University of Trieste
Department of Chemical and Pharmaceutical Sciences

Doctorate in Chemistry

2023

Cycle 39 PNRR

Research Projects

Positions PNRR/9-12: DM 117/2023

Positions PNRR/13-15: DM 118/2023

University of Trieste
Department of Chemical and Pharmaceutical Sciences

Projects for positions PNRR/9-12 DM 117/2023

Project for position PNRR/9 CHIM/08

Development of Alternative Synthesis of Active Pharmaceutical Ingredients

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The synthesis of active pharmaceutical ingredients (APIs) is an area of research of great interest, both because of its economic, environmental and social impact. Indeed, the search for new synthesis routes or the optimization of some synthesis steps of already known routes may allow to obtain the desired molecule at a lower cost (economic impact), which may translate into a cheaper sale and, consequently, a better accessibility for the patient (social impact). New strategies mean patentability and thus economic gain for the company. In addition, pharmaceutical companies are strongly interested in finding environmentally friendly synthesis methods that can be applied on an industrial scale. These include both the choice of environmentally friendly reagents and solvents and the use of innovative techniques such as flow chemistry, mechanochemistry, photochemistry and electrochemistry (enviromental impact) (Figure 1).[1]

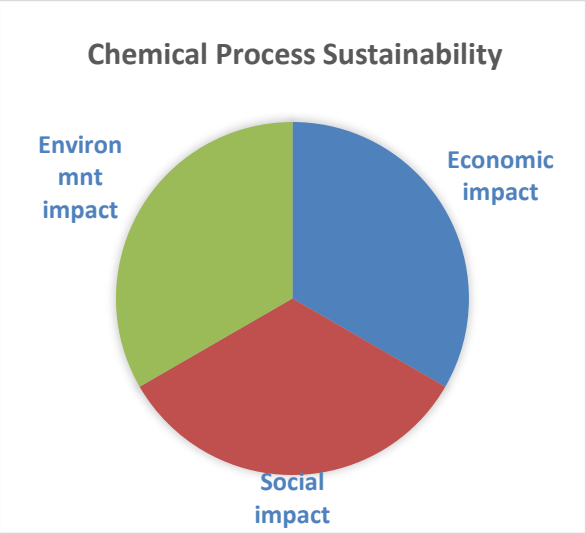

Figure 1. Aspects to be considered during chemical process design

This project is held in collaboration with Dipharma Francis srl and aims to synthesize active ingredients of interest to the company itself, first identifying the critical points (e.g. from a technical, environmental or economic point of view) of the synthesis routes currently used and then exploring new approaches, including the use of technologies such as flow chemistry, mechanochemistry, photochemistry and electrochemistry, or combinations thereof. Objectives may include: i) reducing waste; ii) reducing energy costs; iii) increasing yields; iv) reducing the number of steps; v) reducing the number of by-products; vi) avoiding purification operations.

The Department of Chemical and Pharmaceutical sciences (DSCF) is equipped for organic synthesis at a gram scale, while, in order to explore the flow chemistry technique,[2] the PhD student will spent 6 months at the University of Graz, during her/his second year. Finally, the last year will be spent at Dipharma Francis srl, where the project will focus on Process Chemistry, which concerns the synthetic proccess optimization and the acquisition of all data necessary to scale-up the new synthesis of the selected API (i.e. calorimetry, impurities, and, solid state studies).

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Project for position PNRR/10 CHIM/06

Design, synthesis and study of innovative compounds as foods for special medical purposes

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The ketogenic diet (KD) is a therapeutic protocol for the treatment of subjects suffering from drug-resistant epilepsy[1], a condition which affects around 150,000 people in Italy. KD is characterized by a high fat content, an adequate one in proteins and a limited one in carbohydrates; the reduction of carbohydrates simulates fasting and promotes the metabolization of lipids into ketone bodies from which the body draws energy[2]. KD is the therapy of choice also for subjects affected by the rare diseases GLUT1 and PDCD who, unable to use glucose, can only draw energy from ketogenic bodies[3]. Although the medical community agrees on the utility of KD for the treatment of these pathologies, the clinical efficacy of KD is strongly hampered by the reduced compliance of patients with the diet[4].
To overcome these problems, research has focused on the study of exogenous ketogenic bodies which, once taken orally, can lead to effective levels of ketogenic bodies in the circulation (ketosis)[5], and at the same time free the subject from following KD. Despite these efforts, the exogenous ketogenic bodies on the market have sensory and nutritional limitations that prevent their continued use.

The present project aims to develop innovative exogenous ketogenic bodies, characterized by an improved sensory profile and an excellent ability to develop and maintain ketosis.
During the PhD project compounds functionalizable with ketogenic bodies will be identified and synthesized. Processes and scale-up of the most promising compounds will be developed.
In vitro studies will be also considered to understand the metabolism of the functionalized compounds.
From a commercial point of view, stability analysis of functionalized compounds at different pH and temperature conditions, in order to identify the best food matrices for the delivery of functionalized compounds will be performed.

