30th Young Research Fellows Meeting

from Wednesday 1st to Friday 3rd February 2023

Société de Chimie Thérapeutique

Société de Chimie Thérapeutique

1st-3rd Feb. 2023 Paris, France

YRFM 2023

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Welcome from Prof. Rebecca Deprez-Poulain, the S.C.T. President:

Dear Young Research Fellows, dear colleagues,

Société de Chimie Thérapeutique

On behalf of the French Medicinal Chemistry Society (*Société de Chimie Thérapeutique, SCT*) we are welcoming you to the Young Research Fellows Meeting 2023 (*Journées de Jeunes Chercheurs*).

30th Young Research Fellows Meeting
30e Journées Jeunes Chercheurs

The SCT supports its young members and acknowledges that The Young Research Fellows Meeting is a great opportunity for the future investigators in the field. We are really happy to welcome you again at the "Faculté de Pharmacie" in this beautiful city of Paris.

I would like to thank all people of the Organizing Committee for setting up this meeting. With this three-day symposium the Committee did an excellent work to offer a great scientific event by gathering experts with outstanding contribution in medicinal chemistry and chemical biology.

I am, on behalf of the SCT, thankful to the **international speakers from academia and industry** that accepted to share their expertise with the audience: Florine Cavelier, Yohann Corvis, Bruno Therrien, Steven Ballet, Mauline Nuno, Xavier Coumoul, Nicolas Anton, Caroline Roques, Stéphanie Baillif, Najla Fourati and Nicolas George the recipient of the SCT-Young Researcher in Medicinal Chemistry in Industry Prize. The conferences will tackle themes in different therapeutic areas like cancer or antibioresistance, innovative mode of actions, natural compounds, radiolabeled agents, compounds for photodynamic therapy or antibodies and antibody-drug conjugates. All these case studies will inspire you greatly.
This year, the new **Young MedChem Forum** of the SCT will present what is new at the SCT.

It is of utmost importance that Young Researchers are provided with slots for communications and poster presentations (68) as face to peers essential experience at the beginning of the career. Thus 25 oral presentations and 35 flash poster presentations have been allocated to participants with 71 posters presented in addition during poster sessions. We are looking forward to discover the great works through these presentations and posters.

In the continuing efforts of SCT to support and accompany young talents, career sessions have been also maintained to offer YRF individual one-to-one meetings. We thank warmly all the contributors for their enthusiastic engagement on these sessions.

To recognize young talents and shed light on their work, the SCT is continuingly distributing prizes and awards. Young Research Fellows with the best oral communications and poster presentations will be awarded and offered a registration to an international congress.

Importantly, with your registration to this YRFM, you are automatically member of our Society for 2023. You will thus benefit from a very competitive registration fee for our main scientific events, such as the next thematic meetings of SCT. You will have also the opportunity to have access to free webinars.
On all these forthcoming events you can find more information on our web-site (www.sct-asso.fr) or social networks (Twitter LinkedIn).

Finally, the SCT especially acknowledge our industrial and academic sponsors for their financial support.

The SCT-YRFM is a decades-long success. This year edition will gather about 200 participants and show the continuing international attraction of this event. We wish you all an excellent symposium with good scientific discussions and we hope to see you soon at another event of the SCT.

Prof. Rebecca Deprez-Poulain, SCT President

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SCT Young MedChem Forum

In early 2022, The SCT created a group of young academic and industrial rese
SCT Young MedChem Forum – YMCF, with the aim of supporting young medicinal chemists and students who wish to become by inspiring, training and connecting them.

Frederic Miege
Edelris, Lyon

Nicolas George, chair
Aqemia, Paris

Guillaume Eppe
Evotec, Toulouse

Amanda Garrido
ICBMS/ISPB, Lyon

Drs Sandy Desrat and Nicolas George attend to the YRFM 2023

Léa Bouché
Roche, Bâle

Sandy Desrat
ICSN, Gif-sur-Yvette

Guillaume Compain
CBMN, Bordeaux

Gilles Degotte
UGA, Grenobles

Ask Me Anything

The first event was the *AskMeAnything session* where 2 members of the YMCF (one academic and one industrial) discuss virtually and informally with Master students or PhD students/post-docs to answers their questions. 3 sessions took place in 2022 with > 80 young scientists, and to be continued in next years. Registration is free of charge but completion of a google form is mandatory.

The second event of 2022 was a *Mentoring program* from November to May 2023 with 17 students (Master and 1st year-PhD students) and 14 senior mentors from academia and private company. The objective of this initiative is to give advice on the career orientation of young scientists with an interest in medicinal chemistry, such as non-scientific skills and career planning for instance.

YMCF Mentoring Program 22-23

2023 begins with an *AskMeAnything session* for PhD students and post-docs is planned for Monday 30th January (first session out to 6 for 2023). Other initiatives will follow.

Stay tuned at:
twitter.com/SCT_YMCF
www.linkedin.com/in/young-medchem-forum-sct
www.sct-asso.fr/

Do not hesitate to reach out at ymcf(at)sct-asso.fr

Société de Chimie Thérapeutique

30th Young Research Fellows Meeting - 30e Journées Jeunes Chercheurs

Faculty of Pharmacy – Paris, France

Wednesday, February 1st, 2023

12.00-12.45 **Registration**

12.45-13.00 **Opening of 30th YRFM**

Session chair:

13.00-13.40 **Plenary Lecture 1: Dr. Florine Cavelier, Université de Montpellier, France.**

Neurotensin analogues: targeting two receptors for two therapeutic purposes

13.40-14.40 **Oral Communications**

OC1: Améni Hadj Mohamed, U. Paris U. Paris-Saclay, France
Diarylmethanes as potential anti colorectal cancer agents: synthesis, in vitro and in silico studies
OC2: William Boiledieu, CiTCoM, U. Paris Cité, France
Visible-light photoredox synthesis and functionalization of benzodiazepine and phtalazine compounds via N-centered radicals
OC3: Marco Rizzo, DIFAR, U. Genova, Italy
Novel azaspiro compounds for the treatment of human african trypanosomiasis: synthesis, biological evaluation and docking studies.

14.40-15.15 **Flash Poster Presentation – session 1**

FP 1 : Youssef Bagdad, CiTCoM, U. Paris Cité, France
FP 2 : Chloé Rémondin, CERMN, U. Caen, France
FP 3 : Roberta Listro, Dept. of Science, U. Pavia, Italy
FP 4 : Karam Chamoun, UMR-1144, U. Paris Cité, France
FP 5 : Marie Hanot, AGIR, U. Picardie, France
FP 6 : Constance Dalton, School of Pharmacy, U. Nottingham, U.-K.
FP 7 : Vincent Baran, UMR-CNRS 6230, U. Nantes, France.
FP 8 : Viktor Savic, Inst. of Appld. Synth. Chem., U. Vienna, Austria
FP 9 : Clara Faure, CiTCoM, U. Paris Cité, France
FP 10 : Félix Torres, NexMr GmbH, Zurich, Switzerland
FP 11 : Marie Julie Tilly, UMR 7177, U. Strasbourg, France
FP 12 : Xiaoqing Ye, CiTCoM, U. Paris Cité, France
FP 13 : Sandra Kovachka, ICN, U. Côte d'Azur, France
FP 14 : Salim Benmaouche, CiTCoM, U. Paris Cité, France
FP 15 : Philipp Peslalz, Organische Chemie I, U. Dresden, Germany
FP 16 : Hugo Roux, U. Marseille, France
FP 17 : Gianmarco Gualtieri, Dept. di Scienze della Salute, U. Catenzaro, Italy
FP 18 : Amélie Laversin, UMR 1172, U. Lille, France
FP 19 : Dominik Schnalzer, Inst. of Appld. Synth. Chem., U. Vienna, Austria
FP 20 : Monica Bosco, UTCBS, U. Paris Cité, France
FP 21 : Marie Cornu, CERMN, U. Caen, France
FP 22 : Bo Li, CBMN UMR 5248, U. Bordeaux, France

15.00-16.00 **Coffee break – Poster session**

16.00-16.30 **Keynote Lecture 1: Dr. Yohan Corvis, Université Paris Cité, France**

Nanocrystals engineering for drug delivery: new perspectives for personalized therapies.

16.30-17.50 **Oral Communications**

OC4: Gwenaëlle Jézéquel, HIPS-DDOP, U. Saarbrucken, Germany
Complementary hit-finding approaches afford inhibitors targeting SARS-CoV-2 Nsp10
OC5: Carole Guimard, ICSN, Gif-sur-Yvette, France
Design, synthesis and biological evaluation of first OSBP degraders
OC6: Morgane Baudoin, DPM, U. Grenoble Alpes, France
Copper-free click chemistry as a tool for two-colors dSTORM imaging of peptidoglycan and teichoic acids in S.pneumoniae
OC7: Cécile Alleman, ISCR, U. Rennes, France
Fusicoccin-A derived molecular glues: synthesis of analogs

17.50-18.30 **Plenary Lecture 2: Dr. Bruno Therrien, University of Neuchatel, Switzerland.**

Metal-based drugs : past, present and future

18.30-18.45 **Commercial presentation : Mark Harding (CDD Vault)**

18.45-20.00 **Welcome Reception**

Enjoy the artists of the Faculty of Pharmacy, music and show by our pharmacy's students.

Thursday, February 2nd, 2023

Session chair:

9.00-9.30 **Keynote Lecture 2: Dr. Gilles Phan, Université Paris Cité, France**

Structure and function of multidrug efflux pumps in Pseudomonas aeruginosa.

9.30-10.10 **Oral Communications**

OC08: Katharina Schlögl, TU Wien, Vienna, Austria
Photoswitchable azo-reboxetine inhibitors for the light-induced control of the human
norepinephrine transporter
OC09: Roberta Ibba, Dept. Medicine Surgery and Pharamcy, U. Sassari, Italy
Design, synthesis and anticancer evaluation of novel VEGFR2/microtubule dual inhibitors for the treatment of metastatic cancers

10.10-10.50 **Plenary Lecture 3: Dr. Sébastien Ballet, Bruxelles, Belgium.**

Peptide modalities for improved pain treatment: adding tools to the toolbox

10.50-11.30 **Coffee break – Poster session**

11.30-12.10 **Plenary Lecture 4: Dr. Nuno Maulide, Vienne, Austria**

Making difficult bonds with rearrangements

12.10-12.30 **Flash poster presentations-session 2**

FP 23 : Mehdi Oudahmane, GBCM, le Cnam (Paris), France
FP 24 : Rihanna Lenham, School of Pharmacy, U. Nottingham, U.-K.
FP 25 : Eka P. Gusti Ngurah P., Institut Curie (Orsay), France
FP 26 : Fabiana Guerra, Faculté de Médecine, Montréal, Canada
FP 27 : Aleksandra Rancic, LCBPT, U. Paris Cité, France
FP 28 : Nicolo Bisi, BioCis, U. Paris Saclay
FP 29 : Mathis Guiraud, IBMM, U. Montpellier, France
FP 30 : Marta Cozzaglio, Dept. Pharmaceut. Pharmacol. Sc., U. Padova, Italy
FP 31 : Marion Sisquellas, CiTCoM, U. Paris Cité, France
FP 32 : Morgane Rivoal, Infinite, U. Lille, France
FP 33 : Laura M. Cantudo, Dept. Quimica Bioquimica, U. San Pablo, Spain
FP 34 : Jean Roussel, ICBMS, U. Lyon, France
FP 35 : Yelda Aboukhalil, CiTCoM, U. Paris Cité, France

12.30-14.00 **Lunch break – Poster session**

14.00-14.10 **News from the SCT**
Presentation of the Young MedChem Forum (YMCF)

Session chair:

14.10-14.50 **Plenary Lecture 4: Pr. Xavier Coumoul, Université Paris Cité, France**

Exposome, chemical contaminants and breast cancer

14.50-15.10 **Oral Communication from the Paul Ehrlich EuroPhD Network Selected during the network's meeting in Barcelona (July, 2022)**

Lhana Tisseur (IICiMed, U. Nantes, France).
Imidazo[1,2-a]pyrazines targeting casein kinase 1 for the design of antileishmanial agents

15.10-15.30 **Oral Communications**

OC10: Peter Ibrahim, Drug Discovery Unit, U. Dundee, UK
Binding pose prediction of protease inhibitor using Supervised Molecular Dynamics (SuMD)

15.30-16.00 **Keynote lecture 3 - SCT award in medicinal chemistry. Nicolas George**

16.00-16.35 **Coffee break – Poster session**

16.35-17.15 **Plenary Lecture 5: Pr. Nicolas Anton, University of Strasbourg, France**

Innovative lipid nano-formulations

17.15-18.55 **Oral Communications**

OC11: Alice Wang, CERMN, U. Caen, France
Novel pleiotropic prodrugs with potential therapeutic interest in Alzheimer's disease

OC12: Virgyl Camberlein, HIPS-DDOP, U. Saarbrucken, Germany
Discovery of Pseudomonas aeruginosa elastase LasB inhibitors by in situ click chemistry

OC13: Marc Panosetti, ICN, U. Côte d'Azur, France
Modulation of the circadian clock for cancer chemotherapy using new synthetic RNA ligands

OC14: Matej Jaklin, Physical Chemistry, U. Ljubjana, Slovenia
Effect of Buffer Identity on lactoglobulin amyloid fibrillization

OC15: Chaimae Majdi, CHROME, U. Nîmes, France
Synthesis, antibacterial activities, and synergistic effects of novel juglone and naphthazarin derivatives against clinical methicillin-resistant Staphylococcus aureus strains

18.55-00.00 **Let's go to a party**

Friday, February 3rd, 2023

Session chair:

9.00-9.30 **Keynote Lecture 4: Caroline Roques, UTCBS, U. Paris Cité, France**
Functionalized cerium oxide nanoparticles as promising antioxidants

9.30-10.10 **Plenary Lecture 6: Pr. Stéphanie Baillif, University of Nice, France**
Choroidal and retinal angiogenesis : the long journey to finding a treatment that works

10.10-10.50 **Oral Communications**

OC16: Jay Tromans, School of Natural and Environmental Science, Newcastle, UK

Synthesis of plasmalogens: iconic phospholipids with an Alzheimers connection

OC17: Chloé Gilliot, Dept. chemistry and Biochemistry, U. San Pablo CEU, Madrid, Spain

Development of folate conjugates based on aromatase inhibitors as novel anticancer agents

10.50-11.30 **Coffee break – Poster session**

11.30-12.30 **Oral Communications**

OC18: Martina Pacetti, Dept. of Pharmaceutical Sciences, U. Perugia, Italy
Lead optimization of influenza polymerase PA-PB1 subunits interaction disruptors

OC19: Laurie Bibens, AGIR, U. Picardie, France
Development of new quinolines as FabZ in inhibitors to struggle antimicrobial resistance.

OC20: Nina Compagne, U1177, U. Lille, France
Optimization of a pyridylpiperazine hit as an efflux pump inhibitor in E. coli to fight antimicrobial resistance

12.30-14.00 **Lunch break – Poster session**

14.00-15.40 **Oral Communications**

OC21: Rémi Chatre, IC2MP, U. Poitiers, France
Tumor activated therapy for the treatment of solid cancers

OC22: Feras Oyoun, UTCBS, U. Paris Cité, France
Organic solvent-free nanoparticles preparation based on therapeutic deep eutectic solvents for cancer treatment

OC23: Giacommo Rossino, Dept. of Drug Science, U. Pavia, Italy
Bivalent ligands targeting Sigma Receptors and TSPO: new tools for studying oncogenic pathways

OC24: Erika Adhel, ITODYS, U. Paris Cité, France
Modified fluoroquinolones as antimicrobial compounds targeting Chlamydia trachomatis

OC25: Marion Michel, ICOA, Orléans, France
Tryptophan 2,3dioxygenzyse (TDO) : the new promising target of 18F PET tracers as markers of neuroinflammation

15.40-16.20 **Plenary Lecture 7: Najla Fourati (Cnam, Paris)**
Trends and perspectives in biosensors for prostate cancer diagnosis

16.20-16.30 **Pharma' fayrewell**
A short show performed by our musicians

16.30-16.45 **Concluding remarks – Awards**

17.00 **End of the meeting**

PLENARY LECTURES

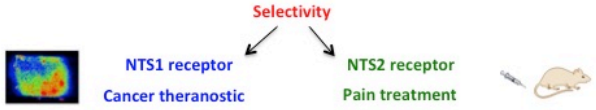
Neurotensin analogues: targeting two receptors for two therapeutic purposes

Santo Previti[1,2], Mélanie Vivancos[3], Sacha Bodin[4,5], Emmanuelle Rémond[1], Jean-Michel Longpré[3], Clément Morgat[4,5], Philippe Sarret[3], **Florine Cavelier[1]**

[1]Pôle chimie Balard, IBMM, UMR 5247, CNRS, Université de Montpellier, ENSCM, 1919 Route de Mende, 340293 Montpellier cedex 5, France.
[2]ChiBioFarAm Department, University of Messina, Messina, Italy
[3]Department of Pharmacology-Physiology, Faculty of Medicine and Health Sciences, Institut de Pharmacologie, Université de Sherbrooke, Sherbrooke, Québec, Canada J1H 5N4.
[4]INCIA, UMR 5287, CNRS, University of Bordeaux, 33400 Talence, France.
[5]Service de médecine nucléaire, CHU de Bordeaux, France.

Neurotensin (NT) is a tridecapeptide, which was first isolated from bovine hypothalamus.[1] The C-terminal fragment NT[8-13] is the minimal bioactive sequence, which induces antinociceptive action and other physiological side effects such as hypothermia and hypotension by interaction with its receptors. Among the NT receptor subtypes, Sarret *et al.* showed that the selectivity towards NTS2 is fundamental to exert an analgesic activity without unwanted effects.[2] Several structure-activity relationship studies point out the importance of Tyrosine residue in position 11 to drive the selectivity NTS2/ NTS1. Based on these results, we developed several NT[8-13] analogues using different approaches including unnatural amino acid incorporation[3] and peptide bond modification in order to improve their affinity, their stability and their activity. In addition, since the interaction between neurotensin and its receptor NTS1 has been clarified by crystallization with the NT[8-13] ligand,[4] we explored the differences between NTS1 and NTS2 by molecular modeling to understand the rule of this selectivity.[5]

On the other hand, recent studies demonstrated that NTS1 is overexpressed in breast cancer, pancreatic adenocarcinomas, prostate and stomach cancers among others.[6] In this context, we have synthesized new radiolabeled NT[8-13] analogues, highly selective towards NTS1 with an increased plasmatic stability and lipophilicity for imaging and therapy of those tumors.[7,8]



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2. Roussy, G. *et al. Mol Pain*. **2009**, *5*, 38-53.
3. a) Vivet, B.; Cavelier, F.; Martinez, J. *Eur. J. Org. Chem*. **2000**, *5*, 807-811. b) Fanelli, R.; Cavelier, F. *et al*. *J. Med. Chem.* **2015**, *58*, 7785-7795. c) Hapău, D.; Cavelier, F. *et al. Eur. J. Org. Chem.* **2016**, *5*, 1017-1024.
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5. Fanelli, R.; Cavelier, F. *et al. J. Med. Chem.*, **2017**, *60*, 3303-3313.
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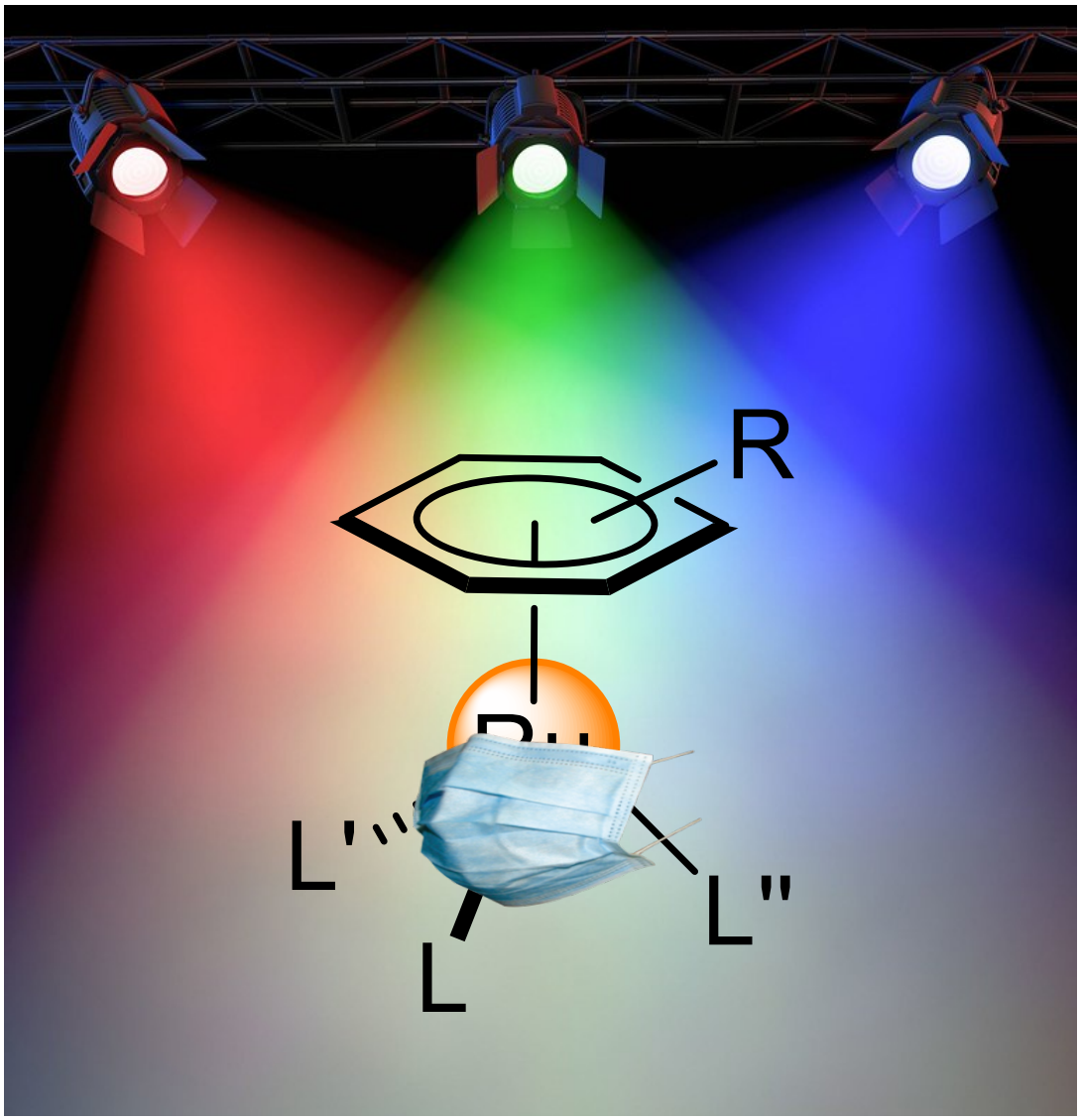
7. Fanelli, R. Cavelier, F. *et al. Bioconjugate Chem.,* **2020**, 2339-2349.
8. Bodin, S. *et al*. *ACS Omega*, **2022**, in press.

Metal-based drugs : past, present and future

Bruno Therrien

Institute of Chemistry, University of Neuchatel, Switzerland

For nearly 15 years, we have focused our research on arene ruthenium building blocks as bricks to construct added-value objects. Such adaptable organometallic complexes have been used to build cages, to develop supramolecular materials, or to transport drugs to cancer cells. During this short presentation, we want to give the basic reasons behind our choice, and unmask our most successful examples, with an emphasis on the foreseen applications.



Peptide modalities for improved pain treatment: adding tools to the toolbox

Steven Ballet

Research Group of Organic Chemistry, Departments of Bioengineering Sciences and Chemistry,
Vrije Universiteit Brussel (VUB), Brussels, Belgium.
Email: steven.ballet@vub.be

Abstract:

To address the different types of pain different classes of medications, mainly non-steroidal anti-inflammatory drugs and narcotics (opioids), are used. The alleviation or treatment of moderate to severe pain states, in particular, commonly invokes the use of opioids. Unfortunately, their chronic administration induces various undesirable side effects, such as for example physical dependence and tolerance. Two strategies to overcome these major side effects and to prolong the antinociceptive efficiency of the applied drugs involve: a) the creation of multifunctional compounds which contain hybridized structures (**Part 1**), and b) the design of peptide-based hydrogels as delivery systems for the controlled-release of painkillers (**Part 2**).

Part 1
Combination of opioid agonist and antagonist pharmacophores in a single chemical entity has been considered and extensively investigated, but opioids have also been structurally combined with other bioactive neurotransmitters and peptide hormones that are involved in pain perception (e.g. substance P, neurotensin, cholecystokinin, cannabinoids, melanocortin ligands, etc.). Such novel chimeras (also called designed multiple ligands (DMLs) or multitarget ligands), may interact independently with their respective receptors and potentially result in more effective antinociceptive properties. The designed multiple ligands presented in this work include opioid-non-opioid (non-)peptide dimer analogs, such as for example opioid-neurokinin 1 receptor DMLs and opioid-neuropeptide FF DMLs. During the presentation, a main focus is placed on the design and biological evaluation of these multiple opioid compounds.

Part 2
To overcome the need of repeated high dose administration, hydrogels have been reported as suitable controlled drug-delivery systems. More specifically, peptide hydrogels loaded with active ingredients can liquefy during injection, followed by quick hydrogel reformation once injected. These systems present several advantages such as the protection of the drug against the enzymatic degradation by encapsulation in the hydrogel network, while maintaining the therapeutic plasma drug concentration over a long period via diffusion from the hydrogel or by degradation of the network.[1] Consequently, lower dosage and frequency of administration are possible and result in an improvement of the drug efficacy while reducing the risk of side effects. Here, a new family of short, tunable and amphipathic hexapeptide hydrogel-forming peptides was designed. In order to study their eventual therapeutic potential, the hydrogels have been used for entrapment and sustained release of opioid drugs. The *in vitro* drug release properties and hydrogel toxicity were, for instance, determined. Based on the best physicochemical, mechanical, and noncytotoxic properties, selected hydrogels were investigated for *in vivo* release of opioids. Opioid administration by subcutaneous injection and subsequent testing in the tail-flick assay (acute pain model), showed sustained antinociceptive effects over longer periods of time (up to 96 hours), as compared to drug injections in saline solutions (<3 hours).

Selected references:
Guillemyn, K. et al. Bifunctional Peptide-Based Opioid Agonist−Nociceptin Antagonist Ligands for Dual Treatment of Acute and Neuropathic Pain. *J. Med. Chem.* **2016**, 59, 3777.

Martin, C. et al. Controlled-release of opioids for improved pain management. *Materials Today* **2016**, 19, 491.

Martin C. et al. Biodegradable amphipathic peptide hydrogels as extended-release system for opioid peptides. *J. Med. Chem*. **2018**, 61, 9784.

Making difficult bonds with rearrangements

Pr. Nuno Maulide

Institute of organic chemistry, University of Vienna, Austria

Our research group has devoted the past decade to the development of rearrangements as tools for C-C bond formation in contexts where the state-of-the-art was either elusive or appeared to mandate harsh conditions or the deployment of transition-metal catalysis. In this talk, the intersection of this expertise with unusual hypotheses for bond-forming processes that advance our understanding and the art of synthesis will be presented. Acknowledgments

We thank funding from the Christian-Doppler Association, the European Research Council, the University of Vienna, the Austrian Academy of Sciences and the Austrian Science Fund.

Exposome, chemical contaminants and breast cancer

Pr. Xavier Coumoul

INSERM UMR-S 1124 - T3S, Environmental Toxicity, Therapeutic Targets, Cellular Signaling & Biomarkers,
Université Paris Cité, Faculté des Sciences, UFR des Sciences Fondamentales et Biomédicales, Paris, France

- Human populations and ecosystems are exposed to more than 100,000 molecules of anthropic origin, and the toxicity of 70,000 of them is poorly little characterized. These molecules defines part of the chemical exposome, which is therefore a part of the exposome (all exposures to which an individual is exposed throughout his life). Among these molecules, persistent organic pollutants (or POPs) accumulate in the lipidic fractions of our organisms (such as adipose tissues) and can be released at low levels throughout life, influencing their microenvironment. In this context, we have shown that some POPs accumulated in the peri-tumoral adipose tissue of the breast could be associated with a higher risk of metastasis; we also characterized their modes of actions. These clinical and experimental studies allowed us to produce a new tool that could be particularly used in a few years to improve regulatory assessment.

Innovative lipid nano-formulations

Dr. Nicolas Anton

INSERM 1260, CRBS- Centre de recherche en biomédecine de Strasbourg, *University of Strasbourg, Strasbourg, France*

Drug formulations made from lipid vehicles have still aroused considerable interest, owing to their low toxicity, biodegradability, simple formulation processes, and high loading capability. Among lipid-based carriers, like, *e.g.*, liposomes, cationic lipid nanoparticles, solid lipid nanoparticles, one family of particles has particularly attracted the attention of researchers from the last two decades: nano-emulsions. Nano-emulsions are nanocarriers only composed of oil nano-droplets, stabilized by surfactants, and able to disperse lipophilic drugs in the aqueous phase with high concentration and high stability. Our research group, *Biogalenic and Therapeutic Innovations*, laboratory Inserm 1260, University of Strasbourg, has developed a multidisciplinary research on nano-emulsions, from fundamental aspects, up to applications. The presentation will first focus on the different stakes and challenge related to emulsion and nano-emulsion formulations. Beside mechanical methods used in industrial processes to produce sub-micron emulsions, the formulator can take advantage of the physicochemical behavior of nonionic surfactants to fabricate nano-emulsions. Such methods are called temperature phase inversion method or spontaneous emulsification, and, are commonly associated with the formulation of nano-emulsion. An important research effort was devoted to understanding the relationship between surfactant behavior and nano-emulsification process. A second part of the presentation will concern the use of these lipid nano-droplets to encapsulate lipophilic molecular imaging probes. Lipophilic fluorescent dyes solubilized in the nano-emulsion oily core showed very singular properties, conferring to the droplets an outstanding brightness, comparable to quantum dots. These properties are mainly due to steric hindrance between dyes, giving rise to high quantum yield at high dye concentrations. Studies of fluorescent nano-emulsions were performed *in vitro* and *in vivo*, allowing single particle tracking in zebrafish, or evidencing the droplet passive targeting in tumor models in mice, and following the droplet stability *in vivo* with Förster energy transfer. Contrast agent nano-emulsions were also applied to other imaging modalities, X-ray imaging, and MRI imaging, for which specific chemistry and formulations were developed. A third part of the presentation will present works on the surface functionalization of the nano-emulsion droplets. Since water/oil interface of nano-droplets is a dynamic system, and, amphiphilic molecules, or potential ligands are only adsorbed at the interface, surface functionalization remains a challenge in terms of stability. Adsorption is indeed a reversible process, all the more so since the hydrophilic ligands have a large molecular weight –*e.g.,* antibodies– and are susceptible to desorb. To control the chemical modification of nano-droplets' surface, we have developed several experimental approaches, with, as objective, active targeting of such nanocarriers. These strategies involved the use of amphiphilic polymers, or *in situ* chemical modification of the droplet interface, or the design of specific lipophilic anchors able to react with ligands in solutions after formulations. To conclude, all these studies dealt with different nano-emulsion formulations to be used as targeted drug delivery purpose and/or contrast agents, focused on theoretical aspects, processes optimization, and their characterization.

