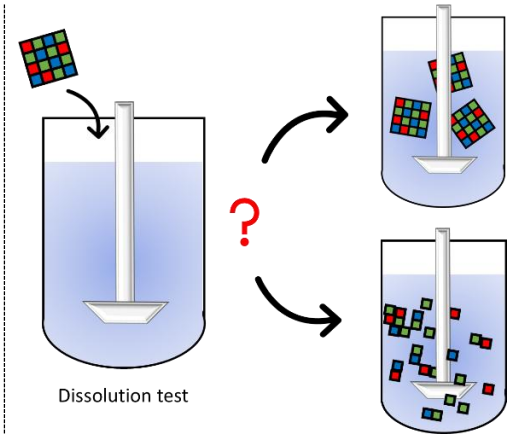

Figure 2. Possible scenarios when a cocrystal comes into contact with physiological fluids (non-exhaustive, two examples reported for brevity).

An in-depth characterization of the obtained materials will be performed through solid-state characterization techniques, solubility and dissolution rate evaluation compared to corresponding binary cocrystals, and stability assessment under environmental and simulated biological conditions. Particular attention will be devoted to the solution stability of the cocrystal (Figure 2) to address a still unmet issue: whether dissolution coincides with cocrystal dissociation, if the intermolecular interactions that stabilize the cocrystal in the solid state persist in solution, or if more complex scenarios (e.g., transformation into a binary solid) are likely to occur.

References:

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Project 5 for position 10 CHEM-02/A

Accurate electronic gradients with TDDFT using Hellmann-Feynman theorem

Supervisor: Mauro Stener
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The project consists in the development of a theoretical method for the efficient geometry optimization of excited states of extended systems. In particular, the gradients of the excited states will be implemented and tested at the TDDFT level to determine the evolution over time of the molecular geometries following the photoabsorption. This will allow the accurate description of photochemical and photocatalytic phenomena. In particular, a completely new and original method based on the Hellmann-Feynman theorem [1] will be implemented, which allows to calculate the energy gradients in an extremely efficient way. However, the use of the Hellmann-Feynman theorem is subject to the use of sets of basis functions that must satisfy specific criteria [2,3]. Besides efficiency, excited states optimization are also plagued by the problem of the presence of avoided crossings in the adiabatic potential energy surfaces which make the minimization problematic in standard TDDFT. For this reason we will implement the method within the polTDDFT method [4], which should be more regular since uses a 'window' of states instead of one single state. Therefore, the project includes a first implementation phase within the AMS program, followed by a second optimization phase of the basis set, to conclude in the third phase of application to photochemistry and photocatalysis. As for the applications, both valence (photoabsorption, CD) and core (XPS, NEXAFS) phenomena will be considered. On larger systems, plasmonic effects will also be studied, and in particular their role in photocatalysis.

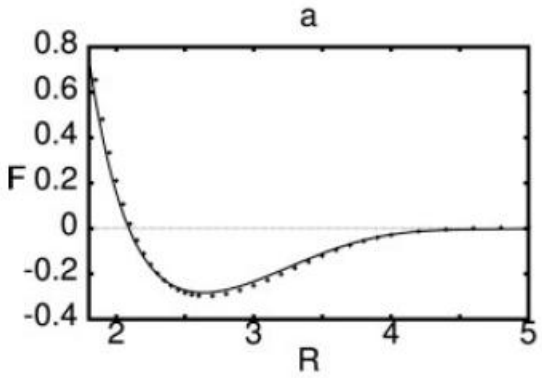

Figure. Force curves in N_2. Dots: forces on N. Solid line: energy derivative.

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Project 6 for position 10 CHEM-05/A

Discovery of new agonists and antagonists of Farnesoid X receptor from natural products