References:

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Project for position PNRR/11 CHIM/06

Formulazioni avanzate per cosmetica, dispositivi medici e farmacia

Supervisor: Prof. Silvia Marchesan
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Durante il progetto di Dottorato, verranno preparati dei derivati di biomolecole, come ad esempio derivati di amminoacidi e peptidi, per sviluppare formulazioni innovative per applicazioni nell'ambito della cosmetica, dispositivi medici e farmacia. Le attività quindi includeranno una prima fase di preparazione, purificazione e caratterizzazione di semplici biomolecole e loro derivati, nonché il loro studio per ottenere delle formulazioni per le applicazioni indicate sopra tramite diverse tecniche, incluse la spettroscopia e la reologia. L'obiettivo è di sviluppare dei nuovi agenti biocompatibili, idealmente con ruolo strutturante, per formulazioni avanzate, in cui verrà anche studiato il rilascio di principi attivi e le relative cinetiche. Il progetto è altamente multidisciplinare, in quanto spazia dalla chimica organica alla chimica supramolecolare, alla scienza dei materiali, alla tecnica farmaceutica. Inoltre, i nuovi sistemi andranno studiati nel dettaglio non solo a livello macroscopico, ma anche a livello di scale inferiori, come quello microscopico, della nanoscala, e molecolare. Queste nuove formulazioni saranno sistemi a base acquosa o comunque innocui per l'uomo e per l'ambiente in quanto la biocompatibilità sarà la priorità delle attività di ricerca. Le attività saranno coerenti con le attività di ESI (www.esi.it) che dal 1975 opera nel settore dei prodotti fitoterapici, dietetici e degli alimenti naturali e oggi è tra le primarie aziende produttrici nel settore. Il/La dottorando/a godrà di un periodo formativo di 6 mesi presso ESI ed un altro di 6 mesi presso lo Jozef Stefan Institute di Lubiana che gode di strumentazioni avanzate ad elevate competenze nell'ambito delle nanotecnologie e materiali avanzati, che rientrano tra le Key Enabling Technologies identificate dalla UE come priorità per mantenere la competitività europea.

References:

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Project for position PNRR/12 **ING-IND/27**

Valorization of organic and industrial waste as energy carrier sources

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The project will address circular economy themes together with future energetic scenarios and environmental risk prevention. Thermal degradation routes - pyrolysis – will be employed to investigate the efficiency of the waste-to-energy conversion, as a sustainable waste-elimination process (1). Specifically, reactions will be carried out to valorize organic waste, side-products and/or industrial waste, that typically cannot be treated by other processes, such as thermosetting polymers and their composites. The processes will be optimized with the aim of maximizing both the yield and purity of the generated gases, while ensuring the non-toxicity of the residuals. The research will be carried out in tight connection with the Enecolab innovative SME, using their patented technology, under industrially relevant conditions.

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University of Trieste
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Projects for positions PNRR/13-15 DM 118/2023

Project for position PNRR/13 **CHIM/03**

Exploring molecular strategies to design hybrid nanomaterials for the electrocatalytic CO_2 reduction

Supervisor: Dr. Federico Franco
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The catalytic CO_2 electroreduction powered by renewable energy is a promising sustainable route to carbonaceous fuels and value-added chemicals using CO_2 as feedstock. However, the control over selectivity represents a major challenge for an efficient electrocatalytic CO_2 reduction, due to the competitive formation of multiple products and the hydrogen evolution reaction. In this regard, rational catalyst design represents a powerful tool to improve the efficiency of the process.[1] In the last years, the surface functionalization of metal electrodes with organic modifiers in the form of single molecules or polymers was recently shown to be an effective strategy to enhance the performances of nanostructured metal electrodes.[2] In particular, the presence of organic additives was found to significantly boost the CO_2 reduction efficiency of nanostructured catalysts over the hydrogen evolution reaction in aqueous media, directing the selectivity towards the formation of specific C_1-C_{2+} target products. However, the optimization of these systems is currently limited by the poor understanding of the molecular metal interface.

The project aims to tailor the electrocatalytic CO_2 reduction performances of nanostructured catalysts in aqueous electrolytes by rationally designing hybrid molecular interfaces. The candidate will explore multiple strategies to design hybrid organic-inorganic nanomaterials, primarily focusing on the in situ electrodeposition of molecular films on metal surfaces from water-soluble nitrogen-containing organic salt precursors.[3] Other approaches, such as drop-casting and wet-chemistry methods will be also comparatively studied. The aim of the project is twofold:

- Improve the rational understanding of the role played by the molecular layer on the electrocatalytic properties of metal electrodes, highlighting how the molecular coating affects the local microenvironment of the surface catalytic sites;
- optimize the CO_2 reduction performances of nanomaterials in terms of efficiency, selectivity and stability by tuning the physico-chemical properties of the hybrid interface.

The candidate will explore a variety of metal/metal oxide substrates focusing on transition metals of interest for CO_2 reduction applications. This multidisciplinary project offers the opportunity to develop multiple skills at the frontier between molecular chemistry and heterogeneous catalysis, including the preparation and characterization of the hybrid nanomaterials, as well as the investigation of their electrocatalytic performances.