Choroidal and retinal angiogenesis : the long journey to finding a treatment that works

Pr. Stéphanie Baillif

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Ocular angiogenesis, or ocular neovascularization, is responsible for the leading causes of blindness in the developed countries. It affects many ocular tissues such as the cornea, the iris, the retina, and the choroid.

In retinal neovascularization, new vessels extend from the inner retina into the avascular vitreous gel. With time, these new vessels become fibrotic and traction retinal detachment or vitreous hemorrhages may develop. Retinal neovascularization often originates in the vicinity of areas of ischemic retina. The most frequent diseases leading to retinal neovascularization are diabetic retinopathy and, central vein occlusion but it also occurs in hemoglobinopathies or retinopathy of prematurity, and radiation retinopathy.

The choroid is a vascularized and pigmented tissue that nourishes the outer layers of the retina and plays a role in heat dissipation. Choroidal neovascularization occurs most exclusively in the central macular regions of the retina. New vessels grow from the choriocapillaris, break the Bruch's membrane end develop into the retinal pigment epithelium and subretinal spaces. Choroidal neovascularization is the trademark of age-related macular degeneration but is also associated with high myopia or in retinal pigment epithelium changes.

Few treatments are available to treat these diseases: only anti-VEGF therapies are at disposal, injected intravitreously every 4 to 12 weeks. New molecules are under way, with new dosing regimen, and delivery sites.

This lecture will focus on retinal and choroidal neovascularization and the long journey to developing a treatment that would work.

KEYNOTE LECTURES

Nanocrystals engineering for drug delivery: New perspectives for personalized therapies

Yohann CORVIS*

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Up to 90% of the APIs currently in development present low solubility in aqueous media since around 65% and 15% belong to class II and class IV of the Biopharmaceutics Classification System, respectively[(a)]. Consequently, many approaches have been proposed to overcome bioavailability issues during drug development by using physico-chemical modulation of pharmaceutical ingredients[(b)]. Among them, formulations obtained after nanonization process such as nanocrystallization – that allows maximizing the loading of the API dispersed in liquid or solid dosage forms – have been engineered to optimize the therapeutic efficiency of drugs with better safety, targeting and administration through various routes[(c)].

UTCBS lab pioneered the bottom-up approach with minimal amount of Pluronic® F-127 as stabilizer to engineer etoposide nanocrystals (NCs) for anti-cancer therapies[(d)]. Surprisingly, since the first commercialized NC preparation of an API in 1982, no antitumoral NC-based drug has been marketed. By contrast, about 20 NC drugs have been approved by the Food and Drug Administration, including only three marketed products that can be parenterally delivered (*i.e.*, Invega Sustenna®, Ryanodex®, and Cabenuva® approved in 2009, 2014, and 2021, respectively). Therefore, the latter UTCBS project reinforced the legitimacy of drug NCs as potent forthcoming delivery systems for nanomedicines through parenteral administration and presenting less side-effects than the related conventional marketed product, Toposar®[(e)].

Parameters such as the nature of the API and that of the stabilizing agent, as well as their relative ratios, have been screened with the bottom-up solvent/anti-solvent approach to optimized each formulation and apprehend the key factors for convenient nanocrystallization[(c)]. Furthermore, a microfluidic approach has been implemented for robust production of crystalline nanoparticles with green chemistry concerns[(f)]. Based on these promising results, APIs with other therapeutic indications[(g)] have thus been chosen for the formulation of original nanocrystalline multiphase systems with tunable properties endowed with pharmaceutical, biomedical, or diagnostic function as third and fourth generation of nanomedicines for personalized therapies[(b)].

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Structure and function of multidrug efflux pumps in *Pseudomonas aeruginosa*.

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In the context of antibioresistance, there is an urgent need to develop new molecules, adjuvants or inhibitors, able to restore the efficiency of existing antibiotics. Several bacteria are particularly alarming, especially the Gram-negative pathogens *Pseudomonas aeruginosa*.

Among the different antibiotic resistance strategies, the active efflux of molecules by membrane transporters is one of the most important. In particular, the efflux pumps of the RND family (Resistance Nodulation cell Division) are the major actors of the multiresistance. Importantly, multidrug-resistant bacteria strains found in hospitals generally overexpress the RND efflux pumps.

These transporters are multimers constituted of three different proteins (RND transporter, Membrane Fusion Protein, MFP, and Outer Membrane Factor, OMF) which association forms a long assembly crossing the two membranes in order to expulse molecules, thus efficiently decreasing the intracellular concentration of antibiotics. It is thus tempting to target these pumps for the development of inhibitors, assembly blockers, or alternative substrate decoys in order to restore the efficacy of existing antibiotic pharmacopeia.

Our project focuses on the constitutive RND pumps $MexA_{MFP}$-$MexB_{RND}$-$OprM_{OMF}$ (or MexAB-OprM) which exports almost all the antibiotic families used against *Pseudomonas* (ß-lactams, fluoroquinolones, chloramphenicol and tetracyclines). Significant structural and functional data were obtained for the assembled system MexAB-OprM, including the crystal structure of OprM [Monlezun et al. 2015] and the cryo-EM structure of the whole system [Glavier et al. 2020, Boyer et al., 2022]. So far MexB appears as the main actor of the primary stage of antibiotic recognition and transport, but we have highlighted a significant role for MexA as an activator of MexB. For these reasons, we suggest to block the MexAB-OprM efflux pump by targeting different levels of the assembly.

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2022 SCT Award for Young Industrial Investigator in Medicinal Chemistry

Discovery and lead-optimization of 2-pyrazolines as mono-kinase selective and orally bioavailable RIPK1 inhibitors

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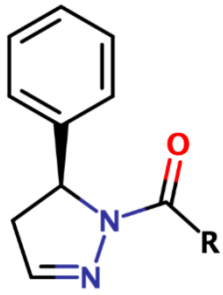

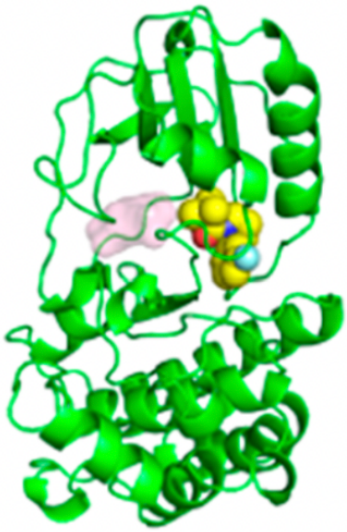

RIP1 kinase (RIPK1) is a serine/threonine-protein kinase that has recently emerged as a central regulator programmed necrosis (necroptosis), an inflammatory form of cell death, with important roles in inflammation and neurodegeneration. GSK performed pioneer studies leading to the entry on clinical trials of several RIPK1 allosteric inhibitors with the hope of raising new opportunities for treating a variety of autoimmune, inflammatory, and neurodegenerative diseases.
The presentation focuses on the discovery of a 2-pyrrazoline allosteric series, neglected scaffold, and its optimization as mono-kinase selective and orally bioavailable RIPK1 inhibitors.

Functionalized cerium oxide nanoparticles as promising antioxidants

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Oxidative stress results from an imbalance between the production of reactive oxygen species and the antioxidant capacity of endogenous systems. Accumulating evidence suggests that numerous pathologies with high socioeconomic impact such as cancer, cardiovascular and brain diseases share common mechanisms, such as oxidative stress. Oxidative stress plays a major role in neurological disorders whether they are acute, such as trauma or stroke or chronic, i.e. neurodegenerative diseases.

Cerium oxide nanoparticles (also known as nanoceria) have potent, self-regenerating anti-oxidant properties. However, bare nanoceria show rapid aggregation at physiological pH, thus calling for surface modification through polymer coating. The antioxidant effect of nanoceria being linked to their surface reactivity, the impact of polymer coating was closely investigated. We could show that nanoceria surface modification preserved their antioxidant capacity as well as cellular uptake. These results open further options for innovative therapies.

ORAL COMMUNICATIONS

Imidazo[1,2-*a*]pyrazines targeting casein kinase 1 for the design of antileishmanial agents

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the Paul Ehrlich EuroPhD Network

According to a recent WHO report[1], leishmaniasis - visceral leishmaniasis (VL), cutaneous leishmaniasis (CL) and mucocutaneous leishmaniasis (MCL) - affects nearly 12 million people, with 350 million others at risk, and is responsible for nearly 40,000 deaths per year. This parasitic disease is classified as one of the 20 neglected tropical diseases and is endemic in nearly 100 countries worldwide. In 2012, mainly due to global warming, visceral leishmaniasis (VL) was declared as a new emerging disease in Europe. Today, there is no effective vaccine, and only 5 treatments -pentavalent antimonials, amphotericin B, miltefosine, pentamidine, paromomycin[2]- which are unfortunately still too toxic, costly and for which there is an emergence of resistance. In this context, it's really urgent to develop a new generation of drugs, safer, more effective and with a new mechanism of action to overcome these parasitic resistances. We previously reported the discovery of **CTN1122**[3], an imidazo[1,2-*a*]pyrazine derivative with promising antileishmanial properties and targeting a protein of interest: *Leishmania* Casein Kinase 1 paralog 2 (L-CK1.2)[4]. (**Figure 1**)

CTN1122

IC_{50} (amastigotes *L. major*) = 0.80 µM (CL)
IC_{50} (amastigotes *L. donovani*) = 2.74 µM (VL)
SI (RAW cells/amastigotes *L. major*) = 52.5
SI (RAW cells/amastigotes *L. donovani*) = 15.3
IC_{50} (*Lm*CK1) = 0.72 µM
SI_{CK1} = 1.3

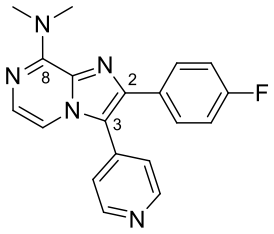

Figure 1. The hit compound **CTN1122**.

Through a research program dedicated to this series, we will focus on the biological results obtained by both phenotypic and target-based approaches. Finally, new pharmacomodulations of **CTN1122** leading to the discovery of potential new drugs against leishmaniasis will be presented[5].

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Diarylmethanes as potential anti colorectal cancer agents: Synthesis, *In vitro* and *In silico* studies

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OC01

Distinctive structural, chemical, and physical properties make the diarylmethane scaffold an essential constituent of many active biomolecules nowadays used in pharmaceutical, agrochemical, and material sciences. 33 novel diarylmethane molecules aiming to target colorectal cancer were designed. Two series of functionalized olefinic and aryloxy diarylmethanes were synthesized and chemically characterized. The synthetic strategy of olefinic diarylmethanes involved a McMurry cross-coupling reaction as key step and the synthesis of aryloxy diarylmethanes included an *O*-arylation step. A preliminarily screening in human colorectal cancer cells (HT-29 and HCT116) and murine primary fibroblasts (L929) allowed the selection, for more detailed analyses, of the three best candidates based on their high inhibition of cancer cell proliferation and non-toxic effects on murine fibroblasts (<100 µM). The anticancer potential of these diarylmethane compounds was then assessed using apoptotic (phospho-p38) and anti-apoptotic (phospho-ERK, phospho-Akt) cell survival signaling pathways, by analyzing the DNA fragmentation capacity, and through the caspase-3 and PARP cleavage pro-apoptotic markers. (2-(1-(4- methoxyphenyl)-2-(4-(trifluoromethyl)phenyl) vinyl) pyridine, Z isomer) was proved to be the most active molecule. The binding mode to five biological targets (i.e., AKT, ERK-1 and ERK-2, PARP, and caspase-3) was explored using molecular modeling, and AKT was identified as the most interesting target. Finally, the most active compounds were predicted to have appropriate drug-likeness and good Absorption, Distribution, Metabolism and Excretion (ADME) profiles.

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Visible-Light Photoredox Synthesis of benzodiazepine and phtalazine compounds via N-Centered Radicals

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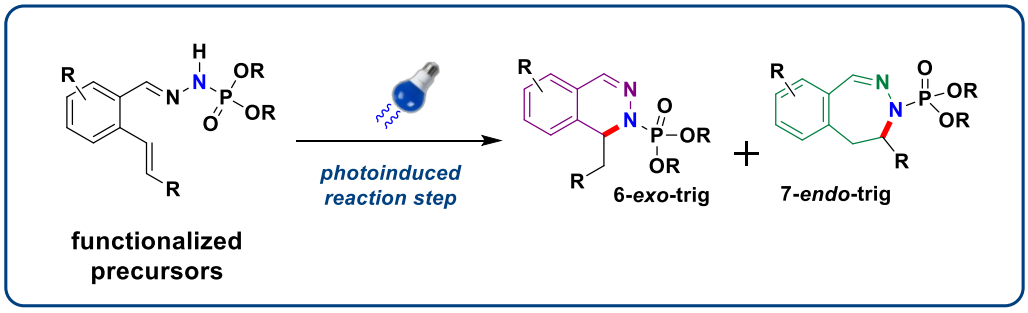
OC02

For the chemists' community, the ubiquitous presence of nitrogen-containing heterocycles in natural compounds have been the source of many inspirations for design and synthesis of new biological molecules. But the synthesis of these heterocycles remains an important challenge for pharmaceutical industry. We report on this work a mild and easy to setup method to obtain functionalized benzodiazepine and phtalazine scaffolds.[(a)] These kind of heterocycle are already used as inhibitors (Vatanalib), or for anxiety treatment (Diazepam). The key point of this work is the use of visible-light photocatalysis that could allow us to go through drawbacks and difficulties of conventional organic chemistry. To our knowledge, this work represents the first example of photo-induced 7-endo-trig cyclization involving nitrogen-centered radicals.

To develop new bioactive compounds and synthetized unprecedented structures, our team is interested on visible-light photocatalysis. Using visible-light as an exclusive energy source has proved his ability to generate nitrogen centered radical. Previously interested on N-tosylhydrazones as radical precursors,[(b)] our team is now working on phosphonohydrazone precursors that have a different behavior.[(c-d)]

In our lab, we synthetized and functionalized some phosphonohydrazones substrates. Then, the possibility of generating a nitrogen centered radical via photoinduced reaction was evaluated and optimized. At this step, the expected 6-exo cyclisation product was obtained but also the 7-endo one with a good ratio. In addition, further experiments shown that it was possible to manage selectivity with modifications of the conditions. This work using visible-light photocatalysis demonstrates that this method has a great potential on synthesis of new bioactive compounds.



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Novel Azaspiro compounds for the treatment of Human African Trypanosomiasis: synthesis, biological evaluation and docking studies.

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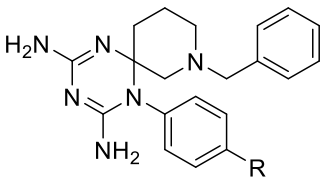
Center for Molecular Biology (ZMBH), DKFZ-ZMBH Alliance, and Interdisciplinary Center for Scientific Computing (IWR), Heidelberg University, Im Neuenheimer Feld 282, 69120 Heidelberg, Germany.

OC03

Trypanosomiasis is a life-threatening neglected tropical disease (NTD), which is endemic in several countries in South and Central America and Africa. Progress has been achieved with the introduction of fexinidazole and the combination drug eflornithine-nifurtimox. However, the use of these drugs is hindered by side effects and high toxicity. Moreover, the drug resistance issue, and the existence of animal reservoirs make the development of new safer and more efficient drugs a compelling need.
A strategy for the treatment of Human African Trypanosomiasis (HAT) is the inhibition of two major enzymes of *Trypanosoma brucei* (*Tb*), namely dihydrofolate reductase-tymidylate synthase (DHFR-TS) and pteridine reductase 1 (PTR1), that are involved in the folate pathway. Cycloguanil (CYC) is a well-known DHFR inhibitor, which has also been shown to act as a PTR1 inhibitor[(a)]. Binding mode analysis of CYC in complex with *Tb*DHFR-TS and *Tb*PTR1 active sites, allowed us to design and synthesize two novel series of compounds that maintain the 2,4-diamino-1,6-dihydrotriazine moiety of CYC[(b)]. The novel azaspiro compounds (A) and (B) have been obtained by replacing the C6 dimethyl group of CYC with a bulkier motif in order to increase the interactions with the two parasite targets and modulate the lipophilicity. The compounds have undergone evaluation of their on-target activity (TbPTR1 and TbDHFR-TS) and human DHFR off-target inhibition to ascertain their selectivity for the protozoan enzymes, cytotoxicity and antiparasitic effects. Docking studies and molecular dynamic simulations are ongoing, with the intent to better understand at a molecular level the binding mechanism of these compounds versus their putative targets. This information will guide the rational design of more promising antiparasitic compounds. This project is based upon work in the COST Action CA2111 "One Health drugs against parasitic vector borne diseases in Europe and beyond".



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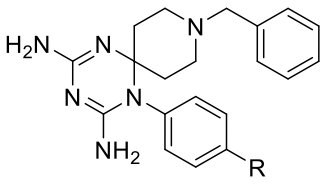

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Complementary hit-finding approaches afford inhibitors targeting SARS-CoV-2 Nsp10

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OC04

The end of the year 2019 saw the emergence of SARS-CoV-2, a new coronavirus that led to the worldwide pandemic of the Covid-19 disease. Despite the fast development of vaccines, there is a strong need for efficient antiviral drugs to cure infected patients. Nsp14 is a non-structural protein that displays an essential exoribonuclease (ExoN) activity, made possible by its interaction with Nsp10. Targeting this protein-protein interaction is therefore a promising strategy.[(a)]

In target-directed dynamic combinatorial chemistry, the target protein selects its binders and amplifies them from a pool of building blocks and potential binders at thermodynamic equilibrium.[(b)] We used this strategy to accelerate the identification of inhibitors of Nsp10. On the other hand, we have screened a halogen-enriched fragment library against Nsp10 using surface plasmon resonance (SPR). Following these results, further analogues were developed using virtual synthesis and molecular docking.

Several hits thus obtained were synthesized, and were characterized through SPR (K_D = 2–100 μM), near-native MS and an enzymatic assay measuring the ExoN activity. Finally, phenotypic assays against hCoV-229E and SARS-CoV-2 confirmed the activity in a whole-cell setting. Some of the hits found by those two complementary strategies displayed promising activity in all the assays, thus opening the way to an encouraging medicinal-chemistry program towards new SARS-CoV-2 antivirals with an unprecedented mode of action.

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(b) Hartman, A. *et. al.* Protein-Templated Dynamic Combinatorial Chemistry: Brief Overview and Experimental Protocol. European J. Org. Chem. 2019, 3581–3590 (2019).

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Design, synthesis, and biological evaluation of the first OSBP degraders

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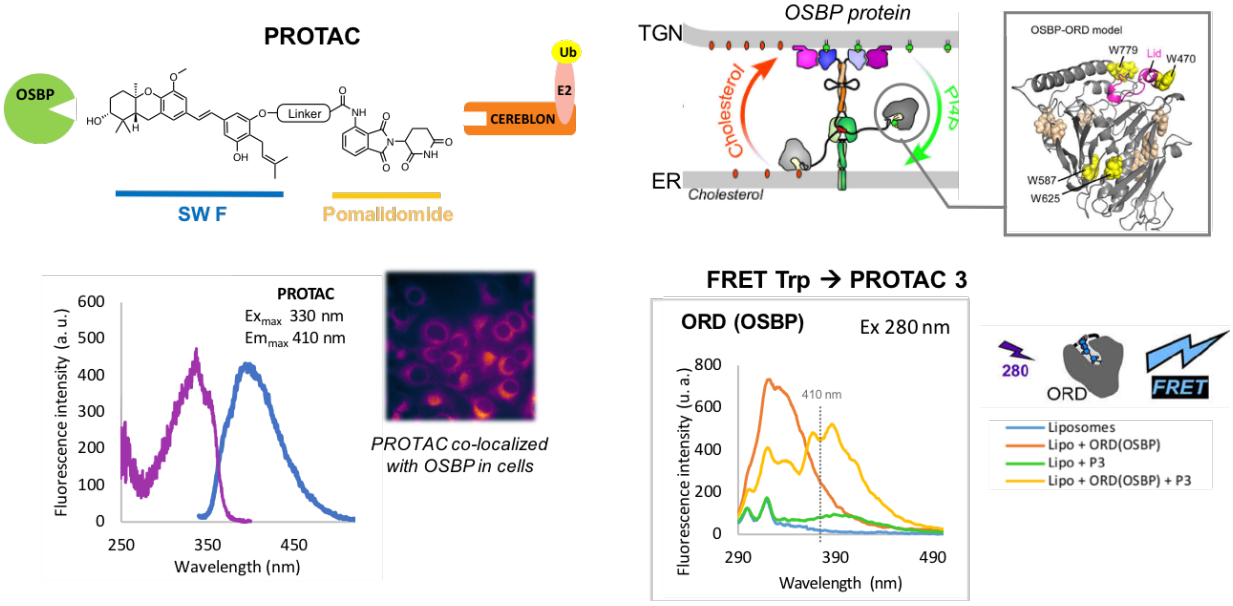
OC05

Schweinfurthins (SW) are a family of natural molecules of great interest for the development of new therapies, due to their strong cytotoxic potential on specific cancer cell lines. Their original mechanism of action involves an intracellular cholesterol transport protein: OSBP (OxySterol Binding Protein).[1] The ICSN Plant Metabolites team has been working for several years to design SW derivatives for therapeutic applications.[2] In order to go further in the development of active molecules, we are currently developing SW-derived PROTACs (PROteolysis-TArgeting Chimeras). These bifunctional molecules are designed to induce the degradation of the target protein by hijacking the ubiquitin-proteasome system of the organism. Widely studied nowadays, this therapeutic strategy became very promising for the treatment of certain cancers.[3] We have thus synthesized a series of PROTACs with a SW-F moiety and a pomalidomide-like ligand connected by linkers of different sizes and types, for targeting OSBP.

We will describe herein the synthesis of these bifunctional molecules but also their cytotoxic activity on different cancer cell lines. The study of the degradation of OSBP induction depending on the nature of the linker will also be presented.



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Copper-free click chemistry as a tool for two-colors dSTORM imaging of peptidoglycan and teichoic acids in *S.pneumoniae*	***OC06***

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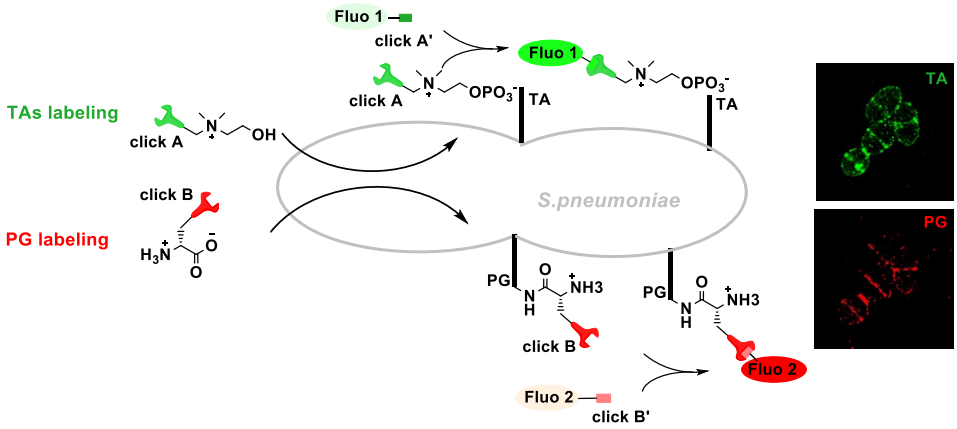
The Gram-positive bacterial cell wall is composed of two main biopolymers, peptidoglycan (PG) and teichoic acids (TAs). Their highly dynamic biosynthesis involves spatiotemporally controlled processes that shape the morphology, elongation and division (septation) of the bacterium. In contrast to rod-shaped bacteria where elongation and septation are clearly dissociated in time and space, in ovoid-shaped bacteria like *Streptococcus pneumoniae*, these events are synchronous and located at midcell in an annular region of nanometric dimensions. A combined approach of metabolic labeling using copper-free click chemistry and high-resolution dSTORM (direct stochastic optical reconstruction microscopy) has recently revealed the specific PG synthesis sites for cell septation and elongation, and their relative dynamics along the cell cycle.[a] Whether TAs are assembled at septation and/or elongation sites, the degree of coordination with PG synthesis, and the molecular mechanisms ensuring such regulation remain unknown. This study has long been limited by the lack of tools to label TAs but we have recently developed probes that are metabolically and selectively incorporated into new TAs.[b,c] We now need to label and observe PG and TAs in two colors in a same cell to detect fine variations in the localization and architecture of their synthesis site(s). Preliminary co-labeling experiments show that the use of copper is a limiting factor, pointing to the need for new pairs of probes and fluorescent dyes whose conjugation does not require catalysis. In this communication, we would like to report the development of chemical approaches using coppe-free click chemistry for two-color labeling of PG and TAs and their study by high resolution dSTORM. The main purpose of this approach is to unravel the biosynthesis of the cell wall which would thus permit to identify new therapeutic targets for the synthesis of new antibiotics in the future.



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Fusicoccin-A derived molecular glues: Synthesis of analogs

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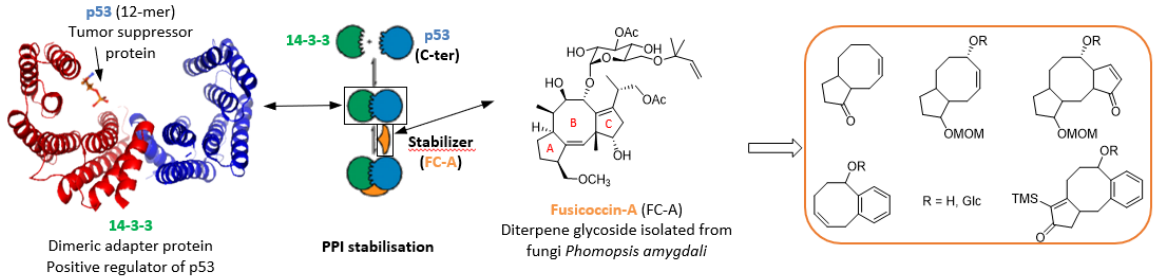
OC07

Protein-protein interactions (PPI) are crucial in living systems as they regulate cellular events (cell cycle, protein transport, …). PPI imply an adaptor protein which positively or negatively regulates an effector protein involved in a biological process. Regulation of PPIs is possible through two different mechanisms. PPI inhibition is well known and constitutes a validated therapeutic approach. However, PPI stabilization is less investigated but opens alternative and highly promising therapeutic horizons.

In this project, we focus on the 14-3-3 adapter protein interacting, among all its partner proteins, with the p53 effector protein.[(a)] The latter is a known tumor suppressor protein which regulates DNA repair and apoptosis. In half of cancer situations, the p53/14-3-3 interaction is prevented, stopping cell cycle regulation and thus allowing cancer cells proliferation.[(b)]

Fusicoccin-A (FC-A), a diterpene glycoside, was found to stabilize the 14-3-3/p53 PPI. [(b, c)] Indeed, FC-A acts as a "molecular glue" and lodges in the valley formed by 14-3-3. However, this natural product displays a complex [5-8-5] tricyclic core structure which is difficult to access either from natural sources or organic synthesis.[(c)] Thus, conception of FC-A simplified analogs represents an attractive strategy to deeply study this PPI stabilization.

The aim of the project consists in the synthesis of the minimal core structure of FC-A that allows PPI stabilization. In this view, bicyclic compounds of type A-B or B-C as well as tricyclic compounds are considered. Original strategies involving a Pauson-Khand reaction or a metathesis - Pauson-Khand reaction sequence have been investigated. The results of this work will be presented here.



Scheme 1: p53 – 14-3-3 PPI stabilization by fusicoccin-A and core structures of analogues

Bibliographic references:

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Photoswitchable azo-Reboxetine Inhibitors for the light-induced control of the human Norepinephrine Transporter

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OC08

Norepinephrine is one of the human bodies' monoamine neurotransmitters, besides dopamine and serotonin. By terminating the norepinephrine related signaling pathway, the human norepinephrine transporter (hNET) plays an important role influencing e.g. human emotions and sleep. Malfunctions of hNET are associated with diseases like depression, anorexia nervosa, cardiovascular diseases and orthostatic intolerance[(a)]. Therefore, hNET is an interesting target for the design of novel drugs addressing these illnesses like antidepressants.
Our approach towards control and investigation of hNET utilizes methods and principles of photopharmacology. Photopharmacology enables light-induced, highly precise temporal and spatial control of ion channels and enzymes by reversibly switching ligands between their *E*- and *Z*-configurations *via* irradiation with light of different wavelengths. However, photoswitchable ligands for transporters and pumps are still quite rare and underdeveloped[(b)]. By the introduction of a photoswitchable azo-handle into the known NET-selective substrate Reboxetine, we obtained novel photoswitchable inhibitors for hNET and present their synthesis and *in vitro* behavior.

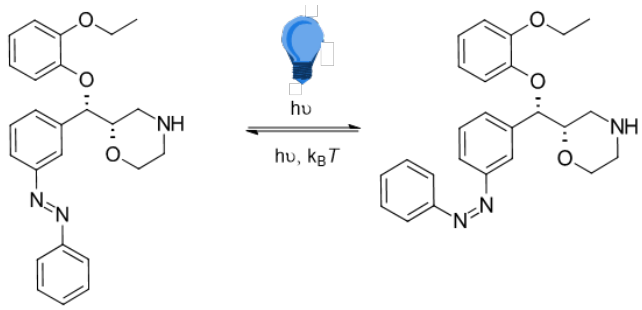

Fig. 1: Photoswitchable, modified Reboxetine as its *E*- and *Z*-isomer

A small library of eight photoswitchable hNET ligands showing different biological activity between their *E*- and *Z*-isomers has been synthesized and biologically tested. Our compounds allow reversible, light-controlled inhibition of hNET at several inhibitory concentrations.