Supervisor: Cristina Forzato
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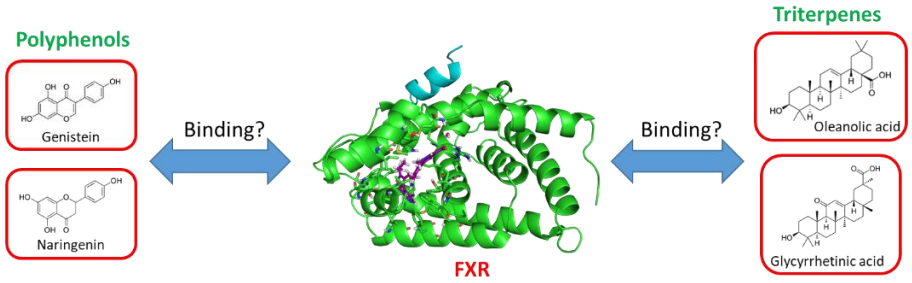
FXR is a nuclear receptor that regulates several important aspects of mammalian physiology. Bile acids were identified as endogenous FXR ligands and FXR is a key modulator of enterohepatic circulation of bile acids, controlling transcription of key regulatory genes in bile acid synthesis, bile acid secretion, and trans-intestinal bile acid transport to the liver via portal blood circulation. It is highly expressed in the liver, intestine, kidney, and adrenal glands, with low levels of expression in adipose tissue and heart.[1,2] Apart from regulating the bile acid homeostasis (FXR inhibits bile acid synthesis in the liver), FXR regulates also lipid, glucose, and amino acid metabolism. Indeed, if dietary cholesterol reaches elevated intracellular levels, activated FXR induces protective gene expression circuits against bile acid toxicity in the liver, intestine, kidneys, and adrenal glands.

Due to these different roles in the metabolism, targeting FXR is a promising route in the treatment of various kidney diseases. Several drugs acting as agonists or antagonists of FXR are under clinical trials. However, new safe therapeutics with fewer side effects are in great demand. In traditional medicine, several plant extracts are used as natural remedies against hypercholesterolemia and hyperglycemia, suggesting that natural products such as polyphenols and triterpenes present in plant extracts could serve as promising starting points for structural modifications to provide potential FXR ligands.[3] In the last 20 years (2000–2020), 127 natural products were discovered from natural resources targeting FXR, 72 agonists and 55 antagonists.[4] Among them there are terpenes and flavonols but most lead compounds failed in preclinical and clinical developments, often because of toxicological and/or pharmacokinetic issues. Structural modifications of natural products could provide derivatives with a higher affinity for FXR and less side effects. Since several polyphenols and triterpenes of natural origin (such as oleanolic acid, glycyrrhetinic acid, genistein, and naringenin) are commercially available in large amounts and at low cost, different derivatives could be synthesized in order to obtain potential drugs with increased activity toward FXR.

The present project will focus on the design, synthesis and evaluation of natural product derivatives targeting the FXR receptor. The doctoral candidate will have the opportunity to work in an interdisciplinary contest working in the field of organic synthesis, molecular modelling, crystallographic analysis and expression of FXR in bacteria (*E. coli*), acquiring competences in different fields and techniques.



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Project 7 for position 10 CHEM-07/A

Integrating AI-Predicted and Experimental Structures for Drug Selectivity Modeling

Supervisor: Emanuele Carosati
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Background: The integration of AI-predicted protein structures (e.g., AlphaFold) with experimental crystallographic data presents new opportunities for understanding molecular selectivity. While traditional structure-based approaches relied heavily on experimentally resolved structures, AlphaFold now provides high-accuracy predictions for understudied proteins, enabling systematic selectivity analysis across homologous families such as kinases, GPCRs, and ion channels. However, challenges remain in leveraging hybrid structural datasets to predict drug selectivity. This project aims to bridge this gap by developing machine learning (ML) models that unify experimental and predicted structures to identify key selectivity determinants in critical protein families.

Research Project: This project will design ML frameworks to predict ligand selectivity across protein classes using hybrid structural datasets (AlphaFold + crystallography), based on structure-based approaches such as BioGPS as foundation [1] and docking and molecular dynamics simulations as refinement tools. Multitask ML models will be trained to predict selectivity across kinases, GPCRs, and ion channels, incorporating structural features from both experimental and AI-predicted models and leveraging recent AI-based frameworks [2].
Model validation will involve benchmarking against established selectivity datasets (e.g., kinase inhibitors, GPCR agonists/antagonists) and collaborating with experimental research groups to validate predictions. Structural dataset curation will add AlphaFold-predicted models (for understudied homologs) to a large set of experimental structures (e.g., PDB). Various ML architectures—including decision trees, gradient boosting, and graph neural networks—will be evaluated to determine the most effective predictive framework.

Expected Outcomes: The project will deliver a publicly available ML framework for predicting selectivity across protein families and generate case studies in collaboration with research groups working on key drug targets where selectivity is crucial.