During the project, the candidate will have the opportunity to work for six months at the Institute of Chemical Research of Catalonia (ICIQ) in Tarragona (Spain). At ICIQ, the student will have the access to advanced techniques for the characterization of both molecular systems and materials that will be beneficial for the full development of the project, as well as to the instrumentation necessary to carry out the CO_2 electrocatalytic tests.

References:

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Project for position PNRR/14 CHIM/06

Development of materials for diagnostic imaging with low environmental impact

Supervisor: Paolo Pengo
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Diagnostic imaging is widely employed when detailed anatomical analyses are deemed necessary and largely rely on magnetic resonance imaging (MRI) which requires, in many cases, contrast agents based on gadolinium chelated complexes [1]. The sustainability of MRI diagnostics presents two critical points: the difficulty in sourcing gadolinium which derives from geopolitically unstable countries and the unavoidable, and growing, dispersion of this metal in the environment [2]. Among other techniques, fluorescence imaging using near-infrared (NIR) absorbing and emitting probes has recently emerged as a promising imaging modality as it combines low cost, high sensitivity, good spatial resolution, safety and low environmental impact.
We are interested in developing gold nanoclusters (AuNCs) protected by alkanethiolate ligands as potential NIR fluorophores/luminophores for imaging applications, Figure 1.

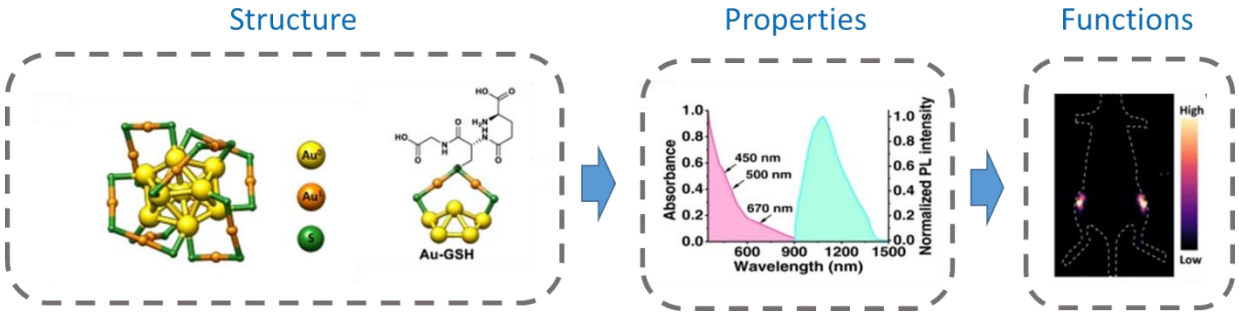

Figure 1. Example of luminescent AuNCs and their applications, adapted from ref. [3].

It is indeed known that AuNCs can emit in the region between 900 and 1350 nm, a spectral range in which biological tissues are transparent [3]. One of the challenges in developing AuNCs for imaging techniques is their very low luminescence quantum yield (QY), often less than 1%, which limits their applications. However, with a suitable choice of the ligand electronic properties, the luminescence of the AuNCs can be modulated [4, 5]; furthermore, the luminescence properties of AuNCs are related to the stiffness of the ligands [6]. Based on recent preliminary findings from our laboratory, we foresee that the use of rigid fluorinated amphiphilic thiols as ligands for gold nanoparticles/AuNCs may allow to tune their luminescence properties and QY. The project will require: (i) the development of new fluorinated and non-fluorinated rigid amphiphilic thiols to be used in a structure-property correlation study; (ii) a systematic study of the synthetic conditions to optimize the luminescence properties of nanoparticles; (iii) the development/optimization of synthetic methodologies for the preparation of well-defined AuNCs with NIR luminescent properties. The ideal candidate should have expertise in the synthesis and characterization of nanomaterials and in the synthesis and characterization of organic compounds.

References:

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Project for position PNRR/15 **CHIM/02**

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

Supervisor: prof. Daniele Toffoli
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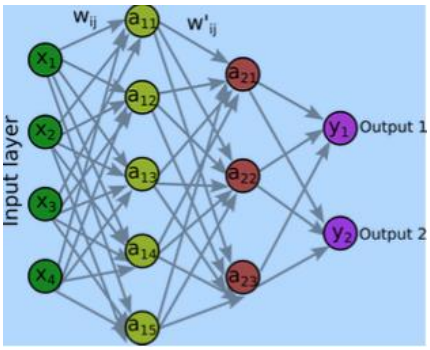
The objective of this project is to establish X-ray absorption and photoemission spectra data analysis through machine learning (ML) assisted forward (structure to spectrum) and reverse (spectrum to structure) mapping. The aim is to provide quantitative prediction of XAS and XPS of gas-phase molecules, 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].



References:
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[2] Stoehr, J. NEXAFS spectroscopy; Springer Verlag, 1992.
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