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[(b)] K. Hüll, J. Morstein, D. Trauner, *Chem Rev* **2018**, *118*, 10710-10747.

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Design, Synthesis and Anticancer evaluation of novel VEGFR2/Microtubule dual inhibitors for the treatment of Metastatic Cancers

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OC09

The spread of cells from primary cancer reaching distal organs results in metastatic cancer formation, the deadliest tumor form. Neo-angiogenesis is a key process for tumor growth and metastatic cells migration. VEGFR is a crucial receptor for the development of novel blood vessels, therefore VEGFR inhibitors are frequently used to avoid or treat metastatic cancer. For instance, Axitinib, a potent and highly selective VEGFRI, was approved for the treatment of metastatic renal cell cancer.[(a)] On the other hand, microtubules control cellular vital functions, including cell division and migratory processes implied in metastasis development. Hence, microtubule-targeting agents (MTAs) represent an appealing target. Pursuing a multitarget drug discovery approach, we started from Axitinib scaffold and some MTAs that we recently published,[(b)] to rationally design and synthesize VEGFR/microtubule dual inhibitors. The main chemical manipulations carried out were i) the selection of benzotriazole as main scaffold; ii) the use of the acrylonitrile chain and iii) the substitution of the sulfur bridge with an amide or reverse-amide moiety (Figure 1). Moreover, several polar groups were inserted on the aromatic portion. The designed compounds were previously screening via *in silico* analysis to select the most promising derivatives which were then synthetized. The obtained compounds were subjected to the NCI antiproliferative screening against 60 cancer cell lines. IC_{50} calculation and cell cycle analysis were carried out on a panel of selected derivatives. Some derivatives showed a remarkable activity in different cancer settings, including melanoma and renal ones, encouraging the further investigations into the mechanism of action.

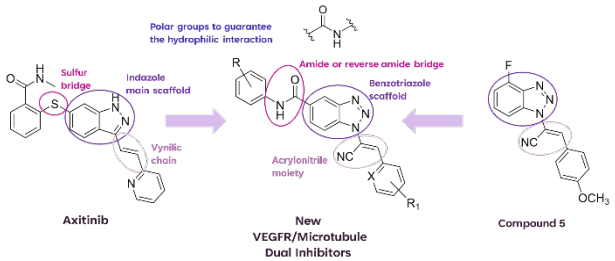

Figure 1. Rationale design of the dual VEGFR/tubulin modulators.

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Binding pose prediction of protease inhibitors using Supervised Molecular Dynamics (SuMD)	***OC10***

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The correct determination of the ligand mode of binding in a biological target binding site is essential to gain insight into the molecular recognition process, understand the nature of the interactions, and drive the molecular design in the drug discovery process. Current in-silico approaches relies mainly on molecular docking that is known to be fast but treats the protein as a rigid body. This creates a significant limitation as several side chains of binding site residues and loop conformation rearrangements are associated with induced-fit binding. To address this limitation, I have been exploring the implementation of supervised molecular dynamics (SuMD) a novel molecular dynamic approach recently developed by Moro et al[(a)], which enables the investigation of the molecular recognition pathway between ligand and receptor. We apply SuMD to Papain-like protease protein (PLpro) for SARS-CoV-2 coronavirus[(b)] as a case study.

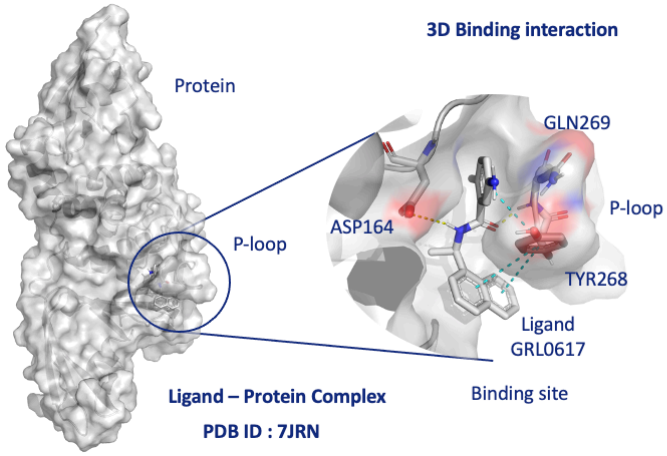

Figure (1) : PDB ID: 7JRN in complex with ligand GRL0617.

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(b) Amin, S. A.; Jha, T. Fight against Novel Coronavirus: A Perspective of Medicinal Chemists. European Journal of Medicinal Chemistry 2020, 201, 112559.

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Novels pleiotropic prodrugs with potential therapeutic interest in Alzheimer's disease	***OC11***

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Alzheimer's disease (AD) is a multifactorial disease which involved severals pathogenic pathways. Thus, to develop news drugs against AD, the Multi-Target Directed Ligands (MTDLs) [a] approach seems promising. In this context, the design of novels MTDLs, carbamoyl prodrugs capable of inhibiting cholinesterases (AChE [b] or BuChE [c]) according to the same mechanism as rivastigmine [d] and then releasing an active metabolite to reach 5-HT_4 receptors [e] is a promising way to treat AD (Figure 1). Several novels compounds were synthesized in benzisoxazole serie, [f] tested and have shown interesting activity, in the nM order, selective on BuChE over AChE and 5-HT_4 receptors. These promising results will be presented for the first time and allow us to investigate the mechanism of inhibition of cholinesterases and the effect of prodrugs on cellular model. This study will generate some first SAR data towards the three targets and will help us to identify the best candidate for future *in vivo* evaluation.

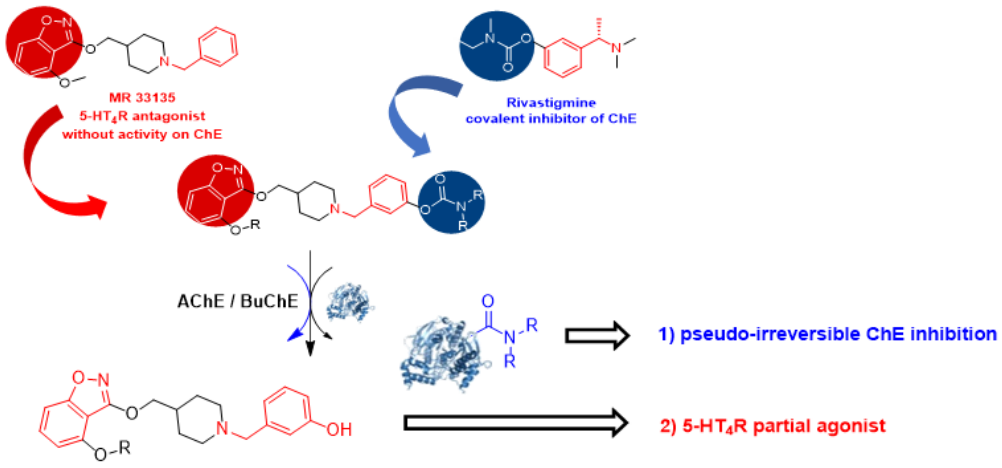

Figure 1: mechanism of action of Rivastigmine and pleiotropic prodrugs

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[b] Eady, N.; *et al.*, *Br J Psychiatry* **2018**, *212* (3), 155–160.
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[f] Lalut, J.; *et al.*, *Sci. Rep* **2020**, *10 (1)*, 3014.

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Discovery of *Pseudomonas aeruginosa* elastase LasB inhibitors by *in situ* click chemistry

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OC12

To combat the spread of multidrug-resistant Gram-negative bacteria, here Pseudomonas aeruginosa, novel innovative anti-infective drugs are needed. Targeting bacterial virulence has thus emerged as a promising strategy, the aim being to disarm bacteria rather than killing them whilst preserving the commensal bacteria [(a)]. The elastase LasB is the most abundant protease secreted by P. aeruginosa and its key virulence factor [(b)]. The extracellular zinc-metalloprotease LasB plays a central role in the virulence process and, therefore facilitates disease progression and the appearance of resistance. Indeed, this enzyme cleaves a broad spectrum of substrates such as tissue components, immune system components, which facilitate host colonization and immune-system evasion, respectively. Moreover, it is also involved in the formation of biofilms, making P. aeruginosa elimination difficult [(c)]. Thus, these characteristics make LasB an attractive target.

The main strategy used to inhibit LasB consists in inhibition of the catalytic activity by targeting the zinc ion through a zinc-binding group (ZBG). Displaying various ZBGs, several inhibitors have been disclosed with modest to excellent potency (micromolar to nanomolar range) [(c), (d)]. However, none of these compounds has reached the market yet, either for selectivity problems or poor druglike properties. With the aim of identifying new chemical scaffolds as inhibitors of LasB, we used a Kinetic Target-Guided Synthesis (KTGS) approach [(e)]. This allowed us to uncover a new chemical class of LasB inhibitors with single-digit nanomolar activities, druglike and excellent selectivity profiles. A rational and tailored assay design enabled extensive biological profiling in vitro, ex vivo and in vivo to guide a successful and efficient multiparameter hit optimization campaign.

Bibliographic references:
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[(e)] D. Bosc *et al*. *J. Med. Chem.* **2020**, 63, 3817−3833

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Modulation of the circadian clock for cancer chemotherapy using new synthetic RNA ligands	***OC13***

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Disruption of the circadian clock is associated with a variety of human pathologies, including cancer, and the expression of several clock genes is perturbed in many tumors[(a)]. The aberrant clock gene expression in tumors likely plays a causal role in the development of cancer and the survival of tumor cells. Numerous observations support the hypothesis that pharmacological modulation of clock-related proteins may be an effective anticancer strategy[(a)]. Recently, Dr. Grimaldi at the Italian Institute of Technology (IIT) reported proof of a close connection between the circadian clock and MAX/MNT transcription networks. Notably, the expression of MNT (tumor suppressor protein) under diverse conditions, such as hypoxia and cancer, appears to be regulated by microRNA-210[(b)]. The laboratory of Dr. Duca at the Institute of Chemistry of Nice (ICN) has experience in the design of multimodal small molecules targeting miRNAs[(c,d)].

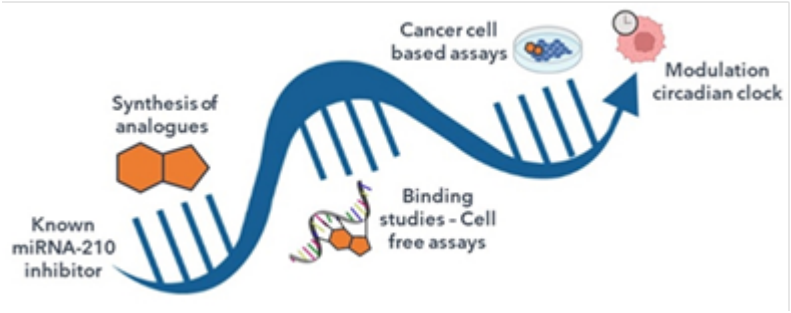

Figure 1 - Schematic representation of our SAR project

The global aim of this project is to identify a novel pharmacological approach that modulates circadian activity through the targeting of the miR-210/MNT axis. To this aim, in collaboration with IIT, we designed and synthesized new compounds targeting the precursors of miR-210 to inhibit its biogenesis and restore physiological expression of MNT. The synthesized compounds, inspired by previously reported inhibitors[(e)] as well as originally designed, have been evaluated for their ability to bind pre-miR-210, block the production of oncogenic miR-210 and induce the expression of MNT in cancer cells thus restoring normal clock genes levels (*Figure 1)*. Some of our compounds showed excellent affinity for the RNA target and an antiproliferative activity against various cancer cells lines without toxicity for healthy cells. The exact molecular mechanism of action is currently under study. The anticancer activity of the miR-210 inhibitors will also be assessed on the most active compounds.
The molecules generated represent a valuable pharmacological tool for studying the role of miR-210 in circadian clock regulation. Moreover, these molecules provide suitable chemical scaffolds for the development of innovative clock modulators for treating circadian-related pathologies.

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[(c)] *ACS Med Chem Lett* **2021**, *12*, 899.
[(d)] *RSC Med Chem* **2022**, *13*, 311.
[(e)] *JACS* **2017**, *139*, 3446

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Effect of Buffer Identity on β-lactoglobulin Amyloid Fibrillization

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OC14

The understanding of amyloid protein aggregates characterized by their well-known cross-β structure and good mechanical properties is of great importance because of their appearance in patients with several untreatable diseases, such as Alzheimer's, Parkinson's, type II diabetes mellitus, and other amyloidosis. Even though amyloid aggregates were discovered several years ago the mechanism of their formation, and their connection to disease is still not fully understood.

The most abundant whey milk protein β-lactoglobulin (18.3 kDa) (BLG) is often used as a model protein to study fibrillization because of its low cost, and good availability. The mechanism of fibril formation by heating BLG solutions in water at low pH and ionic strength is described very thoroughly. Unfortunately, by preparing BLG fibrils by heating in water there will always be a question of pH stability, especially if we start adding excipients. Adding excipients is key in finding possible molecular species that could prevent or disaggregate cytotoxic amyloid species.

In addition to process parameters different added excipients have a unique way of influencing every step in protein aggregation process from denaturation, hydrolysis, disulphide-scrambling, self-association to solutions colloidal stability. The most common excipients that we can find in almost all protein formulations are buffers. The concentration of [H+] ions is a major factor in fibrillization not just because its ability to define molecular charge, but because it also affects the hydrolysis kinetics and protonation state of free sulfhydryl groups.

Effect of buffer chemical identity is often overlooked. In a recent study we showed that by incubating BLG in pH 2 glycine solution the fibrillization path changes from peptide to spheroid oligomer fibril self-assembly which to our knowledge has not yet been detected in BLG aggregation process. These type of fibrillar aggregates are gaining more and more attention because of their pore-like structure and possible cytotoxic mechanism by forming of pernicious ion-channels. We investigated the BLG self-assembly process in different buffers and proposed possible fibrillization mechanisms.

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Synthesis, Antibacterial Activities, and Synergistic Effects of Novel Juglone and Naphthazarin Derivatives Against Clinical Methicillin-Resistant Staphylococcus aureus Strains.	***OC15***
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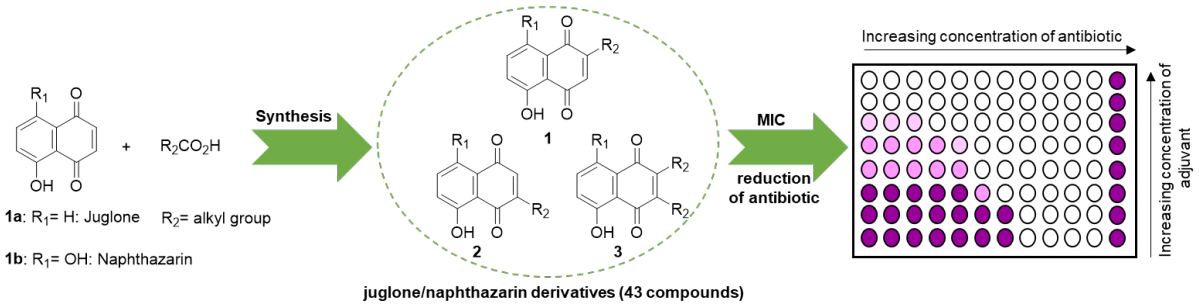
New antibiotics are necessary to treat microbial pathogens, especially ESKAPE pathogens that are becoming increasingly resistant to available treatment [a]. Despite the medical need, the number of newly approved drugs continues to decline [b]. 1,4-Naphthoquinones are known to exhibit an interesting antibacterial activity for instance juglone and naphthazarin, and are a promising new class of compound that can be used to treat bacterial infections. A novel series of 43 juglone/naphthazarin derivatives were synthesized using Minisci-type direct C–H alkylation and evaluated for their antibacterial properties against various clinical and reference Gram-positive MSSA, clinical Gram-positive MRSA [c]. Different compounds of the synthesized series showed promising activity against clinical and reference MSSA (MIC: 1–8 µg/ml) and good efficacy against clinical MRSA (MIC: 2–8 µg/ml) strains. The synergistic effects of active compounds were evaluated with reference antibiotics (vancomycin and cloxacillin), and it was found that the antibiotic combination with those active compounds efficiently enhanced the antimicrobial activity and consequently the MIC values of reference antibiotics were lowered up to 1/16th of the original MIC. These synthesized compounds did not present hemolytic activity on sheep red blood cells. In addition to the *in-silico* prediction of ADME profile parameter which is promising and encouraging for further development.



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Synthesis of Plasmalogens: Iconic Phospholipids with an Alzheimers Connection

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OC16

Plasmalogens are a subclass of phospholipids that mainly populate cell membranes, with ethanolamine plasmalogens (PEs) being the predominant phospholipid in the brain. Over the past 20 years an increasing number of studies have reported a link between plasmalogen deficiency and Alzheimer's Disease (AD).[1] Furthermore, these findings were not observed at the primary site of neurodegeneration in Parkinson's disease or Huntington's disease. This suggests it is specific to AD and may provide a route for targeted and selective AD therapies or novel diagnostic techniques. Despite the growing interest in plasmalogens, no reliable method to synthesise these natural products at scale has been published. This restricts the study of plasmalogens in AD pathology and any therapeutic benefits that can be derived. Plasmalogens have a glycerol backbone functionalised with a *Z*-vinyl ether chain, acyl polyunsaturated chain and a phosphate group (Figure 1). The vinyl ether is labile under acidic and oxidative conditions. The acyl group is susceptible to hydrolysis, especially under basic conditions. Acyl groups can also migrate in glycerolipid precursors bearing a free hydroxyl group within a glycerol derivative. Plasmalogen synthesis must overcome these synthetic challenges. Furthermore, stereoselective synthesis of the *Z*-vinyl ether, and selective functionality of the triol glycerol, must be achieved.

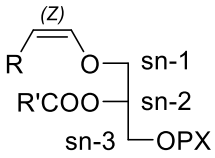

Figure 1 Fischer projection of a plasmalogen. R and R' = saturated or unsaturated chain, P = phosphate, X = choline or ethanolamine.

Herein details the total synthesis of a natural plasmalogen. Synthesis of the *Z*-vinyl ether is achieved by novel modification of the Peterson olefination reaction (Figure 2). Lewis acid catalysed ring opening of a silyl epoxide with a glycerol moiety affords a β-hydroxy silane intermediate. Upon treatment with base the intermediate undergoes a *syn*-elimination to give the desired *Z*-vinyl ether. Additionally, a novel benzyl-type protecting group (PG) is used to selectively mask glycerol hydroxyl functionality. It is designed to be oxidatively cleavable in the presence of unsaturated bonds, which current benzyl PGs are incapable of. These two methodology developments allow for scaleable total syntheses of natural plasmalogens and their analogues.

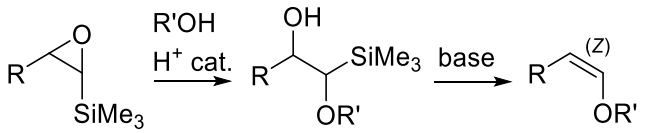

Figure 2 Modification of the Peterson olefination to stereoselectively synthesise *Z*-vinyl ethers.

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FOLATE CONJUGATES AS NOVEL ANTICANCER AGENTS TARGETING AROMATASE

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OC17

Cancer is a group of more than 200 diseases (1) that causes the largest number of deaths in the world.Among them, Hormone-dependent cancers are the most common. Traditional anticancer drug designbased on small molecules continues to be a powerful strategy for the development of novel chemotherapeutics. However, these therapies are facing major problems, such as toxicity mainly caused by non-specific drug delivery. To avoid that, different novel strategies for the development of more effective cancer therapies are being widely investigated (2).

One such strategy is the development of conjugates with tumor-specific ligands, such as folic acid (FA).FA is an important cofactor in one-carbon metabolism and is involved in the biosynthesis of essential components of nucleic acids (3). It is a water-soluble vitamin used by all living cells for their biosynthesis processes (4). Therefore, mammalian cells are not able to synthesize FA and the requirement for folate must be completely supplied by the diet and internalized by the folate receptor(FR) by endocytosis (5). The main folic receptor is FR-a, which is overexpressed in the malignant cells of many types of cancer (6).

Since aromatase plays a crucial role in the biosynthesis of active hormones (7), effective inhibition of this enzyme by selective and non-toxic agents may be beneficial for the development of new methodsof treatment of many types of hormone-dependent cancers. Moreover, considering that the expression of FR increases with tumour progression, the synthesis of folic conjugates (FCs) can providecompounds with higher selectivity toward cancer cells, and make them more effective and significantly less toxic. The greater accumulation of the drug in the tumour tissue also makes possible to reduce thedose required to obtain the desired therapeutic effect, thus limiting potential adverse effects**.**

In this line, we have synthesized a new FC (**Figure 1**) consisting of the aromatase inhibitor - **Aminoglutethimide** that was connected to **FA** via a cleavable linker containing a labile disulfide bond.

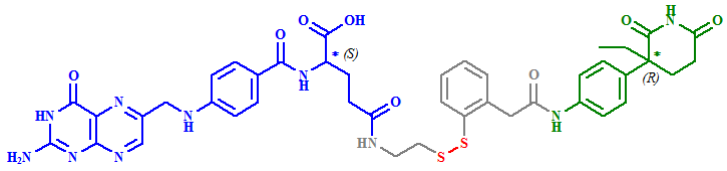

Figure 1. Structure of FC of aminoglutethimide.

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LEAD OPTIMIZATION OF INFLUENZA POLYMERASE PA-PB1 SUBUNITS INTERACTION DISTRUPTORS

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OC18

In the search for next-generation anti-Influenza virus (Flu) agents, the viral RNA-dependent RNA polymerase (RdRP) provides an attractive target given its functional essentiality for viral replication and involvement in virus pathogenicity. RdRP could be ideal for the development of new antivirals, since it is highly conserved among Flu strains while no homologue has been found in mammalian cells. RdRP is a heterotrimeric complex composed by PB1, PB2, and PA subunits which establish, during the infection, crucial and specific Protein-Protein Interactions (PPIs) between themselves and numerous host factors, which could be exploited as drug-targets for the discovery of alternative anti-Flu drugs. (a,b) The main potential advantages of targeting PPIs are the achievement a specific and broad-spectrum of anti-flu activity, as well as a high barrier to drug-resistance, thus overcoming the main limitations that characterize the currently available treatment. In this work, I reported the optimization of cycloheptathiophene-3-carboxamide (cHTC) compounds, previously identified by our research group. cHTC compounds are endowed with the ability to inhibit RdRP functions by hampering the PA–PB1 heterodimerization, and potently inhibit Flu growth. The most active cHTCs also showed to possess a higher drug resistance barrier than that of oseltamivir and other anti-influenza drugs. (c-e) Starting from the recently identified compound, (d,e) two set of analogues were designed and synthesised by alternately exploring the substituent at the C-2 and C-3 position of the cHTC nucleus. Moreover, the best moieties identified were joined in a third set of compounds, some of which showed very potent anti-Flu activity in the nanomolar range. Finally, for the best compounds, the antiviral profile, mechanism of action, and ADME profile were in depth studied to determine the value of these new promising compounds.

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Development of new quinolines as FabZ inhibitors to struggle antimicrobial resistance.	***OC19***

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Up to now, with almost 1.3 million directly accountable deaths and 5 million associated deaths worldwide in 2019, antimicrobial (ATM) resistance is one of the biggest public health issues[(a),(b)]. Multi-resistance is particularly worrying in Gram-negative bacteria isolated of nosocomial infections such as *Pseudomonas aeruginosa*, *Escherichia coli* or *Klebsiella pneumoniae*. Furthermore, the decreasing effectiveness of antimalarial treatments also rises for concern, particularly because of multiplication of multidrug-resistant *Plasmodium falciparum* strains. Indeed, this species of *Plasmodium* is accountable for most of the 627,000 deaths reported in 2020 globally[(bc)].

Consequently, we are facing an urgent need of new ATM drugs with original and selective mode of action. Targeting fatty acid biosynthesis is a promising strategy to develop these treatments. Indeed, fatty acids are the main constituents of bacterial membranes and metabolic intermediates. Their biosynthesis involves fatty acid synthase systems which are divided into two distinct molecular forms called types I and II (FAS-I and FAS-II). FAS-I carries out fatty acid biosynthesis while FAS-II is exclusively found in germs. FAS-II enzymes are attractive targets to develop antimicrobials because (i) fatty acids are essential to maintain vital integrity of the bacterial membrane, (ii) the amino acid sequences of FAS-II enzymes active site are well conserved in the microbial pathogens, (iii) FAS-II does not exist in humans and (iv) crystal structures of FAS-II enzymes are available in the Protein Data Bank (PDB), allowing rational design of inhibitors. Furthermore, FAS-II enzymes are validated targets since two commercial products inhibit them: triclosan[(d)] and isoniazid[(e)]. In this work, we focus on a critical FAS-II enzyme, FabZ, to design new ATMs with limited side effects and minimal chances of cross resistance with existing drugs.

In the PDB, several FabZ 3D structures from different organisms have been reported. Among the few known FabZ inhibitors, the NAS91 family, with a quinoline core, inhibits *Pf*FabZ with IC_{50} in the micromolar range. Additionally, co-crystal NAS91 family-*Pf*FabZ complex structures are described in the PDB. Based on these data, we carried out FabZ-based drug design study to develop novel quinoline structures. Herein, the *in silico* study, synthesis of new quinolines and biological results will be exposed.

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Optimization of a pyridylpiperazine series as a novel class of efflux pump inhibitors in *E. coli* to fight antimicrobial resistance

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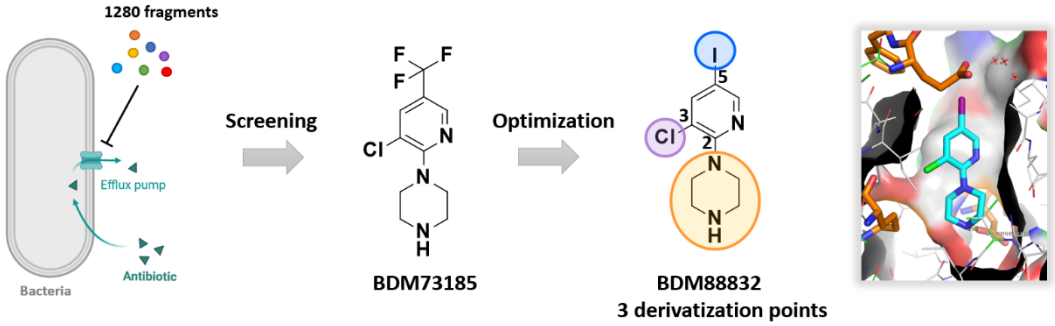
OC20

Antimicrobial resistance (AMR) has become a major global health threat leading to an estimated 4.95 million deaths in 2019.[(a)] One of the most worrying resistance mechanisms in Enterobacteriaceae and Gram-negative bacteria in general is the (over)expression of multidrug efflux transporters. These pumps are able to extrude several classes of antibiotics from the bacteria, decreasing their intrabacterial concentration and eventually rendering them ineffective.[(b)]

AcrAB-TolC is an RND multidrug efflux pump found in Enterobacterales such as *Escherichia coli* and *Klebsiella pneumoniae*. To identify inhibitors of this efflux pump, a 1280 fragment library was screened on *E. coli* in combination with a model antibiotic substrate of this pump and this led to the selection of a hit compound (BDM73185) able to potentiate antibiotic activity through direct inhibition of AcrB.[(c)]

In order to establish structure-activity relationships, the trifluoromethyl group was first replaced by an iodine atom. This compound was co-crystallized with AcrB and was shown to bind a unique site on the transmembrane domain of AcrB. First, the piperazine was replaced with various bioisosteres. Then, the replacement of the chlorine atom in position 3 of the pyridine ring was explored. Finally, diversity was introduced in position 5 of the pyridine ring, including esters, amides, ethers, and several 5-membered heterocycles. The synthesis of the compounds and the structure-activity relationships, in accordance with the co-crystallography, will be presented.



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Tumor activated therapy for the treatment of solid cancers.

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OC21

The discovery of new anticancer drugs able to kill tumor cells while sparing healthy tissues remains one of the major challenges of research in cancer chemotherapy. To tackle the lack of selectivity of standard treatments, novel strategies based on the use of drug delivery systems programmed for releasing potent anticancer agents exclusively in tumors have arisen recently. The validity of this therapeutic approach has been confirmed in human with the approval of twelve antibody-drug conjugates (ADCs) in the last ten years. In parallel to antibodies, albumin also emerged as a versatile carrier for the delivery of anticancer drugs. Extensive studies in this field led to the approval of Abraxane®, an albumin paclitaxel nanoparticle that is employed nowadays for various applications in oncology. Beside albumin-based galenic formulations, we designed enzyme-responsive albumin-binding prodrugs that target the tumor microenvironment in the course of a Tumor Activated Therapy (TAT).[a-f] Within this framework, our lead compound **SKY01** developed by SEEKYO, exhibits an outstanding therapeutic efficacy for the treatment of numerous tumors implanted in mice including pancreatic and triple-negative breast cancers (Fig. 1). Furthermore, **SKY01** demonstrates superior efficacy than the combination Abraxane®/gemcitabine currently used for the therapy of patients with pancreatic adenocarcinoma. The full study of **SKY01** will be presented during the oral presentation.