The research group: The CADD (Computer-Aided Drug Design) Research Group at DSCF specializes in computational medicinal chemistry, integrating chemoinformatics, ML, and data mining into diverse research areas. The project will be conducted under the supervision of an experienced researcher with expertise spanning academia and industry. Interdisciplinary collaborations will ensure exposure to drug development, molecular engineering, and AI-driven approaches in medicinal chemistry. Strengthening the department's expertise in this emerging field will be vital for advancing scientific discovery and fostering innovative applications in medicinal chemistry and beyond.

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Project 8 for position 10 CHIM-07/A

Development of selective degraders of Casein Kinase 1 δ

Supervisor: Prof. Giampiero Spalluto
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In the last decades the roles of CK1δ have been characterized more and more, both in physiological and in pathological conditions. In fact, dysregulation of the expression and activity of CK1δ has been observed in different types of cancers, as well as in different neurological disorders, among them Alzheimer's Disease (AD), Parkinson's Disease (PD), and Amyotrophic Lateral Sclerosis (ALS).[1]
For these reasons, CK1δ has been the focus of many inhibitor and drug development efforts. As a result, many inhibitors have been developed.[2] However, these inhibitors have been associated with off-target activities and they are not isoform-selective. In this field we have recently synthesized a new series of pyrazine analogs (Figure 1) which showed potency in the nanomolar range vs CK 1δ.
Taking into account that the piperazine moiety, by molecular modelling simulations, is located outside from the binding site, we could consider this free NH a good candidate for further substitution in order to obtain polyfunctional derivatives with various possible application.

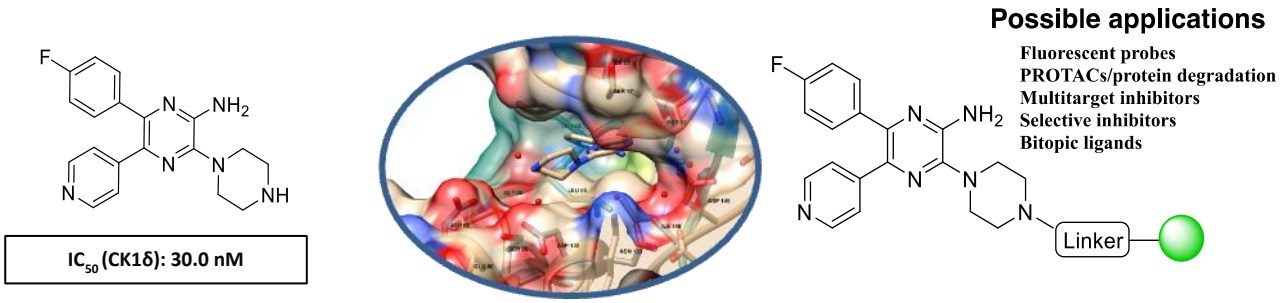

Figure1. Rational design of polifunctionalized CK1 δ inhibitors

In particular, the aim of this work, will be focused on the preparation of PROTACs that are heterobifunctional molecules that exploit the cell's own proteolytic apparatus, the ubiquitin-proteasome system, to induce degradation of a protein of interest.[3]
With the support of molecular modelling studies, the optimization of the length of the linker will be optimized in order to place correctly the ligand for E3 ligases VHL or CRBN.[4]

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Project 9 for position 10 CHEM-03/A

Attacking multi-resistant infections with the toolshed of bacteriophages

Supervisor: Rita De Zorzi
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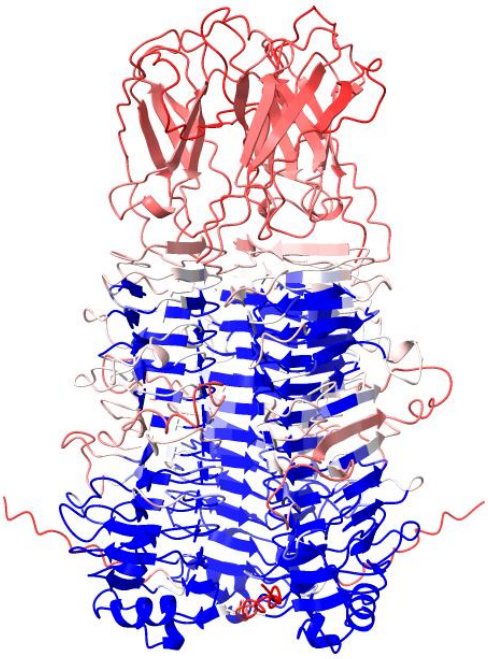
Antimicrobial resistance is emerging as one of the most serious threats to global health, both for human well-being and animal breeding. The excess and improper use of antibiotics increases the occurrence of resistant microbial strains, unresponsive to the available pharmacological therapies. According to the World Health Organization, the number of deaths per year attributable to AMR will reach 10 million by 2050, becoming the first cause of death.