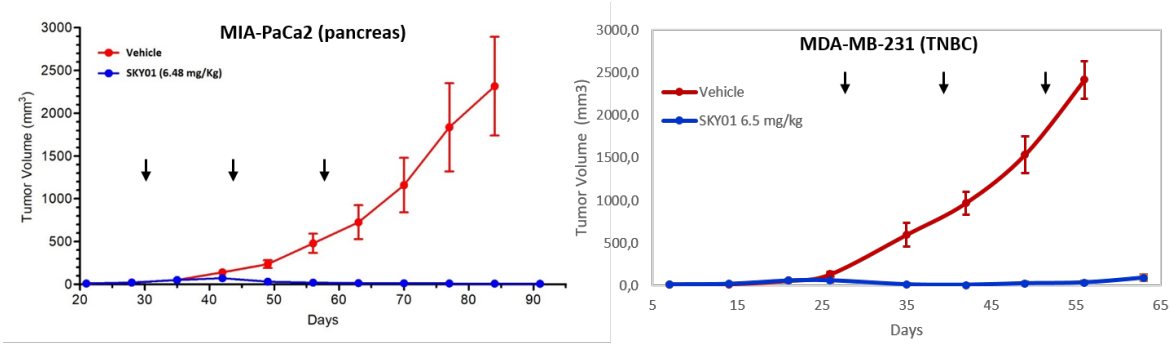

Fig. 1. *Tumor growth over time under therapy with vehicle and **SKY01** (6.5 mg/kg).*

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Organic solvent-free nanoparticles preparation based on therapeutic deep eutectic solvents for cancer treatment	***OC22***

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The interest of using nanomedicine during the last years has been growing in different medical applications, including diagnosis, imaging tools, vaccine development, and drug delivery. Nanoparticles, *i.e.*, submicron particles, have been developed to treat many diseases but the most prominent disease focus has been in cancer[(a)]. However, the presence of organic solvents in the process of nanoparticles preparation can have a significant impact on production cost, but also on human health. Over the past decades, therapeutic deep eutectic solvents (THEDESs) were deeply studied as potential alternatives to organic solvents due to their potential low toxicity, low cost, high adjustability, biodegradability, and easy preparation[(b)]. Therefore, previous studies have demonstrated the interest of using these eutectic solvents for various pharmaceutical applications[(c)]. The future of THEDESs is quite challenging, notably in the nanomedicine field, but the potential physicochemical and biological characteristics of THEDESs toward human health are essentially important to be explored prior to their usage in the medical sectors. In this work, we prepared THEDESs comprising an active pharmaceutical ingredient (API) with potent anticancer activity by using two different bottom-up approaches: eutectic solvent manual injection[(d)] and a microfluidic tool[(e)]. Original nanoparticles based on the obtained THEDESs and stabilized by pH-sensitive and biocompatible copolymers were prepared. The physicochemical properties of these nanoparticles were determined by using different analytical techniques, namely, dynamic light scattering (DLS), Transmission electron microscope (TEM), and differential scanning calorimetry (DSC). Finally, *in vitro* tests were performed in order to evaluate and compare the therapeutic activity of the most promising formulations.

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Bivalent ligands targeting Sigma Receptors and TSPO: new tools for studying oncogenic pathways.	***OC23***

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According to the World Health Organization (WHO), cancer is one of the main causes of death worldwide, accounting for almost 10 million deaths in 2020. The identification and validation of novel therapeutic targets and oncogenic pathways may lead to the development new effective anticancer agents. Our aim is to develop multitarget-directed ligands (MTDLs) for targeting Sigma Receptors (SRs) and the 18kDa Translocator Protein (TSPO). These proteins are overexpressed in cancer and represent potential therapeutic and/or diagnostic targets[1,2]. Such MTDLs will serve as pharmacological tools to understand correlations between the pathways regulated by these proteins and to evaluate the therapeutic potential of their simultaneous modulation. We designed a series of compounds based on the chemical structures of RC-106 and PK11195. The first is our in-house developed pan-sigma modulator (i.e. it binds both SRs subtypes, Sigma1 and Sigma2) with cytotoxic activity on prostate, glioblastoma and pancreas cancer cell lines[3]. The second is a clinically validated TSPO ligand employed in PET imaging to highlight neuroinflammation and cancer[4]. These scaffolds were properly derivatized and tethered by different linkers to obtain a series of bivalent ligands, as schematized in Figure1. After a preliminary in silico evaluation to support the design, the desired compounds were synthetized and isolated in sufficient amount and purity for a preliminary biological evaluation to assess their cytotoxic activity in vitro.

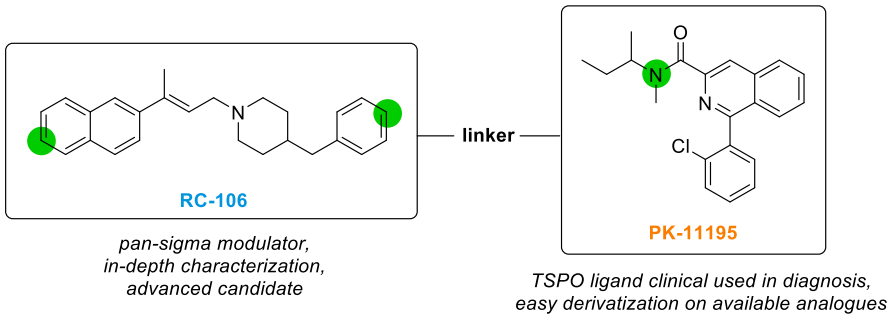

Figure 1. General structure of bivalent SRs-TSPO ligands and model compounds: RC-106 for the SRs-binding moiety and PK-11195 for the TSPO-binding moiety. Green circles represent the linker attachment points.

Bibliographic references:

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(2) Xie, Q. et al. *Photodiagnosis Photodyn Ther* **2021**, *34*, 102209.
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Modified fluoroquinolones as antimicrobial compounds targeting *Chlamydia trachomatis*.	
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Chlamydia trachomatis causes the most common sexually transmitted bacterial infection in the world and trachoma, an eye infection. Untreated infections can lead to sequelae such as infertility and ectopic pregnancy in women and blindness. In a previous study, we enhanced the antichlamydial activity of the fluoroquinolone ciprofloxacin.[(a)] We pursued this pharmacomodulation and obtained nanomolar active molecules (EC_{50}) against this pathogen (Figure 1).[(b)] This gain in activity prompted us to evaluate the antibacterial activity of this family of compounds against pathogenic bacteria from the ESKAPE group. The results show that the novel molecules have selectively improved activity against *C. trachomatis* and demonstrate how the antichlamydial effect of fluoroquinolones can be enhanced.

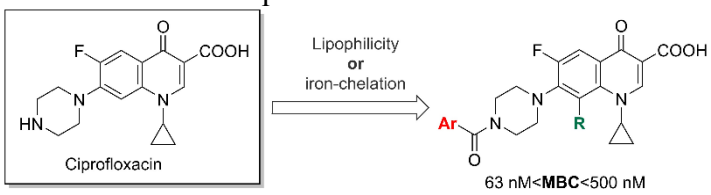

Figure 2: structure and activity range of modified fluoroquinolones.

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Tryptophan 2,3-dioxygenase (TDO) : the new promising target of ^{18}F PET tracers as markers of neuroinflammation

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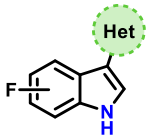
OC25

In the past decades, most research has been focused on the development of molecular probes targeting the central nervous system (CNS) and more particularly the neuroinflammation. Neuroinflammation is the main and early physiological process implicated in neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). According to the 2016 World Health Organisation (WHO) report, the number of affected people could triple by 2050 as a result of population ageing.[a] Consequently, this proves the urge about the development of new tools permitting to visualise the progression of neuroinflammation in neurodegenerative disorders.

Currently, several targets have been listed to be involved in the neuroinflammation phenomenon and have been the centre of attention of clinicians. Lately, tryptophan 2,3-dioxygenase (TDO) has been discovered as a new interesting target taking place in the kynurenine pathway. This enzyme catalyses the first and limiting step tryptophan's conversion into kynurenine which leads to the secretion of neurotoxic species.

To date only two ^{18}F PET tracers could be potential candidates on TDO toward PET imaging application but remain untested on humans.[b,c] However, no ^{18}F radioligands have been placed on the market yet. Consequently, the search of new ^{18}F radiotracers remains essential.

Thanks to literature results our team explored structure-activity relationships through the synthesis of references and analogues and their biological evaluation. Our team is currently providing novel fluorinated indoles and analogues with optimised synthetic routes. Among the 25 tested molecules, one of them have shown promising inhibition effects with high activity and selectivity for TDO toward the Indoleamine 2,3-dioxygenase. The preliminary radiosynthesis attempts starting from a pinacol borane precursor allowed us to prepare the desired radiolabelled tracer in 60 min with a satisfying molar activity but low radiochemical yield (6 %). Some optimisation of the radiosynthesis conditions are currently under review for a forthcoming automated process.



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FLASH POSTER

Machine learning for the prediction of AmpC β-lactamase inhibition to design new antimicrobial agents.	FP01

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Abstract:
Antimicrobial resistance is a major problem that has been growing steadily in recent years, causing millions of deaths[a]. The emergence of multi-drug resistance (MDR) is particularly found among Entero-bacteriaceae such as Escherichia coli (E. coli). E.coli causes serious infections and have multiple resistance mechanisms, the most common being extended-spectrum β-lactamase (ESBL) and AmpC β-lactamase production[b,c]. One of the main mechanisms underlying resistance to β-lactam antibiotics are the AmpC β-lactamases[d]. In this study, we employ in silico approaches to identify new inhibitors of AmpC β-lactamase. First, we collected 384223 compounds experimentally tested on E.coli AmpC. The curation of these data has led to 891 inhibitors and 81720 non-inhibitors of AmpC β-lactamase. We used these compounds to develop new classification machine learning (ML) models to ptredict putative inhibitors of this enzyme. Then, we used generative adversarial networks (GAN) to develop generative models in order to design new molecules capable to inhibit AmpC β-lactamase.

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Design, synthesis and biological evaluation of Membrane Type-5 Matrix Metalloproteinase (MT5-MMP) inhibitors, potential therapeutic interest in Alzheimer's Disease.

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FP02

Alzheimer's Disease (AD) is the most common form of senile dementia in the world and is a main socio-economic problem in health care. The appearance and progression of this neurodegenerative disease are associated with the aggregation of the β-amyloid peptide (Aβ). A therapeutic strategy against AD could consist in the development of molecules able to interfere with specific steps of Aβ aggregation. However, AD is a multifactorial disease and several other targets are implied in its pathogenesis. One of these targets, recently discovered, is MT5-MMP[a], a metallo-enzyme which has two main deleterious activities in brain. MT5-MMP plays a proamyloidogenic role and promotes the formation of neurotoxic peptides (Aβ, CTFβ). Further MT5-MMP exerts also a η-secretase activity and cleaves APP resulting in a newly discovered neurotoxic fragment named Aη-α. In consequence, the inhibition of MT5-MMP could be another therapeutic strategy against AD. With the aim to confirm this new therapeutical approach, this beginning work is to develop strong and selective inhibitors.

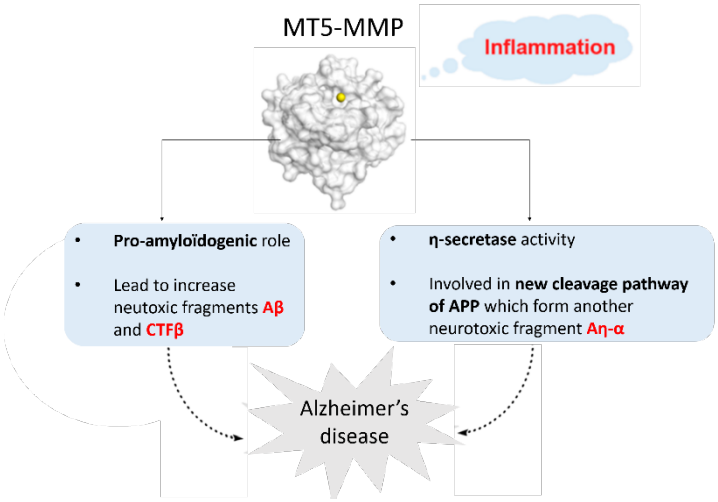

Figure : Presentation of MT5-MMP's activities and APP processing[b]

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New allosteric modulators of FGF/FGFR	
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The discovery in the late 90's of the key role of the kinase-regulated biochemistry pathway in the genesis, sustainment and proliferation of cancer represented a breakthrough for novel effective and selective anticancer therapeutic strategies. Among the plethora of protein kinases, fibroblast growth factor receptors (FGFR) emerged for its implication in angiogenesis-driven diseases. Nowadays, targeting the FGF/FGFR system has been addressed through the development of monoclonal antibodies (i.e., Bemarituzumab), tyrosine kinase inhibitors (TKIs) and FGFs traps (i.e., FP-1039). Our research group started a medicinal chemistry program aimed at the identification of potential small molecules able to bind at the FGF/FGFR interface, thus preventing the interaction between FGF and FGFR and the consequently activation of the signal pathway.
Starting from our previous discovery such as a non-peptidic small molecules **sm27**[(a)] as a promising ligand of FGF2 heparin-binding site and rosmarinic acid and resveratrol[(b)] as suitable natural compounds able to interfere with FGFR signalling, new hits could be identified. Particularly, our aim is to select new compounds potentially able to destabilize the FGFR/FGF complex, by engaging at the same time both the extracellularly heparin-binding site of FGF2 and/or FGFR site for natural ligands.
In this communication, we report on the identification of novel ligands of FGFR. Firstly, a virtual screening of an in-house library of unique drug-like small molecules and secondary metabolites was performed. From such a study, **RBA4** emerged as a potential good ligand. Subsequent STD-NMR studies confirmed its ability to bind FGFR.

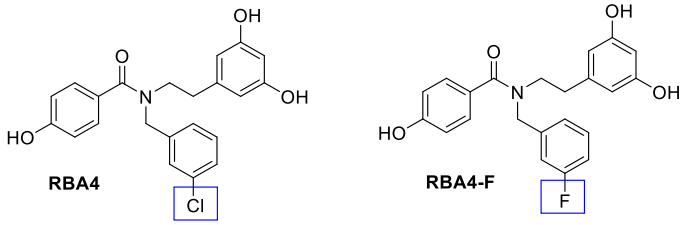

Figure 1. Structure of **RBA4** and its fluorine analogue

The anticancer properties of **RBA4** have been investigated towards a panel of cancer cell lines. Results so far obtained confirmed **RBA4** as starting point for the development of novel antitumor agents.
To guide the design of novel compounds, and explore the chemical space around **RBA4**, we adopted a biophysical approach. To this aim, **RBA4-F** was ad hoc prepared. The combination of different NMR techniques with molecular modeling studies allowed to identify the structural features essential for the interaction with the target.

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[(a)]Colombo G. et al *Journal of Biological Chemistry* **2010**, 285, 12.
[(b)] Pagano K. et al *International Journal of Molecular Sciences* **2022**, 23, 10860.

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Characteristics and comparative severity of respiratory response to toxic doses of fentanyl, carfentanil, morphine and U-47700 in rats.

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FP04

Background: Fentanyl is a synthetic potent opioid that exposes users to serious side-effects including misuse, abuse and respiratory depression that may lead to death (a). It has several analogs, such as carfentanil, which is 10,000 times more potent than morphine. Deaths involving synthetic opioids (primarily fentanyl) represented more than 60% of overdose deaths reported in 2020 (b). This comes along with the growing availability of related compounds classified as novel psychoactive substances (NPS), such as U-47700, which are sold on the internet as recreational drugs (c).

Objectives : To characterize in rats the effects of four opioids on arterial blood gases and plethysmography after IV administration at 50% of their LD(50) in order to identify opioid molecule-specific patterns and classify response severity.

Methods: Sprague-Dawley rats were randomized into five groups to receive solvent (control group), morphine (23 mg/kg IV), Fentanyl (1.5 mg/Kg mg/kg IV), Carfentanil (1.7 mg/Kg mg/kg IV), or U-47700 (1.5 mg/Kg IV). Sedation depth, temperature, whole-body plethysmography parameters and arterial blood gas were measured.

Results: Carfentanil, fentanyl, and U-47700 administration immediately resulted in coma, hypothermia and muscular rigidity associated with Straub tail. Respiratory depression (hypoxemia + hypercapnia) was observed after carfentanil and fentanyl administration with a significant increase in inspiratory and expiratory time. Minute volume significantly decreased with carfentanil and U-47700. Acidosis was observed with morphine, fentanyl, and carfentanyl administration, with a significant increase in lactatemia with all three opioids.

Conclusions: Neurorespiratory toxicity of fentanyl analogs is more marked than morphine with a different impact on respiratory and metabolic parameters. In times of opioid abuse, further investigations must be considered for NPS and fentanyl analogs.

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New 2-heteroaryl-4-aminoquinolines with promising pseudomonal anti-virulence activities

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FP05

The increase of multi-drug resistance in *Pseudomonas aeruginosa* is becoming a critical threat for global public health.[a] In response to the urge of finding new treatments, an anti-virulence strategy has emerged. The objective is to restore the efficacy of conventional antibiotics *via* their combination with novel agents able to quench virulence pathways without inhibiting bacterial growth. This approach circumvents the selection pressure over sensitive strains which is usually mediated by conventional antibiotics.[b]

Pseudomonal pathogenicity is closely related to Quorum Sensing (QS), the bacterial communication network that coordinates gene expression in response to population density. In *P. aeruginosa*, the specific QS system *pqs* is responsible for the production of virulence factors such as pyocyanin. It also plays a significant role in the formation of biofilms that constitute protective barriers against the immune system and antibiotics. The transcription factor PqsR regulates in this circuit the activation of virulence-related genes *via* recognition of its auto-inducer PQS (Pseudomonas Quinolone Signal). Therefore, PqsR appears as a specific choice target for the development of anti-virulence agents to combat *P. aeruginosa*.

In the literature, several bi-aromatic PqsR inhibitors have been described.[c] Meanwhile, our team recently designed a series of 2-heteroaryl-4-quinolones and identified a hit compound that displays interesting anti-biofilm and anti-pyocyanin properties. By structural analogy, we have developed a novel family of 2-heteroaryl-4-aminoquinolines as PqsR inhibitors with promising pseudomonal anti-virulence activities. The synthesis as well as the physicochemical and biological evaluation of those new hybrids will be described in the poster.

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(a) *The Lancet* 2022, 399, 629-655
(b) Duplantier, M.; Lohou, E.; Sonnet, P. *Pharmaceuticals* 2021, *14*, 1262
(c) Starkey, M. *et al. PLoS Patholog*. 2014, *10*, e1004321

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Design and synthesis of novel allosteric modulators for the prostaglandin EP2 GPCR

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FP06

The prostagladin EP2 receptor (EP2) is a widely expressed G protein-coupled receptor activated endogenously by prostaglandin E2 (PGE2), which contributes to the development of chronic inflammation in cancer and has roles in diseases such as Parkinson's, endometriosis, arthritis, intercranial aneurysms, glioblastoma and epilepticus (Figure 1B). [1, 2] EP2 antagonism is therefore considered a possible therapeutic approach to treat these diseases. Previously, numerous orthosteric antagonists (i.e. those that bind to the PGE2 binding site) have been synthesised.[1, 3] In 2020, "**Compound 1**" (Figure 1A) was reported as the first allosteric EP2 antagonist that demonstrates a reversible, agonist dependent mode of action.

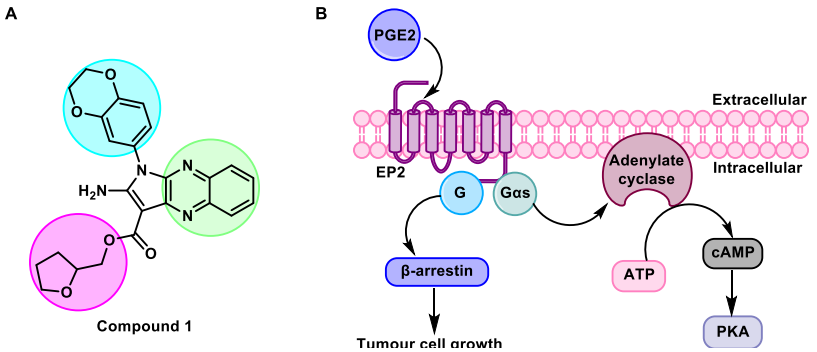

Figure 1. ***A.*** *Structure of "**Compound 1**" highlighting three regions of interest for structural modification in blue, pink and green.* ***B.*** *PGE2 binds and activates EP2, $G_{\alpha s}$ -mediated induction of adenylate cyclase to increase cytoplasmic cAMP levels. Downstream events are then mediated through protein kinase A. EP2 activation also induces β-arrestin which is known to promote tumor cell growth and migration.[1, 2]*

As part of this communication we will report, for the first time, the synthetic route to "**Compound 1**"; as well as our exploration of an expanded structure-activity-relationship dataset focusing on modifications at the tetrahydrofuran (pink), quinoxaline (green) and dioxane (blue- where most structural changes occurred in the literature) moieties. Initial work has identified a key intermediate in the synthesis of "**Compound 1**" having a similar antagonistic response when being pharmacologically characterised using a NanoBiT complementation assay against a known orthosteric antagonist.[3]

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Synthesis of original 3'- modified triazolo-nucleosides to fight (re-)emergent viruses.

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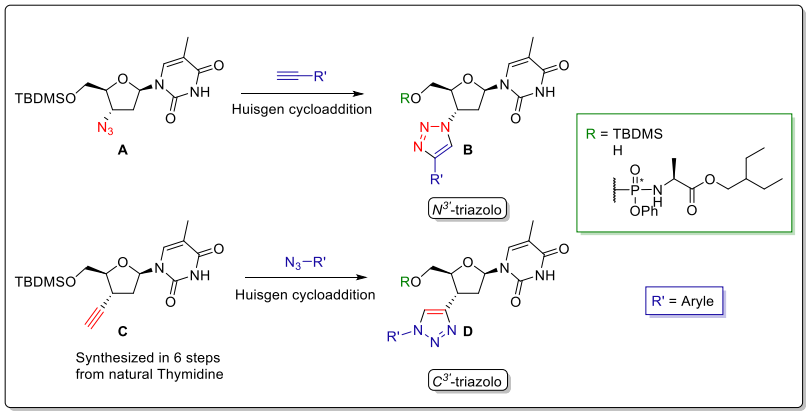
FP07

The prostagladin EP2 receptor (EP2) is a widely expressed G protein-coupled receptor activated endogenously by prostaglandin E2 (PGE2), which contributes to the development of chronic inflammation in cancer and has roles in diseases such as Parkinson's, endometriosis, arthritis, intercranial aneurysms, glioblastoma and epilepticus (Figure 1B). [1, 2] EP2
chemists and also biologists, dedicated to the design, synthesis and evaluation of novel families of nucleoside analogs, on a panel of viruses. The Symbiose team in Nantes has expertise in nucleoside chemistry[(a,c)], and develops strategies to introduce relevant structural modifications in various positions of the furanose ring. In this work novel 3' modified 1,2,3-triazolo-*N*-nucleosides (**B**) have first been prepared from AZT (Scheme 1, **A**) and could give promising activities[(d,e)]. The challenge was also to prepare 3' modified 1,2,3-triazolo-*C*-nucleosides to compare stability and viral activities with triazolo-*N*-nucleosides. This novel family of triazolo-*C*-nucleosides was prepared from the 3'-alkyne precursor (Scheme 1, **C**) obtained in 6 steps from Thymidine[(f)] including radical reaction with a thionocarbonate precursor to form the C-C bond followed by oxidation and a Bestmann reaction. The targeted triazolo compounds (**D**) were then obtained in classical [3+2] Huisgen cycloaddition conditions.



Scheme 1: Click strategy to access to *N*- and *C-3'*-triazolo-nucleosides.

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(f) Sanghvi, Y. S.; Ross, B.; Bharadwaj, R.; Vasseur, J.-J. Tetrahedron Letters 1994, 35 (27), 4697–4700.

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A Modified Phosphatidylinositol for the Investigation of Peptide Assemblies

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FP08

Phosphatidylinositolphosphates (from here on referred as PIPs) are phospholipids, composed of a polar inositol headgroup connected to a diacylglycerol (DAG) *via* a phosphate ester. Playing a crucial role in signal transduction pathways, PIPs mainly serve the purpose of enabling Ca2+-flux from the endoplasmatic reticulum, through enzymatic liberation of inositoltriphosphate (IP3). In recent years, work by Sitte and Schütz *et al1,2* has shown that, apart from serving as a source for the second messenger IP3, PIPs are a critical factor in the stabilization of the serotonin transporter´s (SERT) oligomeric structure. In Sitte´s seminal work, strong evidence was found that PIPs ensure the structural integrity of SERT on the cell membrane through interaction of the polar inositol headgroup with basic patches, found on the surface of the transporter monomers. The assumption was further cemented by Schütz through implementation of a high-resolution single molecule microscopy technique ("Thinning Out Clusters While Conserving Stoichiometry of Labbeling", TOCCSL3) developed in the former´s lab.

To enable in-deep elucidation of the interactions between PIP and SERT, the need for a fluorescent and highly stable analogue of PIP has arisen. Therefore, the presented work will deal with the synthesis of such analogues, spanning from a simple model compound, as a proof-of-concept regarding the feasibility of chemical synthesis of such scaffolds, to structurally and functionally more complex and diverse members of the PIP-family. The structural modifications to the PIP-framework lead to photo-linkable and fluorescent representatives of this class of natural compounds. This will be achieved through introduction of handles enabling "click-chemistry" (e.g. azides) and thereby binding to fluorophores, as well as carbene donors (e.g. diazirines) for means of irreversible photo-linking to SERT on the site of the DAG.

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Visible Light Amination/Smiles Cascade Reaction for an Efficient Access to Phthalazine Derivatives

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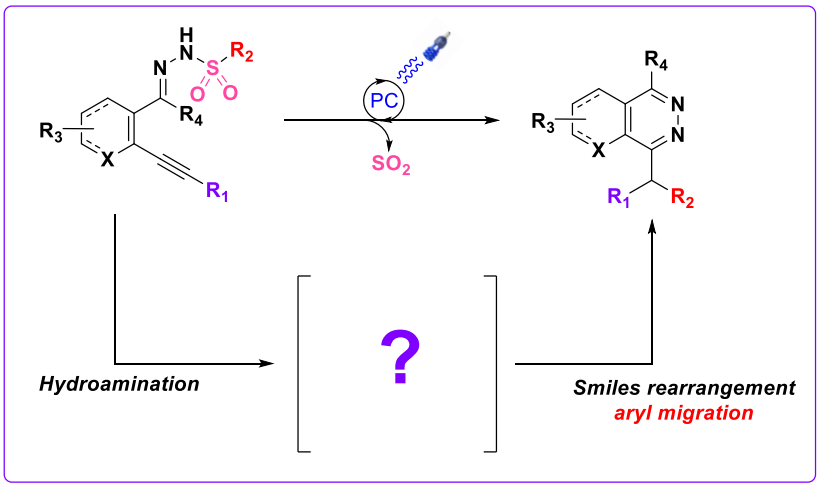
FP09

Phthalazine and its derivatives are certainly one of the most interesting nitrogen-containing heterocycles due to their biological active effects. Indeed, phthalazines have shown therapeutic properties, such as antibacterial or antitumor agents. This is why their formation[1] remains highly requested. Thus, the development of new strategies to efficiently build these compounds is still desirable.

In this aim, we focused our research projects on the development of new photoredox synthetic methods to build the carbon-nitrogen bond[2], *via* the generation of a nitrogen centered radical. This kind of intermediate is attractive because it can be added on unsaturated derivatives for instance and thus lead to the carbon-nitrogen bond formation.

In our laboratory, we developed ortho-alkynylsulfonohydrazone precursors in order to access to a broad scope of phthalazine derivatives[3]. This synthesis *via* a new cascade reaction, is initiated by visible light photocatalysis, involving a radical hydroamination reaction followed by a radical Smiles rearrangement. Thanks to this reaction, many useful phthalazine derivatives are now accessible.



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Ultrafast fragment screening by NMR at low micromolar concentration.	***FP10***

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Nuclear magnetic resonance (NMR) is a tool of choice for hit finding, in particular in fragment-based approaches, as it is particularly suited to detect weak interaction up to millimolar range. However, the lack of sensitivity of NMR is a hurdle to its implementation in drug discovery routine, as it yields long experimental time, highly concentrated samples and expensive magnets costing above a million euros.

Using our expertise in photo-chemically induced dynamic nuclear polarization[a], [b] We invented a method that is able to improve sensitivity and is readily implemented on any spectrometer including cheap benchtop NMR to achieve experimental time in the order of the second and sample concentration in the low micromolar scale. We will present the results of our fragment library screening against PIN1 Prolyl isomerase which was perform at a rate of 1500 samples per day (versus 50 with classical NMR). We will also present how we obtain binding affinities and plan to implement our approach with other methods previously developed in our lab to obtain the 3d structures of target-ligand complexes within a few hours to obtain the complete structure-activity relationship. [c]

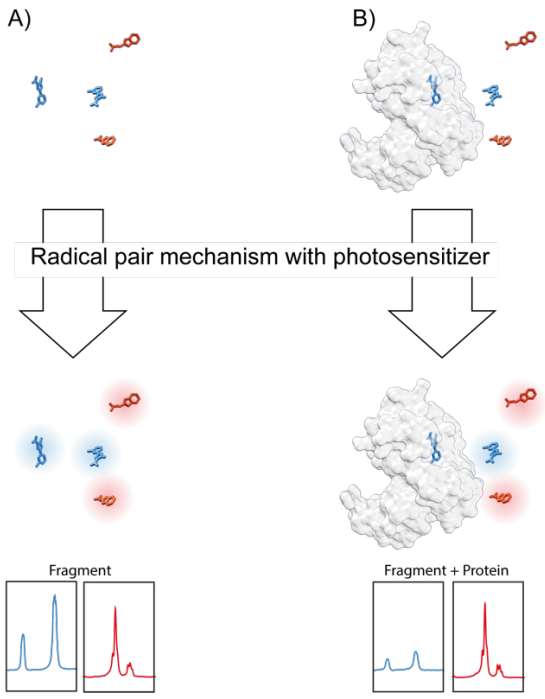

Figure 3:Principle of photo-CIDNP NMR screening. The fragments that bind to the target see their signal perturbed due to equilibrium shift while the non-binding fragment signals remain identical with or without target.

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Design of a ratiometric peptide-based probe to detect Cu(II) in biological fluids by ^{19}F NMR

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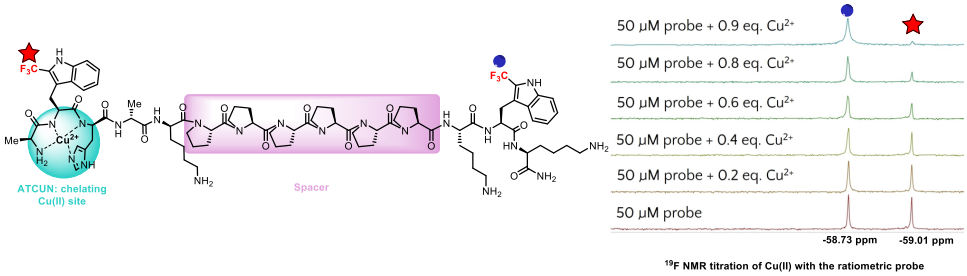
FP11

Copper (Cu) is an essential metal involved in many redox processes necessary to life. Recent studies suggested that dishomeostasis of extracellular Cu(II) could be implicated in neurogenerative diseases, like Alzheimer's disease.[a] In the blood, extracellular Cu(II) is mostly bound to Ceruloplasmin (10 to 15 µM) inertly, but a low concentration of kinetically-labile Cu(II) (1-3 µM), chelated to Albumin, α-macroglobulin or free amino acids, is exchanged in the presence of high-copper affinity chelating agents. Interestingly, elevated levels of exchangeable Cu(II) in serum and urines are observed in disease patients., but can be masked by the larger inert pool when not selectively measured.[b] Therefore, monitoring exchangeable copper levels seems promising to be an interesting diagnostic marker.

The selective quantification of exchangeable Cu(II) is so far performed by combination of a separation step and a Cu-dosage step. We designed a probe inspired by a natural motif found in Albumin: the Amino Terminal Cu and Ni binding motif (ATCUN), known to strongly bind Cu(II) (log $K_{7.4}$ = 13).[c] Our team already developed a luminescent ATCUN probe to detect Cu(II) but the excitation in UV and the low sensitivity limited it application's.[d] We designed here a ratiometric probe with two trifluoromethyl groups (CF_3) as internal sensors to follow Cu(II) titration by ^{19}F NMR spectroscopy. This method is very sensitive to changes in chemical environment due to chemical shift range and ^{19}F is rarely found in biological samples, which enables analysis with minimal interference from background signals.



^{19}F NMR titration of Cu(II) with the ratiometric probe

This innovative ratiometric turn-off probe has been used to detect and quantify amounts of Cu(II) (up to 10 µM) by ^{19}F NMR in various biological samples (urines, cell culture media). Results will be discussed as well as challenges in terms of selectivity and quantification.

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Novel dimerized peptides bind VEGF with high affinity and display anti-angiogenesis activity

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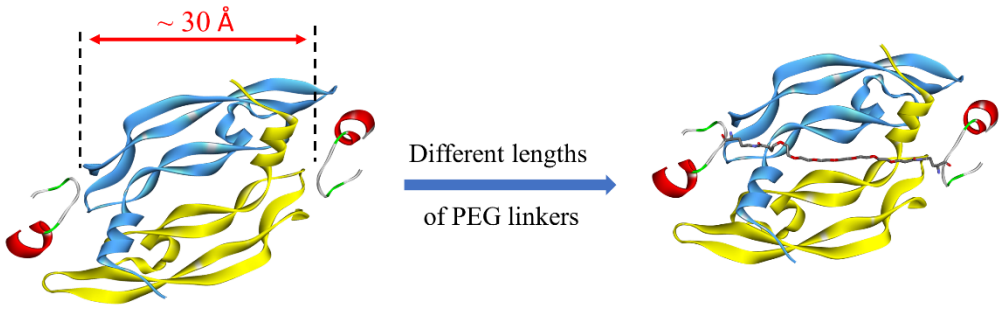
FP12

Macromolecular ligands of VEGF (Vascular Endothelial Growth Factor) used in the clinic comprise antibodies, antibody fragments and receptor fragments [1]. They block the activation of VEGF receptors, thereby decreasing pathological angiogenesis to treat cancers and ocular diseases. However, due to their large sizes, their penetration capacity through the biological barriers is not optimal. Because the penetration capacity usually increases with decreasing size, we describe here small peptide ligands of VEGF, starting with a monomer peptide of 2 kDa [2]. To retain the required high-affinity, we design new dimeric peptide ligands targeting both symmetrical binding sites of the VEGF homodimer. We synthesized a series of eleven dimers with flexible PEG linkers of increasing lengths to connect both peptide monomers. With the optimal linker length in PEG_{25}-dimer **D6**, a 40-fold improvement of binding affinity was observed compared to a monomer control, resulting in a K_d value in single digit nanomolar measured by isothermal titration calorimetry. **D6** affinity for VEGF is close to that of the widely used antibody bevacizumab, whereas its molecular weight is 30 times smaller. The dependence of K_d values on linker length appeared well correlated with a theoretical model. The thermodynamic analysis gave binding enthalpies and entropies, and it was supported by size exclusion chromatography to determine the binding stoichiometries. Finally, we validated the dimerization strategy by evaluation of the activity of control monomers and selected dimers in cell-based assays with HUVEC.



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Inhibition of Patched1 as promising strategy to overcome chemotherapy resistance in cancer cells

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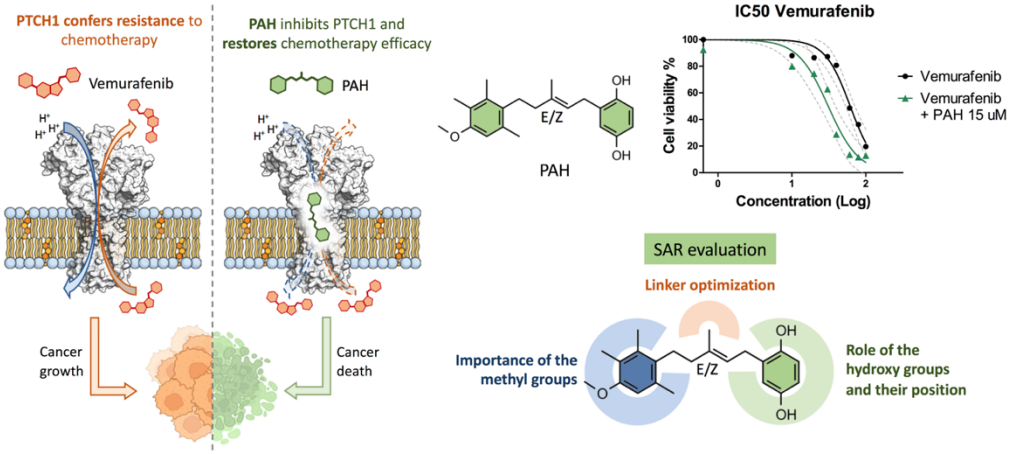
FP13

The development of inhibitors of biological mechanisms involved in multidrug resistance (MDR) in cancer treatment meets an important medical need but still represents a challenging task. Major MDR targets are multidrug efflux systems, such as the ATP Binding Cassette (ABC) transporters. However, none of their inhibitors has been approved for clinical use[(a)] and therefore, alternative therapeutic targets are urgently needed.

The Hedgehog receptor Patched1 (Ptch1), part of the Hedgehog signaling pathway involved in tissue development and homeostasis, was recently shown to transport different chemotherapeutics out of cancer cells thus contributing significantly to MDR phenomena. Ptch1 is over-expressed in many cancers and its inhibition was shown as a successful strategy in improving chemotherapy efficacy without toxicity for healthy cells or potential side-effects. To date, only few compounds were identified as efficient Ptch1 inhibitors, among which panicein A hydroquinone (PAH), a meroterpenoid natural compound[(b)].

Here we describe a straightforward stereoselective synthesis for the E and Z isomers of PAH and we apply the methodology to several analogs with the aim of assessing a structure-activity relationship. The biological activity of the derivatives, in combination with chemotherapy, was evaluated in melanoma cells. Molecular insights into the binding mechanism of PAH analogs to Ptch1 are also addressed by means of *in silico* methodologies[(c)]. Altogether, these data pave the way for the design and development of the next generation of Ptch1 inhibitors.



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From *Catalpa* Fruits to Promising Prostanoïds Precursors

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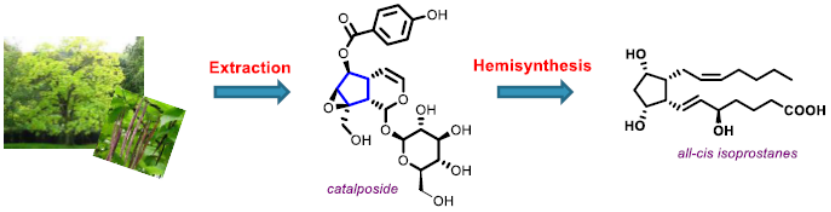
FP14

Nature is a great source of chemical diversity. Currently, it is the origin of the discovery and design of many active molecules.[1] The extraction or the synthesis of complex natural structures can be very challenging. However, nature may also provide abundant small compounds which can be used as polyfunctional chiral skeletons for the hemisynthesis of more complex molecules.

Isoprostanes, metabolites of polyunsaturated fatty acids following non-enzymatic pathway, are an important class of natural products containing polysubtituted cyclopentane ring. Indeed, some of these metabolites are biomarkers of oxidative stress in biological systems and have interesting biological properties, such as anti-inflammatory, neuroprotective and antiarrhythmic activities.[2] In order to study these compounds, various synthetic strategies have been developed.[3] However, some stereoisomers of this family are still synthetically very difficult to obtain in particular the all-*cis* isoprotanes due to the steric hindrance.

To ease access to these molecules, we propose a hemisynthetic route from iridoïds, small bicyclic monoterpenes, as a suitable polyfunctional chiral skeletons (Scheme 1). Catalposide is a relevant iridoïd for this project by its *cis* cycle junction of stereochemistry *cis*. Moreover, catalposide is one of major iridoïds present in *Catalpa bignonioïdes W.* fruit,[4] known as bean tree. This latter is a very common ornamental plant that can be found in our green spaces and along roadsides making it a particularly accessible source.



Scheme 1 : Isoprostanes hemisynthesis from Catalpa fruits

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Selective Activation of TRPC6 Ion Channel by Metallated Type-B Polyprenylated Polycyclic Acylphloroglucinols (PPAP) and AI-based Binding Site Identification	*FP15*

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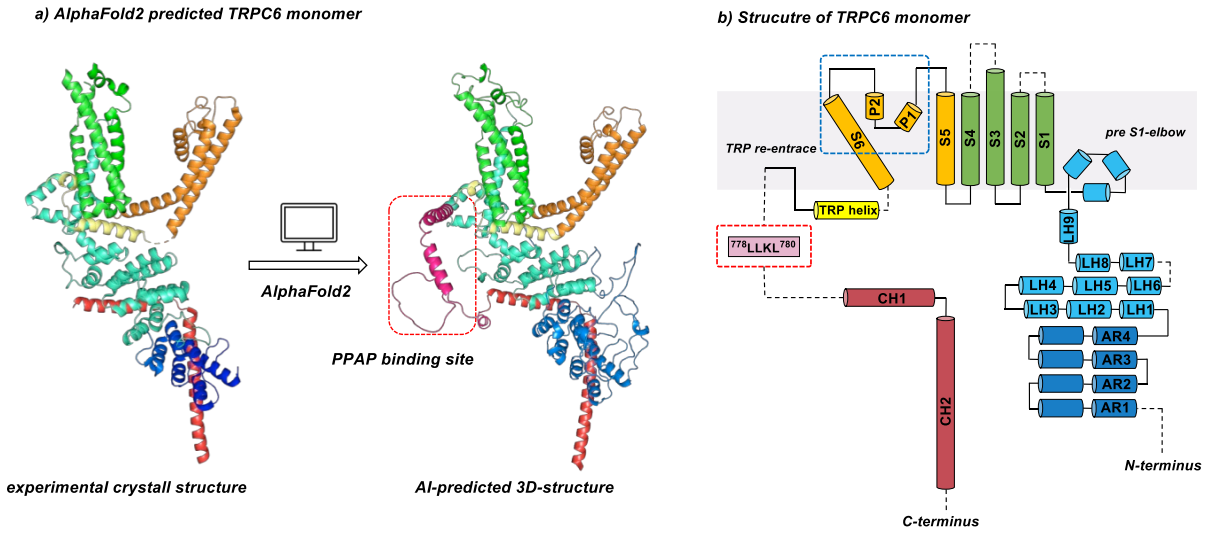
The regulation of TRPC6 ion channels has been proposed as a potential strategy for treating neurodegenerative diseases and depression. [a] In this study, we demonstrate the selective activation of TRPC6 by a metallated type-B PPAP, known as PPAP53. The effectiveness of PPAP53 is due in part to the presence of a 1,3-diketone motif that enables metal coordination. This metallated PPAP is water-soluble and as more potent than hyperforin, a natural compound that is commonly used as gold-standard in this field. [b] Additionally, PPAP53 is resistant to oxidation under photochemical conditions, making it a promising candidate for further development. Mutation studies show that PPAP53 binds to the C-terminus of TRPC6, which had previously not been fully resolved through cryo electron microscopy. To predict the structure of this C-terminus, we employed artificial intelligence-based protein structure prediction algorithms such as AlphaFold2, ColabFold, ESMFold and trRosetta. These predictions, which were supported by experimental data, indicate that PPAP53 binds to the ^{777}LLKL^{780} region of the C-terminus.



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From hit to lead: optimization of capsid-binder regarding pharmacokinetic properties

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Centre de Recherches en Cancérologie de Marseille
Inserm U1068, CNRS UMR7258, Institut Paoli-Calmettes
Pharmacy faculty, Aix-Marseille University
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FP16

Enterovirus (EVs) are responsible for several diseases with serious impact for some patients. Moreover, we have witnessed in recent years the emergence of new variants of EVs with more severe clinical consequences than those previously described. Therefore, we develops broad-spectrum and eligible oral drug candidates against EVs [(a)]. This optimization is conducted with 3 objectives: the discovery of new interactions to improve activity, the use of innovative synthesis strategies to achieve the larger number of modulations and the optimization of pharmacokinetic properties using deep-learning.

To enhance the drug bioavailability, a chemical library has been created and evaluated for their pharmacokinetic properties using GastroPlus[(b)] software. Molecular descriptors are used to predict the ADMET properties of molecules, via a machine learning model. The molecules with the most favorable pharmacokinetics were compared to those with unfavorable pharmacokinetics. For this, a molecular decomposition was performed using the RDKit Molecule Fragmenter function of the KNIME software (v4.6, KNIME AG, Zurich, Switzerland). New promising candidates were identified.

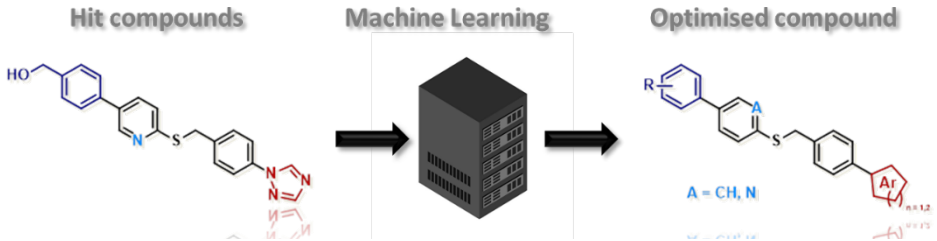

Figure 1: Optimisation process to optimize pharmacokinetic paramaters

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Discovery of PKM2 activators: a computational drug repurposing approach for the treatment of glioblastoma multiforme. **Gianmarco Gualtieri [(1)]*, Isabella Romeo [(1),(2)], Claudia Abbruzzese [(3)], Silvia Matteoni (3), Stefano Alcaro [(1),(2)].** *(1) Dipartimento di Scienze della Salute, Università degli Studi "Magna Græcia" di Catanzaro, Viale Europa, 88100, Catanzaro, Italy.* *(2) Net4Science Srl, Università degli Studi "Magna Græcia" di Catanzaro, Viale Europa, 88100, Catanzaro, Italy.* *(3) Cellular Networks and Molecular Therapeutic Targets, Proteomics Unit, IRCCS-Regina Elena National Cancer Institute, 00144 Rome, Italy.*	***FP17***

Glioblastoma multiforme (GBM), the most recurrent and malignant primary brain tumor in adults, is associated with high morbidity, extremely poor prognosis, and high frequency of recurrences. Given the lack of efficacy of the standard GBM treatment, a broad search for more effective therapies and unexplored GBM targets is currently underway. Targeting key points of GBM metabolism could be an innovative strategy to interfere with its rapid infiltrative growth and aggressiveness [a]. Pyruvate kinase M2 (PKM2) plays a pivotal role in GBM progression through both metabolic and non-metabolic functions [b]. Herein, we aim to describe a combination of structure-based and pharmacophore-based virtual screening to identify PKM2 activators from a database of 2568 approved drugs, filtered by BBB permeability. In silico studies revealed 47 promising hits which could theoretically stabilize PKM2 in the tetrameric state, preventing both dimeric-PKM2 nuclear translocation and upstream metabolites accumulation. Molecular dynamics simulations of the best selected activators in complex with PKM2 were performed to assess their capability to stabilize tetramer formation. In vitro studies on GBM cell lines and enzymatic assays are currently ongoing [c].

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* Correspondence: g.gualtieri@unicz.it

Design, synthesis and pharmacological evaluation of dual ligands targeting A_{2A} and $mGlu_5$ receptors for the treatment of neurodegenerative diseases.

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FP18

Text

Neurodegenerative diseases (ND) such as Parkinson's disease (PD) and Alzheimer's disease (AD) are currently incurable, thus justifying the search for new therapeutic approaches and the development of new drug candidates. In recent years, A_{2A} receptor ($A_{2A}R$) antagonists have emerged as pharmacological compounds of interest, especially for the treatment of neurodegenerative diseases such as PD and AD. Faced with these multifactorial diseases, the design and synthesis of multi-target compounds appear as a promising and growing therapeutic strategy. More and more negative allosteric modulators of $mGluR_5$ are undergoing clinical evaluation in various therapeutic applications such as ND. In addition, overactivation of the $mGluR_5$ also appears to play an important role in pathological conditions associated with AD. Moreover, it seems that these receptors act synergistically with $A_{2A}R$: blocking $mGluR_5$ improves the blocking of $A_{2A}R$. Our current research efforts are focused on developing dual ligands targeting $A_{2A}R$ and $mGluR_5$ with high affinities and good ADME properties.

Based on recently published co-crystallized structures of $A_{2A}R$ and $mGluR_5$ with a dual ligand, we developed different families of compounds. The synthesis of these compounds will be carried out using synthetic methods already known in the laboratory. The affinity and selectivity of these ligands will be measured by radiobinding tests. The antagonist functionality of ligands will be verified using cAMP (A_{2A} activity) and intracellular calcium ($mGlu_5$ activity) assays. The best compounds will be studied for their ability to cross the BBB and their ADME properties.

We expect the development of several families of dual compounds with high affinities and good ADME properties to further validate $A_{2A}R/mGluR_5$ dual ligands in PD and AD experimental models. This work, should it be successful, will allow the identification of new drug candidates for the treatment of ND.

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Abolishing the Benzodiazepine-Site Affinity of $GABA_A$-Receptor Ligands

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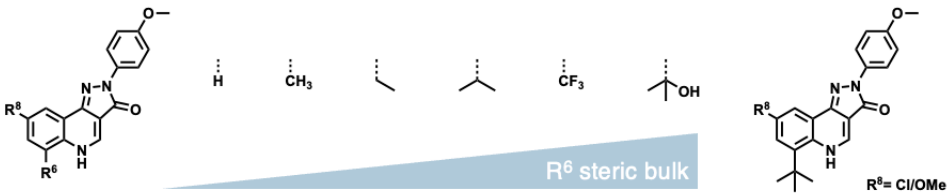
FP19

$GABA_A$-receptors are among the major neurotransmitter receptors in the mammalian brain and are involved with conditions including anxiety disorders, epilepsy, and insomnia. The ligand-gated ion channels are composed of five different subunits encoded by 19 different genes. This results in numerous potential subunit combinations, and hence, a highly complex pharmacology. $GABA_A$ receptors are prominent targets for many pharmacologically and clinically important drugs such as benzodiazepines, barbiturates, neuroactive steroids, anesthetics, and convulsants which bind to various binding sites.
Several pyrazoloquinolinone ligands (PQs) with high potency for $GABA_A$ receptors have been reported. These allosteric modulators potently act via a binding site at extracellular α+/β− interfaces but also show off-target affinity for the benzodiazepine binding (BZ) site at α+/γ− interfaces. Previous pilot experiments, however, showed that the introduction of steric bulk has a sizeable impact on BZ-site affinity.[1]
This work reports the design and synthesis of a series of novel PQ-ligands with increasing steric bulk to abolish BZ-site affinity and to monitor changes in affinity for the binding site of interest at the same time. For the elucidation of these complex structure-activity relationships, radioligand displacement studies and electrophysiological functional assays in combination with *in silico* methods are applied.



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Fingerprint approach using macrocyclic "chemical nose" sensors	
Monica Swetha Bosco, Monica Araya-Farias, Giacomo Gropplero, Florence Mahuteau-Betzer, Vassilis Tsatsaris, Emmanuel Curis, Yves Rozenholc, Jean-Francois Gaucher, Stephanie Descroix, Nathalie Gagey-Eilstein * *Université Paris Cité, Faculté de Pharmacie de Paris*	***FP20***

The biomolecular composition of body fluids are a direct reflection of severity and progression of diseased states. We aim to investigate a non-specific serum-based strategy, which mimics the human olfactory system for differential sensing, thereby generating a unique fingerprint tied back to the serum composition for disease diagnosis.

We developed a sensor array with cross-reactive synthetic receptors based on the host- guest interaction of triphenylamine derivatives(TPA) with the macrocycle Cucurbit[7]uril(CB[7]). The host-guest inclusion complex imposes a structural confinement on the TPA's and enhances their fluorescence intensity, while CB[7] provides diverse binding modes for generation of distinct fluorescent fingerprints upon interaction with biomolecules. This sensing strategy has been extended to a droplet-based microfluidic device to evaluate the array with reduction in sample volumes. Pre-existing cohorts of preeclamptic serum samples have been assessed and the generated fluorescence signatures along with available clinical and biological data will be processed by suitable statistical approaches such as supervised clustering by Linear Discriminant Analysis to obtain classifiers for PE occurrence and outcomes.
We have thus far been able to optimize the photophysical properties of the sensor array and generate fluorescence fingerprints to discriminate a diverse range of 17 protein analytes. The array has been tested for its ability to capture diversity in biofluids like serum and provide successful discrimination of the protein analytes in this complex media. The capacity of the chemical nose to discriminate between preeclamptic and non-preeclamptic patient samples has been evaluated with 17 serum samples to establish a proof of concept with 100% accuracy. The system has further been optimized on a dedicated droplet-based microfluidic platform with minimal utilisation of sample volumes, where the detected fluorescence output signal has been correlated with the initial droplet composition to provide discrimination of selected proteins analytes with 100% accuracy.

Herein, we developed a 'chemical nose' sensor for fingerprinting and pattern recognition of biomolecules. The ability of this system to detect changes in spectral signatures of serum will provide a new diagnostic methodology for complex diseases like preeclampsia and will enable us to propose a strategy for big data analysis based on chemical sensing and machine learning.

Targeted protein degradation strategy based on pyridoclax in chemoresistant ovarian cancer.

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FP21

Delayed diagnosis combined with the resistance of cancer cells to chemical treatments make ovarian cancer the deadliest gynecological cancer. Evading apoptosis of cancer cells is one of the causes of this drug resistance. This escape is due to the overexpression of two proteins in particular: Mcl-1 and Bcl-xL.(a) However, the inhibition of these proteins leads to a cardiac (for Mcl-1) and a platelet (for Bcl-xL) toxicity. Also, inhibition of only one of the two proteins induces an overexpression of the other. Concomitant degradation between Mcl-1 and Bcl-xL could restore balance in cancer cells and then the apoptosis. The objective of this project is to synthesize molecules with the ability to degrade both proteins simultaneously.(b) For this, compounds were synthesized according to the PROTAC (PROteolysis Targeting Chimeras) approach, developed in 2001 by Prof. Crews *et al.*(c)

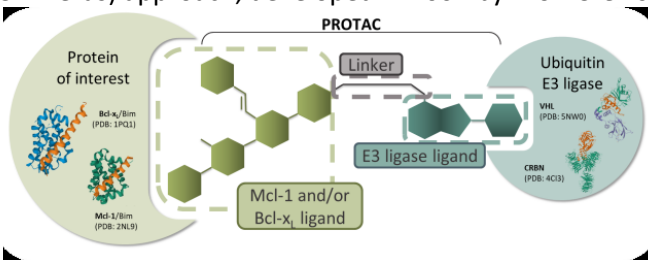

Figure 1. Structure of our PROTAC molecules.(d)

In this way, a first PROTAC molecule was synthesized. On the first side, through alternation of cross-coupling and halogen exchange reactions, we obtained an analog to pyridoclax,(e) a known inhibitor of Mcl-1, as the target protein recruitment ligand. On the other side, the ligand for CRBN ligases was synthetized after a condensation reaction followed by a nucleophilic substitution reaction to introduce the linker. From this first proof of concept, about 30 molecules were synthesized, where the nature and the length of the linker, the nature of proteins of interest ligand and the type of E3 ligase recruited were modulated. In parallel to the *in vitro* evaluation on chemoresistant cancer cell lines by Dr. Poulain's team, we decided to evaluate *in silico* the druggability parameters of our compounds after a bibliographic exploration.(f) Thus, the radar diagram representation of Lipinski's rules allows to determine the appropriate theoretical physico-chemical parameters for druggability and ultimately for oral bioavailability.

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Structure-based design of urea-peptide foldamers as modulators of histone chaperone ASF1.	***FP22***

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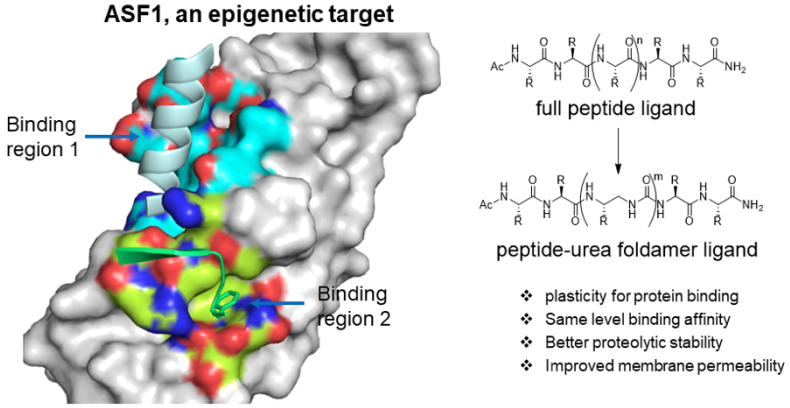
Peptidomimetic foldamers are synthetic molecules that mimic the structure and function of natural peptides. They are attractive to medicinal chemists because they can offer improved resistance to proteolytic degradation and longer in vivo half-lives compared to natural peptides.[(a)] The aliphatic *N,N'*-linked oligourea is a type of foldamer that is able to form defined helical structures similar to alpha-helices. The replacement of a segment of peptide by an urea insert proved no effect on the helical property. [(b)] In the context of looking for new compounds to interrupt the protein-protein interaction between histones H3-H4 and chaperone protein ASF1, which is a promising epigenetic target related to the malignant diseases,[(c)] such as cancers, we have designed a series of urea-peptide hybrid structures to mimic the helical structure of a peptidic ligand ip4.[(d),(e)] The binding mode of the foldamer ligand on the ASF1 surface was studied by crystallography and by NMR. The results showed that urea-peptide foldamers formed helical structures in solution , while the chimeric sequences had good plasticity to adapt to the protein surface. Furthermore, we incorporated the H4 epitope that binds to the second binding region of ASF1, into the peptide-urea helix and achieved nanomolar affinity after optimization. In comparison to ip4, the foldamer ligand showed improved cell permeability and stability against enzymatic degradation in human plasma.



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Predicting Androgen Receptor ligands using a docking protocol taking into account protein flexibility	*FP23*

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Over time, new strategies for protein-ligand docking have emerged, with a shift towards approaches that consider protein flexibility. However, simulating the whole protein flexibility is still associated with computational time that are not compatible with large database screening. In this study, we present a protocol to rationally select a subset of residues whose side chains should be considered as flexible during the docking with no need of prior computational studies. We then evaluate the impact of this choice on the docking prediction performances.

This study focuses on the androgen receptor (AR) [a], which is a member of the nuclear receptor (NR) family. Compounds experimentally evaluated in AR binding assays were extracted from the Environmental Protection Authority (EPA) Dataset Gateway [b] and divided in AR binding (B) and non binding (NB) compounds. AR structures were extracted from the Protein Data Ban and were evaluated using the MolProbity webserver [c]. Different docking softwares (Autodock Vina, smina and GNINA) and scoring functions (vina, vinardo and dkoes_scoring) [d,e] were then evaluated using both rigid and flexible protein protocols. For the flexible protocols, we first set as flexible the side chains of all residues within a 4Å cut-off distance from the co-crystallized ligand. Then, we developed a new protocol by investigating the docking performance associated with different combinations of 1 to 6 binding site residues with flexible side chains. These 6 residues were rationally selected according to the intrinsic flexibility of their side chain, the alternate conformation observed within different AR structures and their position in the binding site.

We demonstrated that taking protein flexibility into account can improve docking performance. In particular, we highlighted that this event can be achieved by selecting only a small number of flexible side chains which is a crucial point to generate results for large compounds libraries with reasonable computational times.

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Synthesis and pharmacological testing of therapeutic agents to enhance insulin secretion

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FP24

Insulin is widely considered to be the most important hormone involved in metabolic homeostasis, however, defects in its action, secretion or both cause diabetes mellitus – a metabolic disorder affecting ~420 million people worldwide[(a,b)]. Despite there being several pharmacological agents designed to manage type 2 diabetes mellitus, their effectiveness often declines overtime. Human trace amine-associated receptor 1 (hTAAR1) is a G protein-coupled receptor expressed in several organs and cells including pancreatic β-cells[(b)]. Figure 1 shows pancreatic hTAAR1 can amplify insulin secretion, thus it is recognised as a potential therapeutic target for novel oral hyperglycaemic drugs[(b,c)].