Among the worst nosocomial pathogens, bacteria belonging to the group ESKAPE (acronym of *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter spp.*) have attracted particular attention for their ability to avoid the action of antibiotics. ESKAPE bacteria are a serious health concern, as they increase both the frequency of treatment failures and the severity of human infections by adapting to altered environmental conditions and by acquiring resistance determinants.

For ESKAPE bacteria, the bacterial capsule is an important virulence factor. The capsular polysaccharide (CPS) is also a major component of bacterial biofilms, which are communities of bacteria living in adhesion to a surface and surrounded by a self-produced polymeric matrix. In the quest to counter drug-resistant bacterial infections, recent studies aim at taking advantage of the ability of bacteriophage enzymes to cleave the CPS and breach the polysaccharide layers of biofilms. Bacteriophages are a ubiquitous and diverse family of viruses that replicate in bacteria. During the infection phase, bacteriophages reach the bacterial membrane by cutting their way through CPS thanks to their endoglycosidase enzymes.

In collaboration with the group of Prof. Paola Cescutti, we are working on the endoglycosidase derived from the phage phiBO1E [1] able to replicate in *Klebsiella pneumoniae* strain KpB-1 belonging to the Clonal Group 258 [2], one of the main responsible in the global pandemic of multidrug-resistant *K. pneumoniae*. This recently discovered enzyme (Figure, representing an AlphaFold model of the protein) is able to hydrolyze the capsular polysaccharides of its target bacterial strain but structural information is still lacking, as well as a complete functional characterization.



The PhD student will be involved in the expression, purification, and structural characterization of the glycosidase using X-ray crystallography and/or cryo-electron microscopy. They will take advantage of the expertise already gained in our laboratory regarding the glycosidase of phiBO1E. In addition, the student will work in collaboration with the group of Prof. Paola Cescutti to functionally characterize the protein.

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Project 10 for position 10 CHEM-03/A

Assembly of Peptide-Metalloporphyrin SupraStructures

Supervisor: Prof. Elisabetta Iengo
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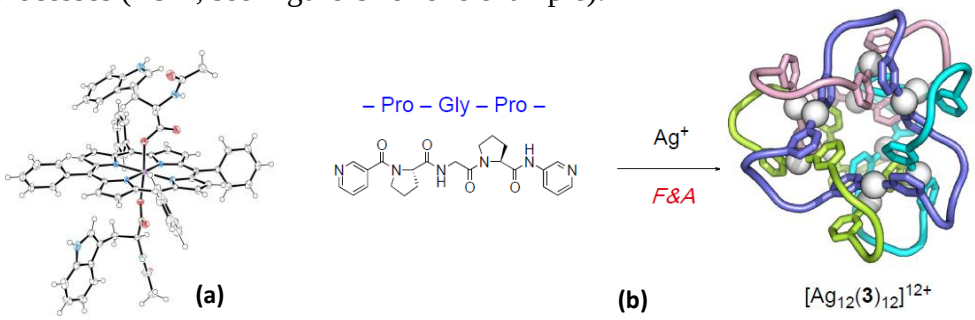
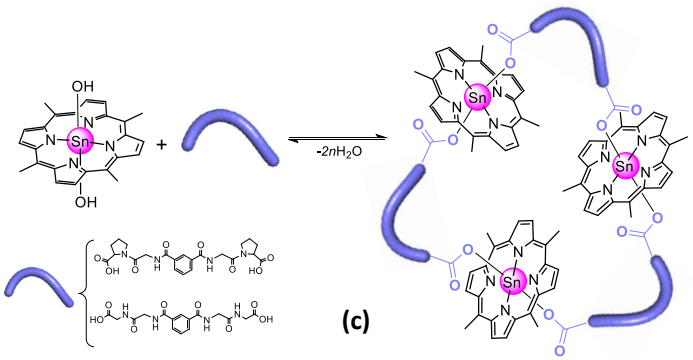
The characteristics of Sn^{IV}-porphyrin – robust binding to two oxyanions, tunable absorption, luminescence, and ease of reduction[1a] – make them intriguing scaffolds for the construction of light-responsive supramolecular assemblies and attracted our interest.[1b] We thus initiated a fruitful investigation on Sn^{IV}-porphyrin/aminoacids conjugates (Figure-a) as biomimetic models for photoinduced proton-coupled electron-transfer.[2] On the other hand, very elegant recent studies by the Group of Fujita demostrated how it possible to access to intruguing entangled discrete or polymeric nanostructures by a cooperative combination of folding and coordinative assembling reversible processes (*F&A*, see Figure-b for one example).[3]



Based on these premises the present project intends to survey on the possibility to combine Sn^{IV}-porphyrin and small symmtric peptide strands as building units for the contruction of light-responsive discrete SupraStructures,, as very schematically exemplified in Figure-c. Inorganic, organic and supramolecular synthetic methodologies will be employed to prepare and react a variety of building units, while multiple characterization techniques will be applied (in solution: ESI-MS spectrometry, NMR, UV-vis, emission and CD spectroscopies, ciclyc voltammetry; in the solid state: X-ray diffraction by means of synchrotron light source). A minimum 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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[1] (a) D. P. Arnold, J. Blok *Coord. Chem. Rev.* **2004**, *248*, 299; (b) A. Amati, P. Cavigli, N. Demitri, M. Natali, M.T. Indelli, E. Iengo *Inorg. Chem.* **2019**, *58*, 4399. **[2]** (a) M. Natali, A. Amati, N. Demitri, E. Iengo *Chem. Commun.* **2018**, *54*, 6148. (b) M. Natali, A. Amati, S. Merchiori, B. Ventura, E. Iengo *J. Phys. Chem. C* **2020**, *124*, 8514; (c) M. Natali, A. Amati, N. Demitri, E. Iengo *Chem. Eur. J.* **2021**, *27*, 7872. **[3]** (a) T. Sawada, M. Fujita *Bull. Chem. Soc. Jpn.* **2021**, *94*, 2342; (b) T. Sawada, M. Fujita *Chem* **2020**, *6*, 1861.

Project 11 for position 10 **CHEM-02/A**

Photocatalytic CO_2 reduction from Ag nanoparticles

Supervisor: Emanuele Coccia
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The topics of energy and sustainability represent a considerable challenge for research today. CO_2 transformation is a challenging topic for chemistry in the context of the green revolution and ecological transition, in accordance with Europe's structural areas of focus [1].
An ideal photocatalyst for CO_2 reduction not only exhibits high efficiency but also high selectivity toward a product [2]. Using a silver nanoparticle, the production of CO or more complex compounds is observed [3]. The mechanism of CO_2 photoreduction on silver nanoparticle is still unknown.
In this project, a quantum approach [4,5] will be applied to study the electronic dynamics in the slow step of CO_2 photoreduction on a silver nanosphere. The simulations will be based on the propagation of the time-dependent Schrödinger equation and accurate quantum-chemistry calculations.
The expected results are: i) understanding of the role of the nanosphere in the photoreduction reaction, including possible plasmonic effects; ii) interpretation of the experimental results, in terms of the reaction mechanism and increased production rate as a function of the pulse frequency [3].

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Project 12 for position 10 CHEM-02/A

Machine-Learning NEXAFS and XPS spectra: from excited-state properties to highly accurate molecular structure determination

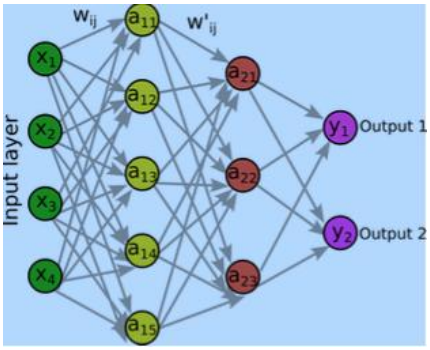
Supervisor: prof. Daniele Toffoli
email: toffoli@units.it