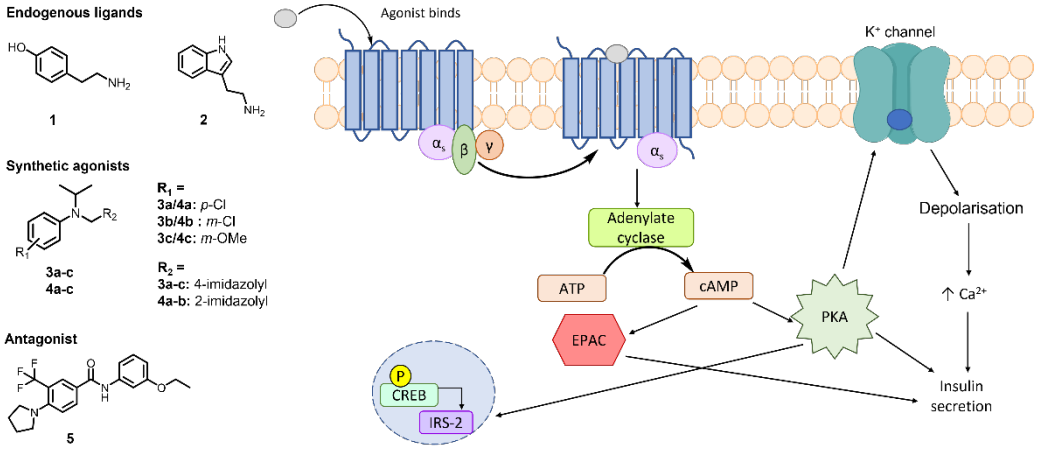

Figure 1: *Structures of TAAR1 ligands (**1-5**) and their therapeutic effects of activated pancreatic hTAAR1. ATP; adenosine triphosphate, cAMP; cyclic adenosine monophosphate, EPAC; exchange proteins activated by cAMP, PKA; protein kinase A, CREB; cAMP response element-binding protein, IRS-2; insulin receptor substrate-2.*

Five known hTAAR1 agonists (Figure 1, compounds **3a**-**c** and **4a**-**b**, K_i = 4-138 nM) were identified and resynthesized to validate the proposed pharmacology assays and to determine their insulin secretion ability[(d)]. One closely related novel compound (Figure 1, **4c**) was designed and its pharmacological properties were evaluated. The results obtained will support future structure-activity relationship studies. As part of this communication, we will describe the synthetic routes of these molecules and for the first time the pharmacological response for the novel and repurposed literature compounds.

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Towards novel chemical tools to study base-excision DNA repair

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FP25

AIM: Unrepaired apurinic/apyrimidinic (AP) sites possess a lethal threat to cellular functions and can lead to genome instability contributing to life-threatening conditions such as cancer, aging, and neuropathies. On the other hand, several cancer chemotherapies exploit the drug-inducing AP sites as a way to trigger DNA damage and cell death. Despite the severe consequences of the unrepaired AP sites, their distribution in the genome is still poorly understood. Genomic mapping of AP sites will impact our ability to elucidate the mechanism of diseases as well as to evaluate and predict the efficacy of chemotherapy drugs; thus, methods to precisely recognize, quantify AP sites and map their genomic loci are highly needed. The major challenges in quantifying and mapping AP sites hold on to the chemoselectivity of the available chemical tools recognizing AP sites with respect to other aldehyde nucleobases that encounter in the genome, 5-formylurcacil (5-fdU) and 5-formylcytosine (5-fdC) [1-4]. METHOD: In a continuation of our previous work, we designed polyamine ligands able to react through different mechanisms with AP sites, 5-fdU and 5-fdC, leading to unprecedented and distinct products whose structures were elucidated using small-molecule analogues. Next, using oligonucleotide models, we studied the reactivity of the ligands with DNA oligonucleotides bearing the aldehyde modifications (AP, 5-fdU, and 5-fdC) and optimized the conditions allowing a selective reaction with AP sites without any additional work-up. RESULTS: Using gel electrophoresis analysis, we show that an optimized ligand preferentially reacts with oligonucleotides bearing an AP site compared to 5-fU and 5-fC (74% vs. 7% and 3%, respectively) even in the presence of a large excess (10,000-fold) of genomic DNA. Moreover, an azide-functionalized ligand can be utilized to selectively label AP sites with a DBCO-tagged fluorophore and can serve as a platform to isolate AP sites via affinity precipitation. CONCLUSIONS: We anticipate our ligand to be a promising chemical tool to selectively recognize AP sites, representing a platform for more sophisticated tools to quantify AP sites and map their distribution in the genome.

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New possible pharmacotherapy for the treatment of osteoarthritic joints

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FP26

Osteoarthritis (OA) is a degenerative disorder, affecting millions of people worldwide (Goldring & Goldring, 2007). It is characterized by progressive loss of cartilage, joint pain, synovial inflammation, and subchondral bone turnover changes (Martel-Pelletier et al., 2005). Two vasoactive peptides, endothelin-1 (ET-1) and bradykinin (BK) are important players in the pathogenesis of OA. We previously showed that concomitant inhibition of ET-1 receptor (ETA) and BK receptor (bradykinin B1, BKB1) using two peptide antagonists (BQ-123 and R-954, respectively) prevents joint cartilage degradation and improves nociceptive tolerance. The current research proposal will investigate the hypothesis that the concomitant inhibition of ETA receptor and BKB1 receptor have the potential to reduce the inflammatory process in osteoarthritis, by modulation of the microenvironment.

Methods: Human chondrocytes were derived from the knees of OA patients and cultured *in vitro* in absence or presence of ETA and BKB1 receptors antagonists BQ123 and/or R954 (12.5, 25, 250, 1000 and 2500 ηM for 24h or 48h). Cells were and examined the cell viability by MTS assay and the membrane integrity examined by LDH activity assay. The MMP2 activity was evaluated by zymography. To confirm the effect on inflammatory proteins expression, Western blot immunodetection was performed using specific antibodies of NFKκb and NOS2 proteins. By immunohistochemistry and immunocytochemistry we determined the expression of ETA and BKB1 receptors, NFKκb activation and Collagen tipe II. Histomorphological staining was performed to measure the cartilage thickness in a rat model of OA, injected in the knees with the combination of BQ123 and R954.

Results: Cellular viability and the membrane integrity of chondrocytes were not affected by the treatment with BQ123, R954 or their combination. Activity MMP9 was reduced in a time-concentration-dependent manner after the treatment of cells for 72h when exposed to the combination of BQ123 and R954. Also, the treatment with the combination of peptides inhibitors showed decreased expression of NFKκb and NOS2 after 24h of exposition. We also observed a significant decreased activity of the MMP13 enzyme after 24 h of treatment. By histology, we observed that ETA and BKB1 antagonists significantly reduced the expression of both ETA receptor and BKB1 receptor, suggesting a synergistic protective effect. Cartilage thickness was significantly increased in the knees of AO Rats treated with B123 and R954 in combination.

Conclusion: In this study we demonstrated that the concomitant inhibition of ETA and BKB1 was efficient in reducing inflammatory proteins, reduced the activity of cartilage degradation enzymes and reduced the expression of ETA and BKB1 receptors. However, the most important result was the increased thickness of articular cartilage, suggesting that this drug combination is as a possible new therapy for OA.

Metabolic stability of tetraethyl-substituted nitroxides for *in vivo* EPR imaging	***FP27***

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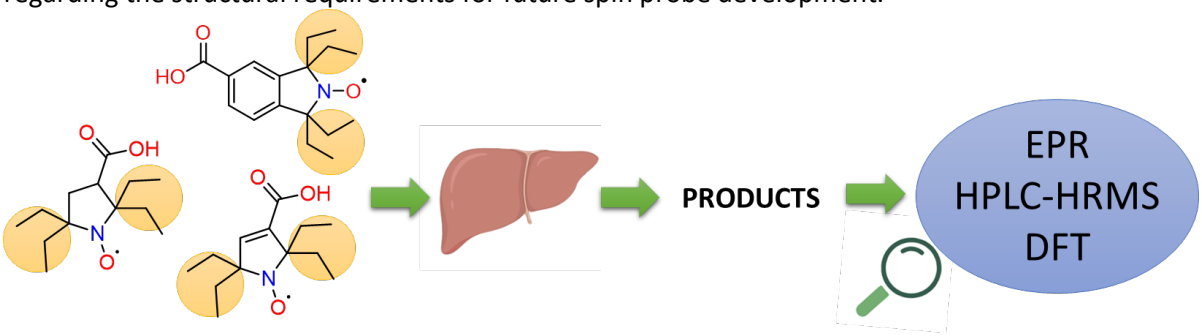
Aminoxyl radicals (nitroxides), in association with Electron Paramagnetic Resonance (EPR) spectroscopy and imaging, are potent tools for evaluating and mapping oxidative distress *in vivo* [1]. As a non-invasive technique apart from the injection of the probes, EPR redoximetry was proclaimed to be a "gold standard" for measuring the redox status *in vivo* by The American Heart Association [2]. The technique was strongly restricted by the insufficient stability of conventional tetramethyl-substituted nitroxides. However, the development of cyclic nitroxides with steric hindrance, such as tetraethyl substitution to the α-position of the aminoxyl group, additionally improved the possibilities for EPR to be applied *in vivo* [1,3,4]. Nevertheless, the information regarding metabolic stability of tetraethyl-substituted nitroxides is limited except for nitroxides with piperidine core [3–5]. Thus, we investigated the metabolic stability of five nitroxides with distinct cores and substitutions by EPR and highlighted the role of cytochrome P450 in their transformation under aerobic and anaerobic conditions. Special attention was devoted to nitroxide with isoindoline core which metabolism was further investigated by HPLC-HRMS and DFT. We will present results of these comparative studies and draw conclusions regarding the structural requirements for future spin probe development.



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New α-Synuclein aggregation inhibitors: design, synthesis, biophysical characterization and evaluations	*FP28*

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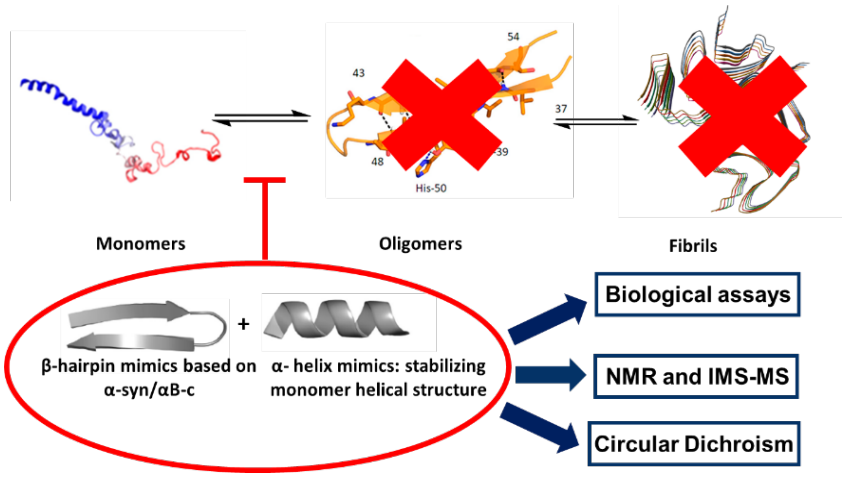
α-Synuclein (α-Syn) is a 140-aminoacids protein whose aggregation in neurons leads to synucleinopathies (Parkinson's disease). In healthy cells, α-Syn is present as unfolded monomers. Under pathological conditions, monomers misfold, forming oligomers and fibrils characterized by β-hairpin-rich structures.[1] These aggregates play a role in neuronal toxicity and death. To our knowledge, no current treatment can avoid neurodegeneration in synucleinopathies. Our objective is to prevent the formation of toxic aggregates and preserve the healthy folding of the monomers. We designed β-hairpin mimics [3] based on small peptides inspired by core sequences of α-Syn oligomers and fibrils. We were also inspired by αB-crystallin (αB-c), a small heat-shock protein engaged in a positive cross-interaction with α-Syn to inhibit its aggregation *in vitro*.[2] Our peptidomimetics were synthesized by solution and solid-phase strategies. Circular Dichroism (CD), IR, NMR, and molecular modelling studies allowed us to elucidate the secondary structure adopted by these aggregation inhibitors candidates. Strikingly, *in cells* assays showed that compounds dramatically decreased α-Syn oligomerization in a neurological model. IMS-MS experiments and other *in vitro* assays are in progress to support these promising data, and further analyse compounds/α-Syn interactions.



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Studies towards mitochondrial delivery of nucleosidic analogs

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FP29

Mitochondria are cellular organelles involved in numerous biological functions such as: energy production, redox homeostasis of the cell, and cell apoptosis.[4] This is one of the main reasons why mitochondrion is considered an important target for drug discovery in the treatment of cancer[5], neurological or cardiovascular diseases[6]. The mitochondrial internalisation of small molecules mostly relies on a physical characteristic of both cellular and mitochondrial membranes, i.e. their polarization, which leads to the accumulation of lipophilic cations into the mitochondria.[7]

Whereas nucleosidic analogs is a well-known family of antiviral[8] and anticancer drugs[9], mitochondrial targeting of nucleosidic analogs has not been reported yet. Such compounds might be relevant for cancer chemotherapy and/or for the treatment of mitochondrial disorders. Herein, we will report the design, the synthesis of original constructs and the study of their subcellular localization using fluorescence microscopy.

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hashuadruplexes formation within the promoter of TEAD4 oncogene and their interaction with Vimentin	***FP30***

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G-quadruplexes (G4s) are nucleic acid secondary structures detected within human chromosomes, that cluster at gene promoters and enhancers. This suggests that G4s may play specific roles in the regulation of gene expression. Within a distinct subgroup of G-rich domains, the formation of two or more adjacent G4 units (G4-repeats) is feasible. Recently it was shown that Vimentin, a protein highly expressed within mesenchymal cells, selectively recognizes these arrangements. Putative G4 repeats have been searched within the human gene proximal promoters by the bioinformatics tool QPARSE and they resulted to be enriched at genes related to epithelial-to-mesenchymal transition (EMT) [(a)]. This suggested that Vimentin binding at these sites might be relevant for the maintenance of the mesenchymal phenotype. Among all the identified sequences, in the present study we selected the one located within the promoter of the TEAD4 oncogene. TEAD4 codifies for a transcriptional enhancer factor, TEAD4, that actively promotes EMT, supports cell proliferation and migration. Moreover, in colorectal cancer cells TEAD4 directly enhances the expression of Vimentin[(b)]. Thus, the possible interaction of Vimentin with TEAD4 promoter could highlight a positive feedback loop between these two factors, associated to important tumor metastasis related events. Here, we exploited spectroscopic and electrophoretic measurements under different conditions to address the folding behavior of the selected sequence. This allowed us to validate the folding of TEAD4 promoter into a G4-repeat able to interact with Vimentin[(b)].

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Machine learning for the prediction of AmpC β-lactamase inhibition to design new antimicrobial agents.	**FP31**

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Abstract:
Antimicrobial resistance is a major problem that has been growing steadily in recent years, causing millions of deaths[a]. The emergence of multi-drug resistance (MDR) is particularly found among Entero-bacteriaceae such as Escherichia coli (E. coli). E.coli causes serious infections and have multiple resistance mechanisms, the most common being extended-spectrum β-lactamase (ESBL) and AmpC β-lactamase production[b,c]. One of the main mechanisms underlying resistance to β-lactam antibiotics are the AmpC β-lactamases[d]. In this study, we employ in silico approaches to identify new inhibitors of AmpC β-lactamase. First, we collected 384223 compounds experimentally tested on E.coli AmpC. The curation of these data has led to 891 inhibitors and 81720 non-inhibitors of AmpC β-lactamase. We used these compounds to develop new classification machine learning (ML) models to ptredict putative inhibitors of this enzyme. Then, we used generative adversarial networks (GAN) to develop generative models in order to design new molecules capable to inhibit AmpC β-lactamase.

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Development of selective NOD1-RIPK2 inhibitors for the treatment of inflammatory diseases

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FP32

Inflammation is a defense mechanism with the function to restore tissue damages and to eliminate pathogens. Inflammation can be triggered by danger signals (DAMPs: Danger Associated Molecular Pattern) delivered from damaged cells or external factors. Inflammation can also be of infectious origin (ex: bacteria, virus) and then involves pathogenic signals (PAMPs: Pathogen Associated Molecular Pattern). These patterns, DAMPs and PAMPs, are recognized by immune cells present in tissues, through Pattern Recognition Receptors (PRRs). PRRs activate these cells, inducing defense mechanisms by the secretion of inflammatory mediators and the activation of cell death pathways[(a)]. Nucleotide Oligomerization Domain (NOD) Like Receptors (NLRs) have been identified to play an important role in innate immunity responses. NOD1 and NOD2 are two of the most investigated NLR for their main role in innate immunity. They both recruit a serine/threonine kinase, Receptor Interacting serine/threonine Protein Kinase 2 (RIPK2) *via* a Caspase Activation and Recruitment Domain (CARD)-CARD interaction to activate their inflammatory pathways: NF-κB and Mitogen-Activated Protein Kinase (MAPK) signaling. It has been reviewed that modulation of NOD1 could be interesting to treat severe infections and inflammatory diseases[(b)]. Until now, only few NOD1 inhibitors have been described and the mode of action of these molecules remains unclear. Recently, a strategy to inhibit NOD1/2 signals has been described and consists in the development of RIPK2 inhibitors. Furthermore, RIPK2 has also been identified as an interesting target to treat Inflammatory Bowel Diseases[(c)]. Based on these recent discoveries, we decided to develop selective NOD1-RIPK2 inhibitors for the treatment of inflammatory diseases. To achieve our objectives, a screening of our chemical library was carried out on Human Embryonic Kidney (HEK)-Blue™-*h*NOD1 cells and resulted in the identification of one *hit* with a half-maximal Inhibitory Concentration (IC_{50}) in the nanomolar range. Starting from this molecule, we investigated the synthesis and Structure-Activity Relationship (SAR) of a series of quinazoline derivatives. New quinazolines were synthesized and tested for their capacity to inhibit the NOD1 signal. Selectivity towards NOD1 *vs* NOD2 and specificity compared to the Tumour Necrosis Factor-alpha (TNFα) pathway was evaluated.

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Synthesis of bivalent ligands for the study of Haspin kinase as an anti-cancer target

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FP34

The human kinome contains more than 500 kinases, regulating the activity of several proteins involved in proliferation, cell survival, angiogenesis, migration and invasion processes. Cellular proliferation depends on signals induced by the activation of protein kinases, controlling their targets through phosphorylations.

Mitotic kinase Haspin (Histone H3 Associated Protein Kinase) plays a key role in mitosis but its recently described inhibitors lack selectivity to further study its role. Considering its growing scientific interest, we are currently developing the synthesis and evaluation of bivalent inhibitors, targeting both the ATP site of the kinase and its site of phosphorylation. The peptidic moiety is reproducing N-terminal Sequence of Histone H3, the only known Haspin substrate, to improve the selectivity of ATP competitive inhibitors (CHR-6494 / LDN-192960) previously described in the literature[1,2].The two parts will be bond together using different length and types of linkers, according to in silico docking using co-crystallized structure of Haspin with its natural substrate.

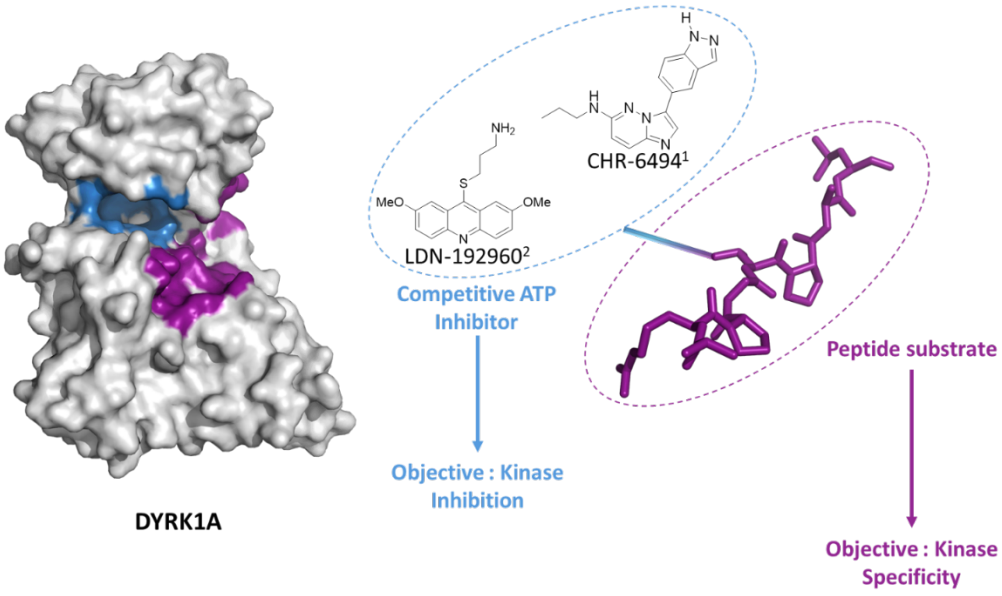

Figure 1: Sc ntation of the principle of a bivalent inhibitor and its interaction with a kinase

This work is organized around 3 axes: synthesis of the ATP targeting heterocyclic scaffold, synthesis of the peptidic part and linking strategy. The inhibition and kinase binding capacity of the conjugated molecules will be tested in collaboration with the KISSf in Roscoff.

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Biochemical screening of molecules targeting the ATP binding pocket of hCINAP in the development of new enzymatic inhibitors.	***FP35***

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Ribosome biogenesis is one of the most complex biological processes leading to the synthesis of ribosomes, molecular machineries responsible for the translation of the information contained in mRNAs into functional proteins[(a)]. One of the last maturation steps of ribosomes is cleavage at side D of pre-rRNA 20S into 18S mature rRNA. Many factors are involved in this maturation step, among them « human coilin interacting nuclear ATPase protein» (hCINAP)[(b)]. hCINAP is an atypical adenylate kinase exhibiting ATPase activity with critical roles in many biological processes. Besides its role in ribosome biogenesis multiple studies underlined the importance of hCINAP in cancer initiation and progression by regulating p53 and cell apoptosis, protein synthesis hyperactivation as well as cellular metabolism regulation via LDHA activation promoting cell invasion and metastasis[(c,d)].

We aim to develop small molecules to inhibit the enzymatic activity of hCINAP by targeting the ATP binding pocket in order to obtain better understanding of the role of the enzymatic activity of hCINAP in ribosome biogenesis as well as provide new therapeutic strategies in oncology. A library of molecules targeting ATP binding sites was screened using the coupled enzymes method. This biochemical assay is based on the quantification of NADH consumption by UV-visible spectrophotometry at 340 nm. In fact, NADH consumption is proportional to the production of ADP from ATP mediated by the enzymatic activity of hCINAP. A few molecules exhibiting inhibitory activity were selected for further modifications and optimization guided by molecular modeling and crystallography data.

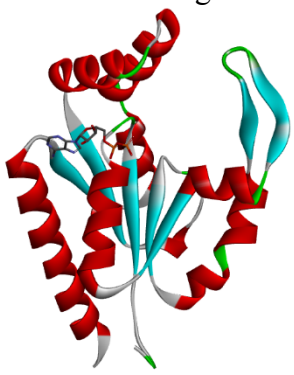

Figure 4: Structure of ADP bound hCINAP [(e)].

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POSTER

Gold (I) mediated radio-iododecarboxylation toward applications in nuclear medicine

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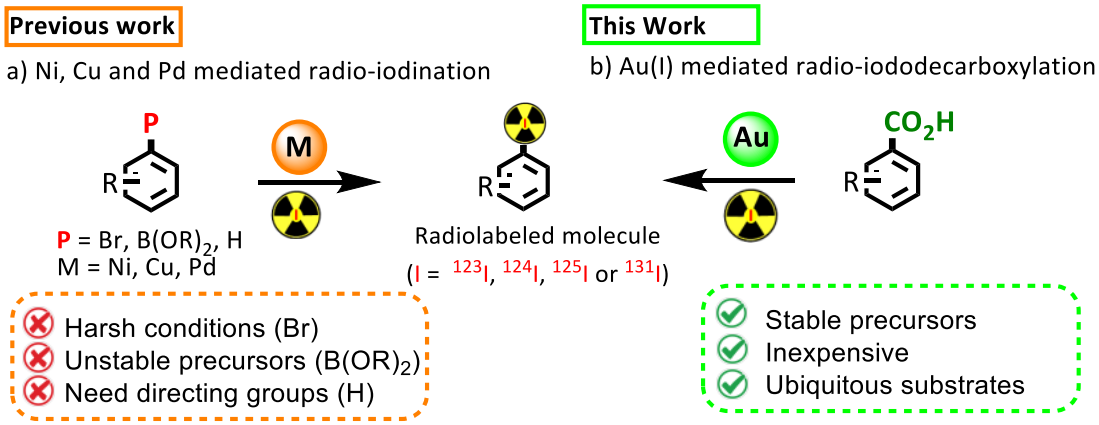
PO01

Labelling of (bio)molecules with radioactive isotopes is of high interest to the scientific community, as it strongly impacts the discovery process in life sciences and nuclear medicine. Radio-labelled molecules have been used to access biochemical reactions by *(i)* measuring the in *vivo* distribution of a substance or *(ii)* performing in *vitro* binding assays or RadioImmunoAssay (RIA).[1] In nuclear medicine, radio-therapeutics for RadioIsotope Therapy (RIT)[2] and radio-tracers for molecular imaging experiments such as Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT) have been described.[3] In this context, four iodine radioactive-isotopes can be used, each one with a specific application: ^{123}I and ^{124}I for SPECT and PET imaging respectively, ^{125}I for binding studies, and ^{131}I for radiotherapy.[4] Considering the difficulties and the cost to develop a radiolabeling process, the discovery of efficient synthetic methods is highly desirable. A variety of new transformations mediated by transition metal (Ni, Cu and Pd) have been developed in recent years (**Scheme 1 a**).[5] Inspired by the gold(I) medieted decarboxylation of arene described by Larrosa,[6] our team recently demonstrated that a carboxylic acid function can be used to promote radio-iodination. In this study, we will present the straightforward decarboxylative gold(I) mediated radioiodination, with iodine-125, of a variety of carboxylic acids. Such reactions were performed in different conditions and without the need of purifying the gold organometallic adduct (**Scheme 1 b**). In addition, to demonstrate the potential of our methodology, we will also present the radio-iodination of known radiotracers or iodinated drugs using the carboxylic acid function as a precursor.



Scheme 1. Transition metal mediated radio-iodination of arenes.

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Identification of small molecule enhancers of natural killer-cell tumoricidal activity.	***PO02***

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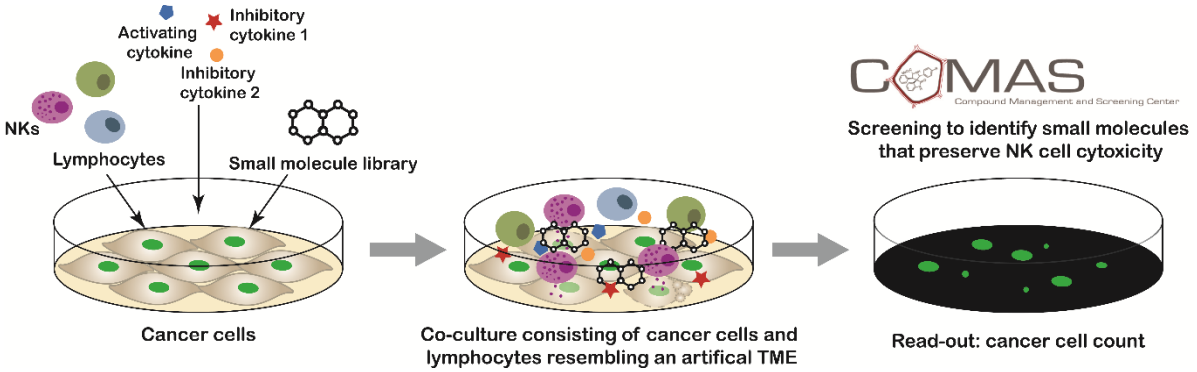
Natural Killer (NK) cells are part of the innate immune system and exhibit many advantageous properties justifying their use for immunotherapeutic purposes. They have the unique ability to sense malignant changes in cells and eradicate them without prior sensitization. Therefore, NKs are critical for the mammalian first-line defense against tumor development. Within the tumor microenvironment (TME), cancer cells co-opt immune inhibitory pathways and reprogram surrounding cell types to promote tumor growth. This allows cancer cells to become less immunogenic, which supports the escape of immune cell mediated cytotoxicity. Many strategies are currently being developed to harness the anticancer potential of NKs and overcome resistance of cancer cells. However, previous clinical studies using NK cells to treat diverse malignancies had mixed outcomes due to lacking efficacy. For this reason, novel strategies to enhance and preserve NK cell tumoricidal activity within the TME are demanded. To harness the power of NKs, we developed a phenotypic co-culture-based system that mimics the TME to monitor NK cell-mediated cancer cell cytolysis. This assay proved to be suitable for the identification of novel small-molecule enhancers of NK-cell tumoricidal activity.



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STRUCTURAL VERSATILITY OF COUMARIN-BASED COMPOUNDS TOWARDS MONOAMINE OXIDASE INHIBITION

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PO03

Monoamine oxidase (MAO) has largely been considered a druggable target. Its ability to catalyze the degradation of biogenic amines has traditionally made its inhibition a viable therapeutic strategy to treat neurodegenerative disorders in which the balance between neurotransmitters is impaired. Depending on the affinity displayed towards each class of biogenic amines, two isoenzymes are described, MAO-A and B. Achieving selectivity between them is a desirable feature for an inhibitor.

The two main reference compounds for MAO-B inhibition are rasagiline and selegiline. These FDA-approved drugs are used in the treatment of Parkinson's disease, and they both bear a propargylamine moiety in their structure. Our group has recently studied the importance of this moiety in the development of drugs targeting neurodegeneration.[1] We have also reported promising preliminary findings by introducing this moiety to the coumarin scaffold (Figure 1), whose versatility has largely been exploited for the design of central nervous system (CNS) targeting agents.[2]

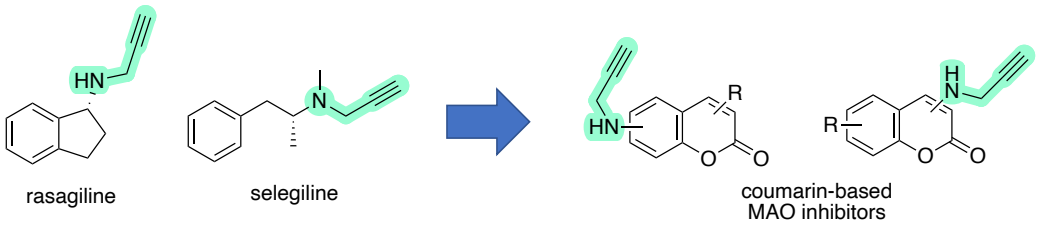

Figure 1. Design of coumarin-based MAO inhibitors inspired by rasagiline and selegiline.

This communication aims to report the trends observed in our group for MAO inhibition using coumarin-based compounds, provide insights into the synthetic versatility of this scaffold[3] and predict the preferred orientation of these ligands using molecular docking to explain the partially reversible mode of binding observed in our studies.

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Biological assessment in terms of cytotoxicity of hyaluronic acid (HA) based electrospun nanofibers	***PO04***

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Purpose of the research**:** Hyaluronic acid (HA)-based electrospun nanofibers are prominent artificial extracellular matrices (ECMs) due to the similarity of HA with the glycosaminoglycans from the natural ECMs' structure and by incorporating active substances such as: propolis, insulin and infusion of *Calendula officinalis* flos potential superior wound dressings are developed. Material and methods: The cytotoxicity degree of HA-PEO-NFs was determined by MTS assay, by using the CellTiter 96®aqueous one-solution cell proliferation assay. For this assay normal human dermal fibroblast cells were grown in alpha-MEM (minimum essential medium) supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin-amphotericin B mixture and seeded at a density of 0.5×10^5 cells/mL into 96-well plates treated with tissue culture and were allowed to adhere for 24 h.
After incubation for 72 h of 100 µL of HA-PEO-NFs ethanolic extract (12.5, 25, 50, and 100 µg/mL) or with 100 µL fresh complete medium (control)+20 µL of the MTS reagent (tetrazolium inner salt) and after 3 h, the absorbance was read at 490 nm on a FLUOstar® Omega microplate reader. Results of the cytotoxicity assay are reflected in the Fig. 1**.**

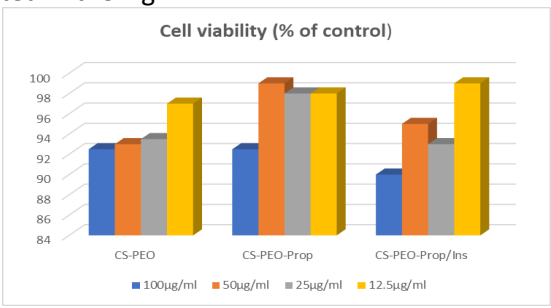

Fig.1. Determination of cell viability expressed in % of control at different concentration of samples

Conclusions: All correlated data of this study show that the developed novel HA-PEO propolis +-insulin/*Calendula officinalis* infusion-electrospun nanofibers are potential materials for wound dressing, in order to further evaluate for *in vivo* testing. Acknowledgments: Scientific research funded by the National Project "Development of new bioactive and biomimetic polymeric nanostructures for wound healing applications", PN-III-P4-ID-PCE-2020-2687, Contract no. 244/2021.

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^{68}Ga-labeled bisphosphonate for preclinical PET imaging of bone metastases: an automated radiosynthesis procedure

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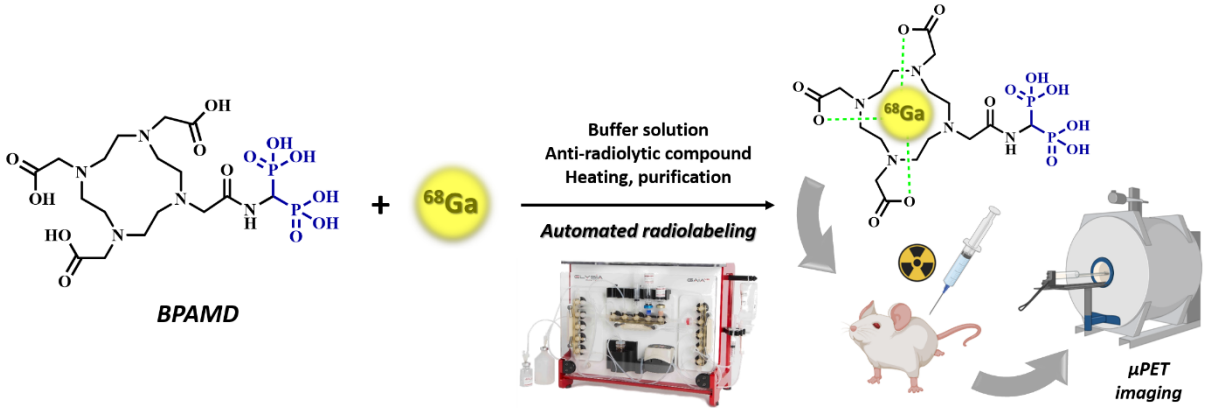
PO05

Bones are one of the most common sites for metastasis, especially for prostate, breast and lung cancers.[a] Thus, early and accurate noninvasive diagnosis of skeletal metastases is essential in the management of these diseases. For this purpose, bisphosphonates are well-known bone-targeting imaging agents. Recently, DOTA-conjugated bisphosphonates have been of particular interest for their potential theranostic applications,[b] depending on the radioelement associated with them (β^- emitting radioisotope for therapy or β^+ emitting radioisotope for diagnostic). Specifically, the DOTA-containing bisphosphonate BPAMD is currently used for both preclinical and human applications, especially for ^{68}Ga PET imaging.[c] To ensure efficient, robust and repeatable ^{68}Ga radiolabeling, automation of this process is possible via a synthesis module.[d] We have therefore developed an automated radiolabeling procedure of BPAMD with ^{68}Ga on the GAIA/LUNA® automaton. A study on the influence of several parameters involved during radiolabeling was conducted and rapidly highlighted that a SiO_2-coated reaction vial was needed for proper radiolabeling. Ammonium acetate 0.2 M pH 5 buffer allowed >95% radiochemical purity (RCP) with no further purification. The addition of an anti-radiolytic compound such as gentisic acid did not show a significant effect on RCP over time. Quality controls appeared to be a critical point and required extensive study. Thus, a radio-HPLC method that took advantage of standard available C18 column was set up, using sodium hydrogen phosphate dihydrate 0.08 M plus *N,N*-dimethylhexylamine 0.03 M at pH 3 as the mobile phase. Radio-TLC procedure using a mixture of acetylacetone, acetone and HCl 30% (10:10:1) as the mobile phase and silica 60 F254 TLC plates as the stationary phase allowed sufficient discrimination of ^{68}Ga-BPAMD and radioimpurities. The bone tropism of the imaging vector thus produced will finally be controlled on a xenografted mouse model.



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Development of serological tests of response to infections by bioluminescence

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PO06

The monitoring of seroprevalence against SARS-CoV2 in the population during the COVID-19 pandemic was performed at the Institut Pasteur from 2020 to 2022 for Santé publique France and Médecins sans Frontières using the development of an ELISA-type plaque immunoassay in which the enzyme is a luciferase and the probe a VHH or nanobody.
The luciferase resulting from the optimization by directed mutagenesis of the catalytic domain of a luciferase from a deep-sea shrimp allows a detection sensitivity in femtomolar and a quantitative measurement of the concentration over 5 to 6 orders of magnitude. It catalyzes the decarboxylation of a heterocyclic substrate in the presence of oxygen and releases a carbon dioxide. No ATP is required. 182 different substrates have been synthesized and tested for improving the activity.
Luciferase is produced in tandem with the heavy chain variable domain (VHH) of the antibody specific to the constant domain (Fc) of the immunoglobulin to be quantified in the sample. The expression of this construct in *Escherichia coli* allows to produce with one liter of culture enough reagent to produce more than one million tests, with a cost 150 times lower than with antibodies produced in eukaryotic cells. The tests are performed in multi-well plates, which can be robotized at a rate of up to 2300 per hour per reader.
We are continuously improving by mutagenesis the affinity of VHH for IgG, IgA and IgM constant domains to have robust and sensitive assays according to the responses sought a few days or several weeks after infection.

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Synthesis and evaluation of a natural antiviral cyclopeptide	***PO07***

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Arboviruses are viruses that are transmitted to humans and other animals through the bites of infected arthropods, such as mosquitoes, ticks, and sandflies. Some common arboviruses include dengue, Zika, and Chikungunya. This viruses can lead to major epidemics with the potential for high death rates in humans.
There are several factors that can contribute to the rise of arboviruses. One factor is the increasing prevalence of urbanization and global travel, which can facilitate the spread of arboviruses from one region to another.[(a)] Climate change may also play a role in the spread of arboviruses, as changes in temperature can affect the distribution and abundance of arthropod vectors.[(b)]
In this context, we realised a screening on Zika virus using the library of plant extracts of ICSN. We were able to isolate and identify a new peptide which has proven to have a high antiviral activity. This new molecule shows low toxicity to cells and strong antiviral activity against the chikungunya, dengue, Zika, Ross River, and SARS-CoV-2 viruses which are positive-sense, single-stranded RNA viruses. Its potential target has been identified.
Our goal is to synthesize this peptide and various analogs to enhance its antiviral activity, physicochemical properties, pharmacokinetics, bioavailabilty and metabolic stability.

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Novel pleiotropic compounds for the treatment of Alzheimer's disease : 5-HT$_4$ receptors inhibitors with antioxidant properties

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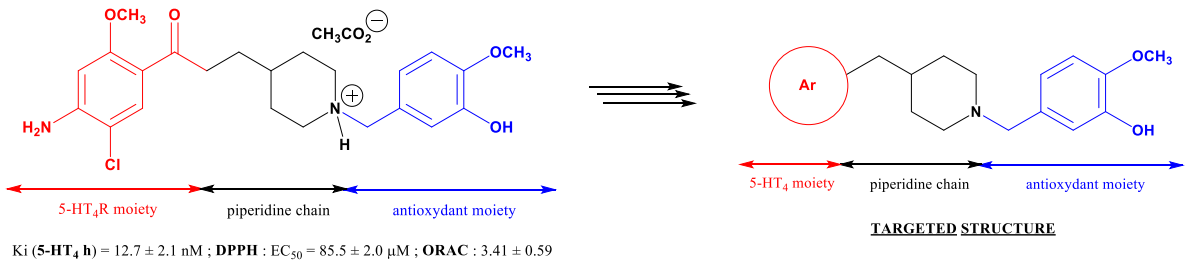
PO08

Alzheimer's disease (AD), the main form of dementia, affects more than 50 million people worldwide.[1] The formation of amyloid plaques is one of highlighted molecular causes. On the other hand, researchers have correlated these aggregations with oxidative stress by overproduction of reactive oxygen species (ROS) which lead to the neuronal death.[2]

The multifactorial nature of AD permits the emergence of a new pharmacological approach: the Multi-Target-Directed Ligands (MTDL) strategy.[3] It consists in developing single molecules able to act on several targets. Then, some compounds with antioxidant properties and able to prevent the formation of amyloid plaques could be promising. For this last target, we focus on the 5-HT$_4$ receptor (5-HT$_4$R) whose the activation with partial agonists promotes the non-amyloidogenic cleavage and so decrease the charge of amyloid.

Some preliminary works highlighted first compounds with this dual activity.[4] From a well-known 5-HT$_4$R scaffold (aminochlorobenzophenone), we have connected different antioxidant scaffold. These two moieties are linked with a piperidine chain, essential for the 5-HT$_4$R activity. Among these MTDL, the isovanilline group appears to be the best compromise for the dual activity.



Ki (**5-HT$_4$ h**) = 12.7 ± 2.1 nM ; **DPPH** : EC$_{50}$ = 85.5 ± 2.0 µM ; **ORAC** : 3.41 ± 0.59

In this present work, we perform the reverse work: we have kept the isovanilline moiety for the antioxidant part and we have connected different 5-HT$_4$ scaffolds or commercial benzoic acids with the aim to obtain MTDL. First description of these molecules together with *in vitro* evaluation will be presented in this communication.

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Design of β-glucuronidase-sensitive albumin-binding prodrugs with high DAlbR for cancer chemotherapy.

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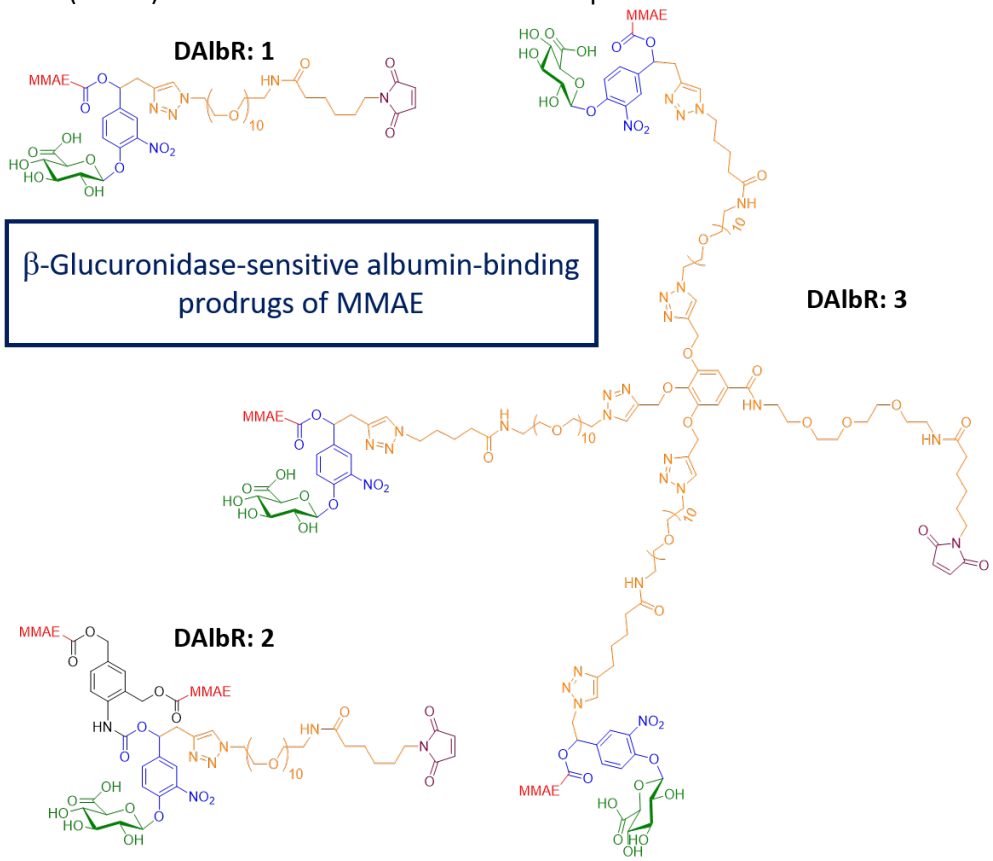
PO09

The selective delivery of anticancer drugs in tumor tissues is an emerging therapeutic strategy that limits side effects usually associated with conventional chemotherapy. Within this framework, we introduced the concept of β-glucuronidase-sensitive albumin-binding prodrugs that target the specificities of the tumor microenvironment. Once in the blood stream, such prodrugs bind covalently to plasmatic albumin and accumulate passively in tumors where extracellular β-glucuronidase triggers the release of the active compound. Recently, we evaluated the therapeutic efficacy of a set of β-glucuronidase-sensitive albumin-binding prodrugs of the potent MMAE possessing different Drug to Albumin Ratio (DAlbR). The results of these studies will be presented.



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Synthesis and study of new aminoalcohol-quinolines as potential antimycobacterial drugs.	***PO10***

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Human pathogenic mycobacteria are classified into two major groups: *M. tuberculosis* complex such as *M. tuberculosis* and Non-tuberculous Mycobacteria (NTM). According to their growth rate, NTM are divided in two categories: slowly growing mycobacteria (SGM) and rapidly growing mycobacteria (RGM). NTM are ubiquitous (water and soil) and opportunistic for patients with chronic respiratory diseases such as cystic fibrosis or chronic obstructive pulmonary disease (COPD). The incidence of NTM infections has been increasing worldwide surpassing that of tuberculosis. NTM such as *M. avium complex* (MAC, SGM) and *M. abscessus* (RGM) can cause various infections, most often pulmonary diseases (65%).[(a)] Current NTM treatments are not necessarily adapted because initially designed to cure *M. tuberculosis*. Unfortunately, these one is less active or inactive against NTM. Moreover, the increasing of azithromycin as anti-inflammatory drug in cystic fibrosis, bronchiectasis or COPD led to select macrolides resistant NTM strains.[(b)] As for tuberculosis cure, NTM treatments require the association of several antibiotics which can cause many side effects, for a long period (12-24 months). For example, the cure of sensitive *MAC* complex infections requires the association of macrolide, ethambutol and rifamycin during at least 12 months after sputum conversion. Moreover, treatment is not well effective as success rate of *MAC* treatment is between 52 to 60%. It is therefore urgent to design antimycobacterial drugs more adapted to treat NTM infections, less toxic and more efficient to decrease the treatment duration and fight resistant strains. Mefloquine is an aminoalcohol-quinoline used to treat malaria and that also has an activity against NTM.[(c)] In the context of NTM treatments, the selectivity index (SI) of mefloquine is too low and requires the pharmacomodulation of the quinoline core. Recently, we developed a first series of mefloquine analogs more active (MIC = 2-16 µg/mL vs MIC = 32 µg/mL for *MAC*, MIC = 9 µg/mL vs MIC = 85 µg/mL for *M. abscessus* R and S)[(d)] that mefloquine. However, SI and physico-chemical properties (lipophilicity and solubility) of these compounds can still be improved. Thanks to the poster of the session, the synthesis and the study of physico-chemical properties of new aminoalcohol-quinolines as antimycobacterial compound will be discussed and the perspectives presented.

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Repositioning of FDA-Approved drugs to interrogate Acyl-CoA synthetase long chain family member 4 (ACSL4) in ferroptosis

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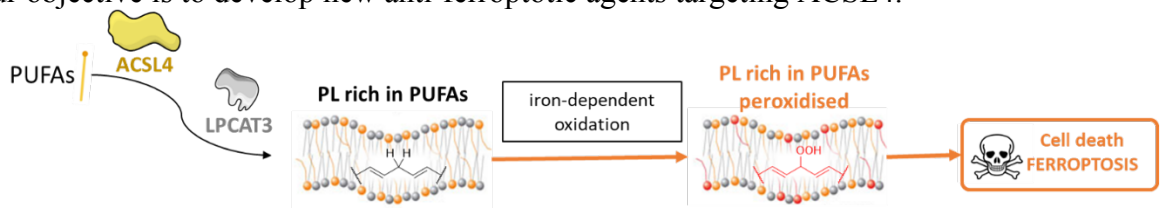
PO11

The regulation of cell death is essential for the development of the organism and the maintenance of tissue homeostasis. Thus, a dysfunction of this process contributes to the progression of many diseases. In recent decades, several forms of regulated cell death (RCD) have been identified. Among these new RCDs, the Brain Biology & Chemistry team (BBC, UMR-S1172) is particularly interested in ferroptosis, an iron-dependent RCD characterized by the accumulation of lipid peroxides to toxic levels.[a] Several studies have highlighted the important contribution of ferroptosis in neurodegenerative diseases such as Parkinson's disease, opening new therapeutic perspectives in the potential treatment of these pathologies. Acyl-CoA synthetase long chain family member 4 is a key enzyme in ferroptosis execution. In this context, our objective is to develop new anti-ferroptotic agents targeting ACSL4.



We developed a robust screening cascade with orthogonal biophysical and biochemical techniques to identify original human ACSL4 inhibitors. By screening an FDA-approved drug library, we were able to identify and validate new inhibitors with micromolar-range activities against ACSL4.[b] The best hit significantly reduced lipid peroxidation and ferroptosis in cells, demonstrating that it is a valuable starting point for a medicinal chemistry program. Current work focuses on improving the ACSL4 inhibitory activity and anti-ferroptotic activity of identified hits, while moving away from their initial pharmacological activity.

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Access and modulation of pyrrolo[2,3-*d*][1,2,3]triazoles using a Regioselective Multicomponent Cyclisation and cross coupling reactions

PO12

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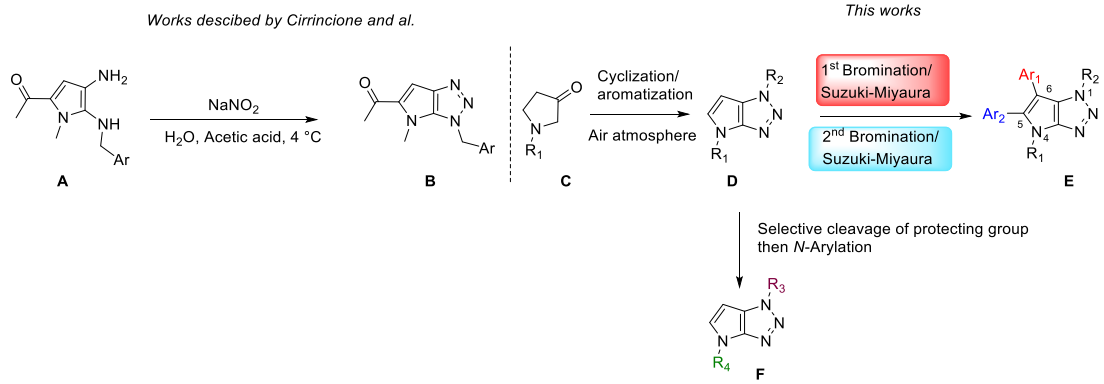
Pyrrole and triazole derivatives are powerful moieties to elaborate drugs which are used in various areas of medicine.[1] For these reasons, their introduction in medicinal chemistry programs has grown, in particular in the context of molecular diversity and innovative chemical space research.[2] These two small heterocycles have been fused in bicyclic systems[3], nevertheless, the literature reports only one example of these two cycles combined together in a [5:5] fused ring to access benzylated pyrrolo[2,3-*d*][1,2,3]triazoles of type **B**.[4] To date, no method is available to introduce the chosen substituents in *N*-*1*, *N*-4, *C*-5, and *C*-6 positions. This lack of references and methods induces a gap in the exploration of the chemical space and prompted us to search for novel and efficient strategies from a unique versatile platform towards highly diversified structures in a minimum number of steps.

In order to introduce a wide range of functional groups, a solution consists in building a library of pyrrolo[2,3-*d*][1,2,3]triazole platforms **D** from commercially available 3-pyrrolidinone **C** patterns using a regioselective MCR cyclisation sequence and then elaborating its selective functionalization using arylation procedures.



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A semi-synthetic pathway to SUMOylated protein mimics

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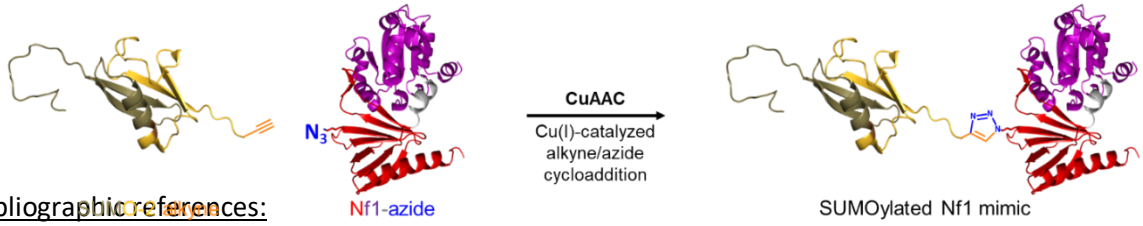
***PO*13**

Post-translational modification (PTM) lead to high proteome diversity and play a major role in regulating protein function. Small Ubiquitin-like Modifiers (SUMO) are a family of small proteins involved in an essential PTM, called SUMOylation. This modification consists of the formation of an "isopeptide" amide bond between the C-terminus of the SUMO and the lysine side-chain of a target protein. SUMOylation regulates many key cellular processes and its dysregulation is strongly correlated to several pathologies as recently demonstrated in neurofibromatosis type 1, a disease caused by the mutation of neurofibromin 1 (Nf1).[(a)] The study of SUMOylation is very laborious. Indeed, the isolation of the modified protein is compromised by the sensitivity of the isopeptide bond to hydrolysis by SUMO proteases. Moreover, *in vitro* enzymatic SUMOylation is very difficult to control. In order to overcome these problems and to decipher the role of SUMOylation in neurofibromatosis, we opted to synthesize a stable mimic of SUMOylated Nf1 through copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction, using a synthetic SUMO-2 protein functionalized with an alkyne at its C-ter and recombinant Nf1 protein containing an unnatural azido amino acid (see scheme). The triazole formed is an excellent mimic of the isopeptide bond[(b)] and is fully stable to the hydrolysis by proteases.[(c)] During an initial synthesis of the SUMO-2 protein by native chemical ligation (NCL), which is the gold standard in chemical protein synthesis, we faced a side reaction: the formation of an aspartimide on SUMO-2.[(d)] Aspartimide is formed by the attack of a nitrogen atom of the peptide backbone on the side chain of an aspartate, and this by-product is troublesome as it can affect the physico-chemical, structural and functional properties of the protein. Oddly, its formation during NCL has barely been reported. We demonstrated that aspartimide formation during NCL was likely a common phenomenon, and we developed a general methodology to overcome it. We have successfully synthesized the native SUMO-2 protein and the derivative containing the alkyne function.[(e)] CuAAC-mediated SUMOylation was first carried out on a model peptide, and further application to Nf1 is ongoing.



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Cardiac and renal toxicity of some new diclofenac hydrazone metal-complexes

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***PO*14**

Introduction: Complexes with aryl-acetic structure, hydrazone derivatives were evaluated from a toxicological point of view. The study was carried out in collaboration with the collective of the "Advanced Center for Research and Development in Experimental Medicine". The purpose of the histopathological examination is to highlight any damage to the main organs produced as a result of the administration of certain substances. In the single-dose toxicity evaluation, after the 14-day observation period, the animals who received a dose of 430 mg/kg body weight and those in the control group were euthanized and their heart and kidney were harvested for histopathological examination. **Material and methods:** The conduct of the study was carried out according to the legal provisions in force developed by FELASA and the EU, transposed in the national legislation through ANSVSA and with the favorable opinion no. 3939/12.02.2020 of the U.M.F. Research Ethics Commission "Grigore T. Popa" Iasi. At the end of the experiment, all the animals were fasted overnight and then euthanasized. The heart and the kidneys were removed. The tissue samples were fixed and specifically processed for paraffin embedding. The sections were stained with hematoxylin and eosin and examined by light microscopy. **Results:** The microscopic exam of the myocardium samples from the control group and the tested group showed a normal morphology, without histopathological alterations. The control group revealed a normal histological aspect of kidney. The second group (copper complexes) presents some tubular dilatations and necrosis of tubular epithelium. The third group (zinc complexes) presents a distinct hyperemia, dispersed in intertubular areas and a moderate tubular epithelium degeneration, while the last group (nickel complexes) reveals a reduced degeneration of tubular epithelium. **Conclusions:** The purpose of the histopathological examination was to test the toxicity, by highlighting the anatomical-clinical and cytohistopathological changes produced by the administration of complexes with the hydrazone structure. At cardiac level, no significant differences in cytohistopathological changes were found in the groups treated with all the studied compounds compared to the control group. Following the histopathological examinations performed on the kidneys, the lesion aspects were of low to moderate intensity in the cytohistopathological changes in the groups treated with the tested compounds compared to the control group.

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Discovery and optimization of new antiviral compounds, inhibitors of the main protease of SARS-CoV-2.	***PO*15**

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The Covid-19 pandemic caused by the coronavirus SARS-CoV-2 has led to more than 6 million deaths worldwide. Currently only few specific antiviral treatments against coronaviruses are available and there is a high risk of emergence of new viruses of this family in the future[(a)]. Thus, effective small molecules with broad spectrum antiviral activity are urgently needed to fight Covid-19 and potential emerging coronaviruses.
The project started in march 2020 in the U1177, aims to develop novel molecules that have the potential to target an essential component for the replication of coronaviruses in order to identify, a therapeutic weapon that is both capable of treating Covid19 but also fighting emerging coronaviruses in the near future.
In this context, the 3CL protease, a highly conserved protease within the coronavirus family and essential to the viral cycle, has been chosen as a promising therapeutic target[(b)]. A high throughput screening of a chemical library of 90,000 compounds was performed in the laboratory on the 3CL protease of SARS-CoV-2 and led to the identification of several chemical series, including the N-Acyl-benzimidazole series which has been optimized.

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Development of new polymeric nanocarriers loaded with Curcumin and Pioglitazone and the antioxidant activity evaluation

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***PO*16**

Introduction. In recent years, the research on new nanosystems developing that contain two or more substances with synergistic action as therapy in different diseases has received increasing attention. Diabetes is one of the most serious chronic diseases, which is considered an important public health problem and a social-economic one due to the increased prevalence from last decades. Oxidative stress plays an important role both in the onset of diabetes and in the progression of this disease through the following ways: development of tissue insulin resistance, β-cell dysfunction, impaired glucose tolerance, and mitochondrial dysfunction. Curcumin (Cur) has a polyphenolic structure which gives it a unique antioxidant activity. Unfortunately, Cur is characterized by chemical instability, low water solubility, low oral absorption and short half-life. Pioglitazone (Piog) is an efficient hypoglycemic therapeutic agent but with a low oral absorption, low solubility and short half–life. **Aims**. In this study were developed new chitosan nanoparticles (CsNPs) loaded with Cur and Piog from the desire to increase their bioavailability and to have a synergistic action, being a potential diabetes therapy. Also, it was thoroughly investigated in vitro antioxidant activity of these nanosystems to determine the free radical scavenging properties. **Materials and methods**. CsNPs loaded with Piog, Cur, Piog with Cur were obtained by ionic gelation method by varying the concentration of chitosan (CS), tripolyphosphate, pH of CS solution, stirring speed, reticulation time and the concentration of the active drug. The free radical scavenging activity (RSA) of these formulations was determined by three methods DPPH•-RSA, ABTS•-RSA and •OH-RSA. **Results**. The best formulation that led to stable particles with a diameter of approximately 250 nm was obtained using CS 0.1%:TPP 0.1%-3:1, Tween 80%-0.05, 30 min sonication and rotation speed 1400 rpm. The values obtained within the three methods that test the scavenger activity of free radicals, values expressed in RSA%, showed a improvement of the antioxidant activity of Cur and Piog by formulating as CsNPs compared to their ethanolic solutions. The average values of DPPH•-RSA, ABTS•-RSA and •OH-RSA for CsNPs loaded with Cur and Piog are 68.23%, 78.23% and 91.53%, respectively compared with the values obtained for ethanolic solution of Cur and Piog 42%, 63% and 86,62%, respectively. The remarkable antioxidant activity of CsNPs loaded with Cur and Piog can be explained by the small size of the nanoparticles that provide a large contact surface of these substances with free radicals facilitating the RAS of these biomolecules.