The objective of this project is to establish X-ray absorption and photoemission spectra data analysis through machine learning (ML) assisted forward (structure to spectrum) and reverse (spectrum to structure) mapping. The aim is to provide quantitative prediction of XAS and XPS of gas-phase molecules, ranging from small systems to macromolecules and weakly interacting adsorbates, from local geometry of the adsorption site and vice versa. The detailed scope of our project can be itemized as follows:

1) Fast and accurate computation of NEXAFS and XPS spectra for new molecules, both free and weakly adsorbed on surfaces. For high accuracy, the quality of the database used to train and validate ML algorithms is very important. For each molecular NEXAFS spectra it is also important to span an energy region from the first transition to the threshold, with a high energy resolution. The databases currently available do not achieve these requirements. The ambitious goal of this project is to achieve the accuracy of first-principle electronic structure methods, at the speed of ML methods [1].

2) Combine the locality of NEXAFS and XPS with ML to automatically extract from given NEXAFS and XPS spectra, information on the local geometric arrangement of atoms in complex structures. Beside the geometric environment, it is possible to extract valuable information on the electron distribution around the absorbing center: charge state, effects of electron delocalization, the presence of electronegative/electropositive substituents. Since K-edge NEXAFS spectra map the p-orbital contributions of the absorber to the virtual (unoccupied) states, while L-edges NEXAFS map the s and d contributions, one can obtain valuable information on the unoccupied electronic states of the molecular target in a site-specific way [2].

3) The assignment problem, which has not been addressed in the literature so far, but which is needed for rationalizing the wealth of information on the electronic and geometrical structure of the molecular target that can be obtained from NEXAFS and XPS. Our goal with this project is to be able to accurately predict the spectrum, but also to be able to assign spectral features to specific core-electron excitations/ionizations [3].



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Project 13 for position 10 CHEM-01/B

Hi-Res Mass Spectrometry for tracing environmental dispersion and human exposures of PFAS and pharmaceutical compounds

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Xenobiotic chemical compounds released into the environment by technological processes, generate human exposure and modification in genetic of microorganisms, as development of antimicrobic resistence (AMR) genes. Among chemicals of emerging concern, attention is posed to Polyfluoroalkyl substances (PFAS) - known for their environmental persitence and thus high bioaccumulation potential. Focus will be posed also to antimicrobial compounds (as antibiotics) exherting selective pressures on environmental bacteria, inducing AMR genes, that can be passed to pathogens, with foreseen high health impacts [Sirwan, 2024]. High resolution mass spectrometry Orbitrap technologies – recently made available at DSCF – coupled with performative separation techniques and sample treatment, as QuEChERS – have potential to identify PFAS and antimicrobials in complex matrices as waste waters (ww) [Miserli, 2023], fish (f) [Koloka, 2025], and biological fluids (b) [Kotlarz, 2020], with both supervised and unsupervised approaches.
A study and research project is proposed to develop, apply and optimize procedures for the analysis of PFAS and antimicrobial pharmaceuticals and personal care products in ww, f, u and b, thanks to collaborations with the local multiservice company, public healthcare system and environmental protection agency.
The development of an analytical data treatment and postprocessing pipeline for the huge amounts of experimental data have a relevant part in the production of analytical information useful to support domain experts in the fields of water treatment technologies, genetics and infective diseases, and will be pursued as well by machine learning methods [Gelao, 2024]. Chemical analysis will thus provide tools that can be further valorized as key enabling technology for developing innovation in the fields of water treatment and exposure sciences and hygiene, also related to new EU Wastewater directive [Kardos, 2025].

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Project for position 11

Project for position 11 CHEM-08/A

Sustainable pharmaceutical technologies for the development of novel nanomedicines

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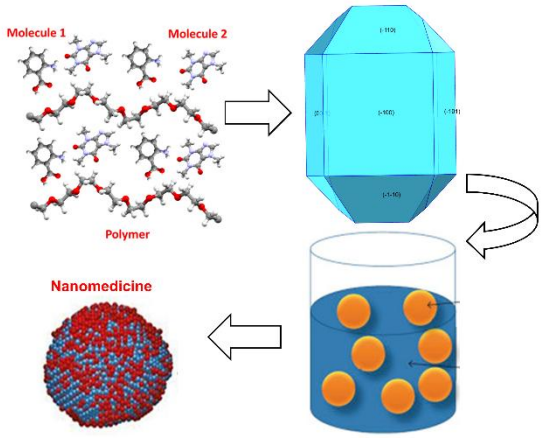

Nanotechnology, the use of matter on an atomic, molecular, and supramolecular scale has been introduced constantly and uninterruptedly in multiple aspects of our daily routine. The use of nanotechnology in the development of new medicines is now a main argument for different important research laboratories in the European Union and it has been recognized as a Key Enabling Technology, capable of providing new and innovative medical solution to address unmet medical needs.[1] Nanomedicine represents nowadays one of the most interesting approaches for solving various issues related to drug delivery, including the use of nanocarriers for optimizing drug formulation through the improvement of the solubility of hydrophobic drugs, stabilization of degradable compounds, and the targeted and localized delivery.Unfortunately, there is a significant disparity between the number of scientific publications about nanomedicines and the number of active clinical trials for such drug delivery systems. One of the major reasons that has hindering the translation of nanomedicines into clinics is related to the low reproducibility and scalability of the formulations. In fact, nanomedicines are currently synthetized in batch methods, often involving multi-step processes that use significant amounts of hazardous and difficult-to-remove organic solvents[2] that cause significant variabilities in terms of physicochemical properties, their homogeneity (size distribution) and purity. The importance of reproducibility of the physicochemical properties such as surface characteristics, momentum and mass transfer rates of nanoparticles is related to their interaction with biological entities, thus affecting the circulation time and biodistribution of such nanotherapeutics. The need for purification adds additional layers to the complexity of commercialising nanomedicines. Finally, the storage of nanomedicines represents a major point of concern. Indeed, nanomedicines are often administered as a pre-formed delivery vehicle in an aqueous solution, thus introducing a notable knowledge gap pertaining to their kinetics of formation and stability in human body fluids.

In this PhD project, we will explore the possibility of using sustainanble technologies for the production of polymer-based solid nanomedicines by using crystal engineering principles,[3] and solvent-free processes.[4] Specifically, the project aims to produce polymer-based cocrystals that show structural versatility upon dissolution. The new formulations will have unprecedented stability, including an initial approach to permit the facile and routine production of cocrystals in the future. Potentially, our this approach will realise the development of previously inaccessible nanomedicnes and new ways to self-assembly by modulating the solid state of the multicomponent solids, giving an important contribution to the recent field of tabletized nanomedicines.[5] The development of these materials requires a multi-disciplinary approach, involving forward-thinking synthetic techniques, the use of unique analytical tools and specialised expertise in polymer crystallization.

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Project for position 12 CHEM-02/A

New variational density functional methods for calculations of excited states

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In this project, a variational, orbital-optimized density functional methodology will be developed for the efficient and accurate calculation of excited electronic states of molecules and periodic systems. While linear-response time-dependent density functional theory (TDDFT) remains widely used, orbital-optimized approaches are emerging as a promising alternative, offering improved descriptions of charge-transfer [1], Rydberg [2], and other excitations involving significant rearrangement of the electron density, key processes in solar energy conversion and photochemistry. Typically, orbital-optimized methods rely on the Kohn-Sham approach, providing computational efficiency, but facing significant limitations, including the difficulty of simultaneously computing the excitation energy and transition probability of multiple states, and the breaking of the spin and spatial wave function symmetry for multideterminant states. Here, a novel approach will be developed using recently proposed strategies for converging on saddle points on the electronic energy surface provided by density functionals, thereby directly optimizing the orbitals for excited states [3]. This methodology will be extended to (1) the simultaneous calculation of multiple excited states using natural orbitals from preliminary TDDFT calculations as optimized initial guesses, and (2) the calculation of multideterminant states without symmetry breaking. The latter will be achieved by optimizing the orbitals within minimal configuration state functions [4] or using novel ensemble density functional theory approaches [5]. The method will be implemented in the open-source grid-based projector-augmented wave (GPAW) software [6], which can use both real-space grid, plane-wave and atomic localized basis sets, and can therefore be used for calculations of both molecular and periodic systems. The newly developed method will be validated on prototypical photochemical models, such as ethylene, butadiene, and azobenzene. Subsequently, it will be combined with molecular dynamics simulations to study photoinduced dynamics in systems relevant for emerging areas of solar energy conversion, such as the charged nitrogen-vacancy center in diamond [7], and singlet fission acene dimers for dye-sensitized solar cells [8]. The simulations will also assist the interpretation of novel time-resolved experiments performed together with international collaborators at synchrotron and X-ray free electron laser facilities [9].

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