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PROTAC technology: a promising tool to develop new cytotoxic molecules in ovarian cancer	***PO*17**

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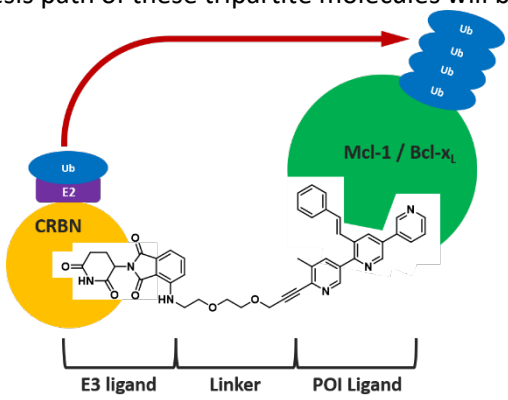
Ovarian cancer is one of the most lethal cancers in women. The poor prognosis of this cancer is due to its low-level evolution, late discovery, resistance to treatment and lack of specific therapies. The current standard treatment consists of cytoreduction surgery followed by chemotherapy using taxane and platinium salt derivatives. However, two new targets of interest are emerging which could overcome the observed resistance phenomenon: Mcl-1[(a)] and Bcl-x_L[(b)]. Furthermore, it has been shown that dual inhibition can lead to better results in terms of cytotoxic activity.[(c)] Thus, the goal is to design a dual inhibitor of Mcl-1 and Bcl-x_L. However, because of their multi-organ localisation, their inhibition results in platelet and cardiac toxicity. [(d), (e)]

In order to avoid these toxicity problems, PROTAC (PROteolysis TArgeting Chimeras) technology is an interesting tool.[(f)] This technology changes the paradigm of the target-receptor model accepted in pharmacology. Indeed, PROTAC uses the cellular machinery, the proteasome, to degradate target proteins and no longer inhibit them. This would make it possible to reduce amounts of compound to reduce undesirable effects.

A synthesis work was initiated in order to develop PROTAC targeting proteins of interest (POI) for the treatment of ovarian cancer: Mcl-1 and Bcl-x_L. First, we should develop a ligand which targets both Mcl-1 and Bcl-x_L. Then, we have to select an E3 ligase ligand to allow the ubiquitination of the targeted proteins in order to achieve their degradation. Finally, these two moieties have to be connected thanks to a linker. Design and synthesis path of these tripartite molecules will be described in the poster.



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Fabrication and evaluation of carboxymethyl guar gum based composites as wound healing dressings	**PO18**

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Summary

The progress of intelligent regenerative approaches towards wound healing will continue to grow in the upcoming years with particular attention on bioactive potentialities and sustainability. Biopolymers, credited to be highly biocompatible, biodegradable and with anti-inflammatory, antimicrobial, hemostatic, cell proliferative and angiogenic activities, are explored for centuries in the fabrication of wound dressings. Currently, numerous studies reported different derivatives of biopolymers[(a)], namely alginate, cellulose, chitosan, collagen, hyaluronic acid and silk fibroin, already applied as wound dressing vehicles in clinical practice. Nevertheless, the achieved favorable results also paved the way towards wound healing without any undesired outcome based on interdisciplinary approaches. To help this problem, we aimed to report the fabrication and characterization of sodium trimetaphosphate cross-linked carboxymethyl guar gum and chitosan networks for faster wound healing application. Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy studies, scanning electron microscopy (SEM) and X-ray diffraction (XRD) were used as analytical techniques for characterization of the wound dressing networks. The prepared scaffolds were evaluated for the carboxyl content and swelling ratio. In vitro release and biodegradation studies were performed in simulated biological fluids. In vivo wound healing studies were carried out for 21 days. In this study we observed a faster wound healing effect within the studied period of the carboxymethyl guar gum and chitosan networks when compared with an alginate commercial dressing.

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Peptidomimetic tools targeting the Vascular Endothelial Growth Factor for anti-angiogenesis therapy

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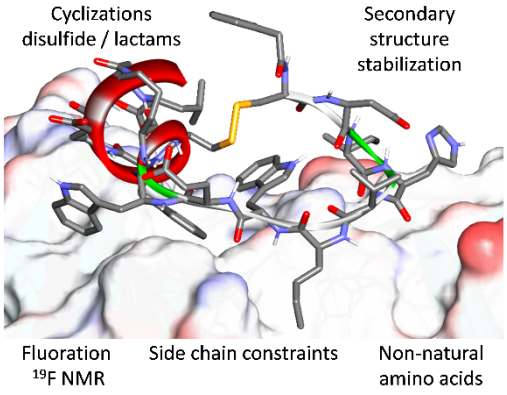
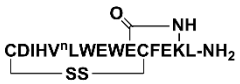
***PO*19**

Angiogenesis is the biological process of formation of new vessels from pre-existing ones. The VEGF (Vascular Endothelial Growth Factor) and its membrane receptors VEGFRs are among the most important actors in angiogenesis. Pathological deregulation of angiogenesis results in a large number of diseases. VEGF ligands are currently used to treat ocular diseases such as wet age-related macular degeneration (AMD) and several types of cancers. The current available VEGF ligands used in the clinic are macromolecules derived from recombinant proteins, like antibodies (bevacizumab, ranibizumab) and receptor fragments (aflibercept) [1]. However, antibodies suffer from poor penetration capacity of biological barriers requiring parenteral administration, high production cost, and variable half-lives. Therefore, our objective is to develop small peptide ligands of VEGF with designed properties that could overcome the drawbacks of antibodies.



Optimization of small peptide ligands of VEGF



X-Ray structure of the peptide at the electrostatic surface of VEGF (PDB 6ZCD)

In the project, starting with a small monomer peptide (15 amino acids, 2 kDa) [2] several structural modifications of the parent peptide will be made to increase its affinity and its resistance to proteolysis in serum: additional cyclization, alkylation of amide bonds and use of non-natural amino acids. This approach will be supported by molecular modeling studies, and the affinity for VEGF will be measured by calorimetry (ITC). Moreover, the anti-angiogenic properties will be evaluated in cell-based assays.
Preliminary results will be presented on the synthesis of new peptides incorporating non-natural amino acids.

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Discovery of novel Glycogen Synthase Kinase 3β inhibitors to combat tauopathy and neuroinflammation in Alzheimer's disease

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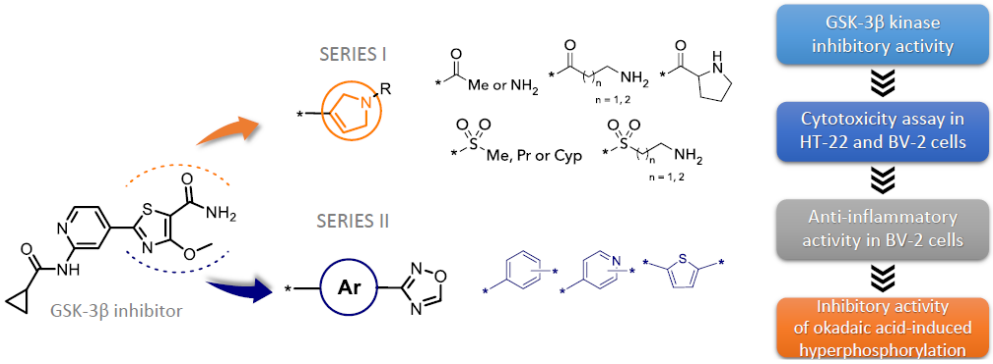
***PO*20**

Alzheimer's disease (AD) is an incurable neurodegenerative disorder and one of the leading causes of death. AD has a multifactorial pathogenesis, in which neurofibrillary tangles (NFTs) and profound neuroinflammation are of particular importance. NFTs are formed of hyperphosphorylated tau protein oligomers and disrupt the axonal transport system. Furthermore, misfolded protein aggregates activate microglia, initiating an immune response by releasing pro-inflammatory mediators that further contribute to disease progression. Glycogen synthase kinase 3β (GSK-3β) activity is upregulated in AD which leads to hyperphosphorylation of the microtubule-associated tau protein, resulting in microtubule destabilisation and neurite degradation[1]. Inhibition of GSK in LPS stimulated monocytes results in increase of anti-inflammatory IL-10 and decrease of pro-inflammatory IL-6 or TNF-α[2]. Therefore, an inhibitory strategy towards GSK-3β is an interesting approach in the search for anti-AD treatment.

In our research, we focused on the development of 2 series of novel GSK-3β inhibitors with *N*-(pyridin-2-yl)carboxamide moiety. Synthesized compounds were evaluated *in vitro* in the Kinase-Glo™ luminescence assay, followed by *in cellulo* anti-inflammatory activity in BV-2 cells and okadaic acid-induced hyperphosphorylation model. Received outcomes will allow for a deeper exploration of GSK-3β kinase modulation in terms of future anti-AD treatment.



This research was funded by National Science Center, Poland grant No. 2019/34/E/NZ7/00090

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Synthesis and characterization of some new complexes of 2-arylpropionic acid derivatives with β-cyclodextrin.	***PO21***

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Introduction. Cyclodextrins are one of the most used host macrocycles and in the last years there has been a growing interest for their use in pharmaceutical field, cosmetics, food or environmental engineering due to bioadaptability and multi-functional features. The most important properties are the formation of inclusion complex that change water solubility or bioavailability, preventing undesired interactions between drugs or improving the toxicological profile. β-cyclodextrin has a hydrophilic external part enriched with OH groups and relatively hydrophobic internal cavity that allows the entrapment of mainly hydrophobic compounds making it excellent carrier for many drugs. Inclusion complexes with non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in literature. Most of these molecules contain both hydrophilic and hydrophobic groups (amphiphilic) and are slightly soluble in water. 2-(4-(2-methylpropyl)phenyl)propanoic acid (ibuprofen) is one of the most common NSAID that is used to treat inflammation or pain having a sparingly solubility in water. Also, some derivatives of ibuprofen with thiazolidin-4-one structure proved to have a potential analgesic and antiinflammatory profile but a low solubility.

Aim. The main objective of the research project was the development of drug delivery systems based on cyclodextrins and new ibuprofen (NSAID) derivatives with thiazolidin-4-one structure as potential therapeutic agents and thereby to improve their water solubility.

Materials and methods. Thiazolidin-4-one derivatives of ibuprofen were included in β-cyclodextrin complexes by co-precipitation (1:1 M) and lyophilization methods. The inclusion complexes were characterized using spectral methods such as infrared analysis (FTIR), NMR spectroscopy and phase solubility studies. Also, the surface morphology was studied using scanning electron microscopy.

Results and conclusions. 4 complexes based on cyclodextrins and originally ibuprofen derivatives were obtained and characterized. These can confirm the theoretical premises for an improved pharmacological and safety toxicological profile.

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Design and synthesis of novel RNA ligands as inhibitors of oncogenic microRNAs production. **Police calibri 14, bold.**	***PO*22**

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Sequencing of the human genome has highlighted that the main part of the genome, approximately 70%, is occupied by non-coding RNAs [a]. During the last decade, stunning progress in the elucidation and understanding of the authentic functions played by these molecules has been established with a particular focus on microRNAs. With an average size of 23 nucleotides, these small RNA molecules play a crucial role in the negative regulation of translation of several genes through a complex and specific mechanism.

Unsurprisingly, altered regulation of microRNAs is strongly linked to the emergence and development of a wide range of lethal pathologies such as cancers. A relationship between tumor proliferation and microRNAs was quickly identified. Effectively, each type of cancer has a specific microRNAs fingerprint marked by the over-expression or deletion of certain miRNAs ensuring the development of significant resistance to treatment via oncogene promotion and stem cell maintenance (CSC) [b]. Being a true tumor biomarker, miRNAs are increasingly attracting attention as a key target in therapeutic interventions and drug development [c].

Our work focused on the design and the synthesis of small molecules that interfere with the biogenesis of oncogenic microRNAs playing a key role in cancer development, especially in cancer stem cells proliferation. Thanks to previously developed structure-activity relationships within the team, we were able to identify a hit based on a bis-thiazole heterocyclic backbone with two side chains that induces very promising biological results. Starting from this pharmacophore, we synthesized various modifications on both extremities to optimize the affinity and the selectivity for the target. Biological evaluations of the new derivatives are in progress, with intracellular testing planned as the next step. The results of these evaluations will allow us to better define the mechanism of action of these derivatives and to confirm their cell-based activity.

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Lead optimization and binding studies of a new diarylurea CXCR2 inhibitor as potent anticancer agent.	***PO*23**

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ELR+CXCL cytokines and their (C-X-C) chemokine receptors, mainly CXCR2, are known to be simultaneously involved in cancer cell proliferation, tumour inflammation, and angiogenesis, making them a highly desirable drug target. We recently described a new family of bioactive molecules, namely *N*-(benzo[d]thiazol-2-yl)-*N'*-phenylurea, interfering with this pathway, and demonstrating strong anticancer activities in vivo in an aggressive kidney cancer model. In the continuation of this work, we are currently optimizing the structure of this compound based on previously established structure-activity relationship (SAR), to enhance the anticancer activity and improve the pharmacological properties. Thus, two series of compounds are developed, by modification of two specific parts of the molecule: the substitution of the phenyl ring, and the replacement of the nitro by isosteric groups. All these compounds prepared were evaluated for their antiproliferative activities on a panel of cancer cell lines, then on 3D spheroid models.

In parallel, chemical probes derived from the lead molecule were synthesized to support the study of the mechanism of action of this family of compounds. They were designed based on a common intermediate, composed of the lead molecule grafted with a diethylene-glycol linker and bearing a terminal functionalizable amino group. First, a fluorescent probe was synthesized using 4-chloro-7-nitrobenzofurazan as fluorophore and used to localize the drug within the cell. Second, a photoaffinity labelling (PAL) probe using a diazirine reactive group was synthesized to identify the binding site on the secondary structure of CXCR2. A biotine-coupled probe is also planned to initiate proteomic studies to evaluate the binding selectivity *in cellulo*. The perspectives of this work are to develop an optimized lead compound to evaluate its efficacy in vivo in tumour growth inhibition models.

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PROTACs synthesis for cosmetics : selective cell extinction of estrogen receptors

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PO24

PROTACs are bivalent molecules able to inactivate a protein of interest (POI). Indeed, the POI ligand is linked to an E3 ligase ligand *via* a linker. In this way, the E3 ligase is able to recruit the protein complex which thenleads to POI ubiquitination and degradation by the proteasome. This strategy is particularly studied for the treatment of cancer (clinical trials are in progress) or for neurodegenerative or viral diseases.[1]

The originality of this project lies in the use of PROTACs in toxicology for the cosmetic industry rather than in therapeutic fields. Accordingly, our group is interested in the conception and the synthesis of PROTACs which target the estrogen receptor (ER), present in human skin cells.

Our main goal is to study the influence of chemical agents used in cosmetics and endocrine disruptors *in cellulo*. We can compare the cellular effects and the potential toxicity of these agents on knock-out cells for ER, with normal control cells. Thus, these PROTACs could be used as *in vitro* predictive tools in order to highlight the toxicity of the tested agents.

In this context, we have started the synthesis of original PROTACs from estradiol derivatives. Our objectives are to identify 1) the importance of the linker's position on the steroid, 2) which E3 ligase is the most efficient, 3) the biological activity in comparison with ER PROTACs already described in the literature.

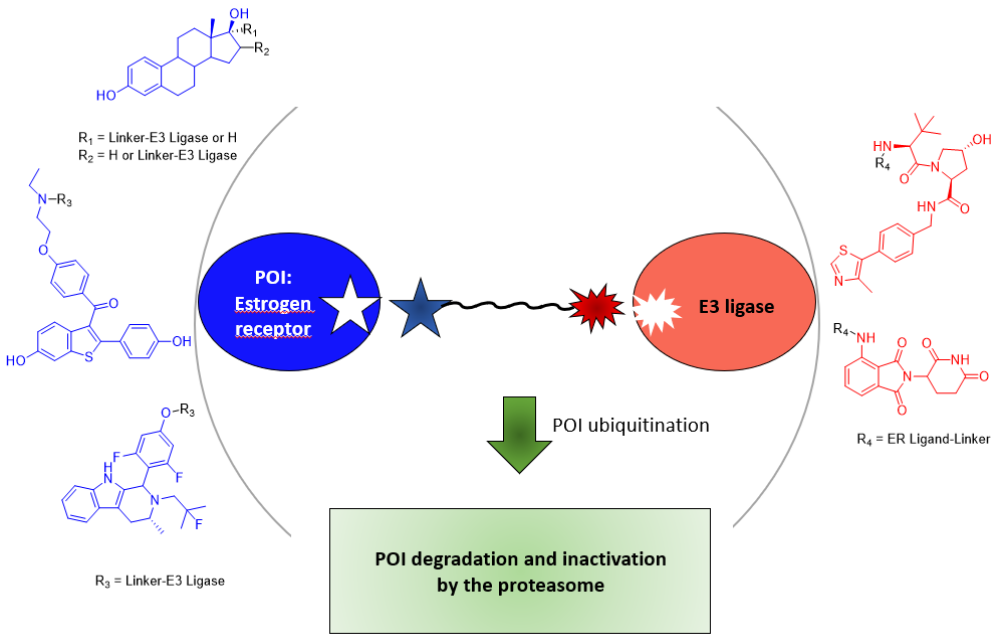

Figure 5 : General structure of expected PROTACs[1] *Nieto-Jiménez et al., Molecular Cancer* ***2022****, 21, 67*

Apoxidole Pseudo-Natural Products Inhibit Kynurenine Production in Cancer Cells.

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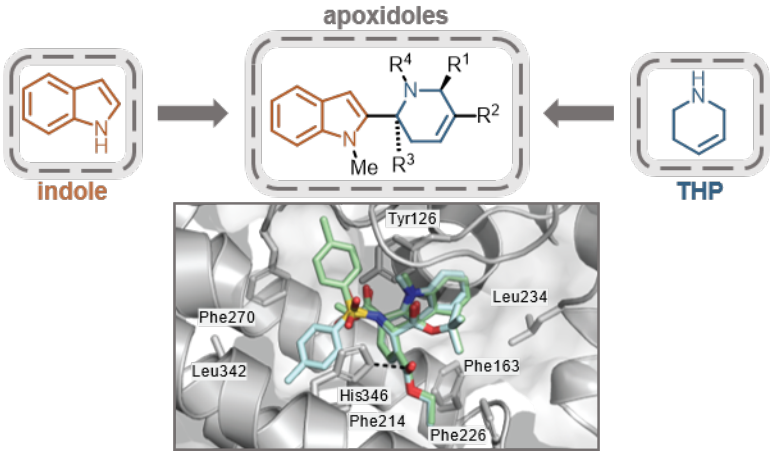
***PO*25**

Natural products (NPs) often serve as inspiration for the design of novel biologically active compounds, since they inherit diverse chemical scaffolds and their bioactivity is pre-validated by nature.[(a)] However, the diversity of NP-derived compound libraries is limited, e.g. by synthetic accessibility, leaving a gap between the NP- and drug-like chemical spaces. To overcome these limitations, the pseudo-natural product (PNP) approach combines NP fragments in *de novo* arrangements to yield biologically unexplored compound classes.[(b)]



We describe the development of apoxidole PNPs, in which indole and tetrahydropyridine (THP) fragments are connected in a mono-podal manner not found in nature.[(c)] The compound collection was investigated in various cell-based assays and gratifyingly, apoxidoles were found to selectively reduce kynurenine (Kyn) levels in cancer cells upon stimulation with the cytokine interferon-γ (IFN-γ). In-depth characterization revealed that apoxidoles inhibit the apo-form of the heme-containing enzyme indoleamine 2,3-dioxygenase 1 (IDO1). The tryptophan-catabolizing enzyme IDO1 is considered a relevant target in immuno-oncology.[(d)] It catalyzes the first and rate-limiting step of the Kyn pathway, in which imbalances can lead to immune suppression.[(d)] Whilst other IDO1 inhibitor types have failed clinical trials, apo-IDO1 inhibitors are still under late-stage clinical investigation.[(e)] Hence, new apo-IDO1 inhibitor chemotypes like apoxidoles are in high demand.

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Small molecules library screening to identify new molecular tools against SARS-CoV-2

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***PO*26**

A virus later known as SARS-CoV-2 spread across China late in 2019 causing a very contagious respiratory infection that shortly thereafter caused a pandemic, infecting more than 640 million people all over the globe (WHO - December 2022). Since the very beginning of the pandemic, both academia and industry directed most of their efforts through the identification of vaccines which effectively stemmed the infections. The access to vaccination and the emerging of novel SARS-CoV-2 variants pose a serious threat to the vaccine efficacy, therefore new drugs active against RNA viruses are still an urgent need. In this context, we planned to screen an in-house library of small molecules to evaluate the SARS-CoV-2 entry inhibition. The selected molecules were previously proved as antiviral compounds as entry inhibitors against other RNA viruses. [(a,b)] We then analyzed the effect of our compounds on SARS-CoV-2 entry stage. For this purpose, we firstly performed cytotoxicity of the panel of compounds on HEK 293T/ACE2 cells and Huh7 cells using Alamar Blue cell viability assay. We then generated a spike-pseudotyped lentiviral vector (LV) and an ACE2-expressing HEK 293T cell line with firefly luciferase as reporter gene. Then, cells were transduced using LVs in the presence of compounds at two different concentrations (5 and 0.5 μM). The percentage of transduction was evaluated by luminescence analysis (luciferase expression). Our screening selected the compounds RI26, RI94, RI95 4SMA, 10MG and 15MG as moderate inhibitors of SARS-CoV-2 entry. The most promising compounds were also tested against SARS-CoV-2, VSV and Coxsackie. Real-time PCR on both cells and supernatants of infected cells confirmed inhibition of SARS-CoV-2 infection, but not of VSV or Coxsackie virus. Some selected derivatives may be considered as lead compounds for future improvements aimed at COVID-19 treatment. Although this effect alone would not efficiently prevent SARS-CoV-2 infection, the dissection of how these compounds affect the cell metabolism and the subsequent MedChem optimization might lead to the generation of novel antiviral drugs against Coronavirus infections.

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Discovery of bioactive compounds that sensitize cancer cells to proteasome inhibitors.	***PO*27**

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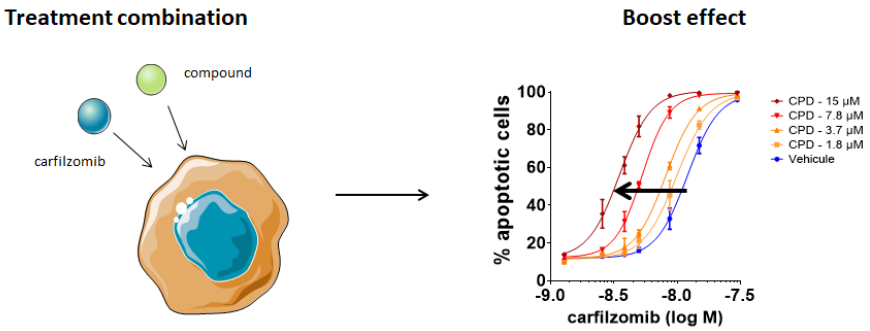
Despite recent progress in oncology, there are still unmet medical needs, and therapeutic combinations provide real opportunities to increase drug efficacy and to reduce side effects. In particular in multiple myeloma (MM), a disease of plasma cells, notable therapeutic progress has been made particularly through the introduction of proteasome inhibitors (PIs), like carfilzomib (CFZ), which led to increases in response and survival rates. However, although most cases of MM respond to cytotoxic therapy in initial as well as relapsed stages, responses are often partial and of short duration, requiring the validation of new modes-of-action and the development of more successful combination therapies.

Thanks to a phenotypic cellular assay, we have discovered original bioactive compounds that boosts dose-dependently the proteasome inhibitor-induced apoptosis in several cancer cell lines, as well as in primary patients MM cells. Furthermore, treatment of PI-resistant MM cells with the inhibitors overcomes their resistance to PI. To understand the mechanism by which the compounds increase the potency of proteasome inhibitors, we used different strategies based on the exploration of targets, transcriptome, proteome and phenotypes. In particular a transcriptomic analysis (RNA-seq) was performed at several time points after treatment and highlighted an integrated stress response leading to apoptosis.

This chemical series pave the way to new therapeutics to treat multiple myeloma



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In Vitro Anti-Denaturation Effects and Red Blood Cell Membrane Stabilization by Copper, Zinc and Nickel Complexes of some diclofenac hydrazones

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***PO*28**

Introduction: The studies on nonsteroidal anti-inflammatory drug (NSAIDs) complexation with metals have established that these drugs exhibit improved biological properties in comparison to free ligands or exhibit different biological activities than the parent. In this context we derivatized the free carboxylic group of diclofenac, a NSAIDs phenylacetic acid class, forming acyl-hydrazones. These compounds having a 2-OH group on phenyl are good ligands, forming complexes with metals bivalent: copper, zinc and nickel. The aim of the study was to evaluate the effects of the metal complexes derivatives on bovine serum albumin (BSA) denaturation induced by temperature and the capacity to stabilization the erythrocyte membrane in hypotonic solution. Frequently, these tests are used to study anti-inflammatory potential of the new compounds. Material and methods. In the BSA denaturation inhibition assay the samples were treated with 1% BSA (aqueous solution), incubated for 20 min at 37°C, then 5 min at 72°C, cooled for 10 min and then the turbidity of the samples was read at 416 nm against distilled water. In the Red Blood Cell membrane (RBC) stability assay, the compounds properties on stabilization the cell membrane was evaluated by determination the absorbance of the supernatant after treating the samples with 0.5 mL RBC solution (10% v/v), in presence of hyposaline solution (0.36% NaCl solution). Results and discussions. Both the BSA inhibitory capacity and the RBC membrane stability for the compounds studied were increased with the concentration, the best results were obtained for the concentration of 125 µg/mL and 111.11 µg/mL. In the inhibition of BSA denaturation assay the most active compound was a nickel complexe, R = 2,4-diOH, which was found to be 3 times more active than diclofenac. Another compound of nickel, R = 2-OH, was found to stabilized the RBC membrane being 4.9 times more active than diclofenac. Conclusions. The structural modulation of diclofenac at free carboxyl group has led to new hydrazone complexes that have proven anti-inflammatory potential evaluated by in vitro methods which opens new perspectives in the treatment of inflammatory diseases

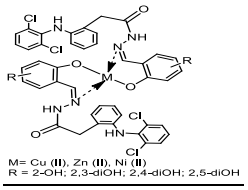

Fig. 1. The structure of complexes

Scientific research founded by the UMF "Grigore T Popa" Iasi, based on contract no. 10308/29.06.2020 and by the grant of UEFISCDI, PN III Program, AUF-RO, contract no. 28/2019.

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Preformulation studies for the development of transdermal pharmaceutical formulations usinging imidazole derivatives

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***PO*29**

Introduction: Currently, imidazoles are one of the most used pharmaceutical ingredients in antifungal therapy, however, to obtain the most effective results on Gram-positive germs, miconazole nitrate is preferred. The advantage of this imidazole is that it penetrates the stratum corneum and remains at this level for up to five days after administration. Transdermal is one of the most preferred by patients. Transdermal therapy uses polymeric films, representing an alternative to other medical products. Our study proposes the development of different types of dermal films containing cellulose derivatives such as HPC (Hydroxypropyl cellulose) FI, HEC (hydroxyethyl cellulose) FIII, or HPMC (hydroxypropyl methylcellulose) FII. **Material and methods**: Miconazole nitrate was purchased from Sigma Aldrich Inc. (Darmstadt, Germany). The three types of cellulose ether polymers were used as matrix formers in ultrapure water (Direct-Q water purification system Merck Millipore, Darmstadt, Germany). Auxiliary substances: propylene glycol from Scharlau Chemie (Barcelona, Spain), polyethylene glycol 400 and polysorbate 60 from Sigma Aldrich Inc. (Hamburg, Germany), ethanol from Stireco LTH (Buzau, Romania). After dermal film preparation, their physicochemical and mechanical parameters were evaluated (thickness, mechanical resistance, adhesion, water vapour absorption, water vapour permeability, and water vapour loss by desiccation). **Results:** 100 mg miconazole nitrate films were prepared, presenting the following characteristics: translucent white due to the suspended miconazole nitrate, a surface of 63.585 cm^2, 0.25 mm thickness. The preparation technique requires drying at a temperature of 40°C. The results of the water loss capacity show that the optimal film is the one based on HEC. The other two transdermal films based on HPMC or HPC confirmed the fact that the solvent did not fully evaporate, which requires another preparation method or changing the used solvent in the future. Adhesion capacity is one of the most important factors for skin application and subsequent release of the active substance. From the elongation point of view the formulation with HPMC presents the lowest values, whilst in terms of adhesion it presents the optimal values. **Conclusions:** In the case of the HPMC films, the water absorption, and water loss capacity, respectively, suggest that a longer drying time and an increased amount of plasticizer could improve tear resistance. The Films with HPC and HEC are more elastic and resistant to stretching which can promote them in the future as new transdermal pharmaceutical formulations with antifungal ingredients.

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THERAPEUTIC APPLICATIONS OF FERULIC ACID

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***PO*30**

The objective of the study: Ferulic acid is a phenolic compound that was first isolated in 1866 from the *Ferula foetida* resin (*Apiace-ae* family) and was later obtained by synthesis. In nature, ferulic acid is found both in free and conjugated form. Due to its antioxidant effects ferulic acid can be used in the prevention and the therapy of diseases induced by oxidative stress, including Al zheimer's disease, diabetes mellitus, cancer, hypertension and atherosclerosis. The strong link between inflamma-tion and oxidative stress suggests that ferulic acid can also be effective in the treatment of inflammatory conditions. Moreover, the specific ferulic acid structure also gives it a strong UV absorption capacity, making it a promising photoprotective agent. **THERAPEUTIC APPLICATIONS**: *Alzheimer's disease.* Alzheimer's disease is a chronic neurodegenerative disorder characterized by progressive cognitive dysfunctions and memory loss. The main role in the pathogenesis of this disease is the accumulation of beta-amyloid (βA), a peptide composed of 36-43 amino acids resulting from the amyloid precursor protein, by a proteolysis process under the action of β- and γ-secretases. Ferulic acid, through its antioxidant and anti-inflammatory properties, can have beneficial effects in Alzheimer's disease. *Neoplastic Disorders.* There are several factors involved in the pathogenesis of cancer, including chronic inflammation, excessive cell proliferation and/or apoptosis resistance and free radical formation. The proven ability of ferulic acid to regulate cell proliferation and growth, to remove free radicals, to stimulate cytoprotective enzymes and to inhibit cytotoxic systems in both in vitro and in vivo experimental models supports the potential adjuvant role of ferulic acid in cancer therapy. *Cardiovascular diseases.* Cardiovascular diseases worldwide are associated with a high mortality rate. Hypertension and atherosclerosis are the main risk factors in the development of cardiovascular disease and, consequently, blood pressure control is particularly important in reducing the incidence of these diseases. It was noted that 50 mg/kg of chronic treatment with ferulic acid resulted in an antihypertensive effect comparable to that obtained with 10 mg/kg captopril. Ferulic acid reduced left ventricular diastolic rigidity, attenuated the infiltration of inflammatory cells and the collagen deposition in the left ventricle. **CONCLUSIONS:** Our study revealed that ferulic acid and its derivatives prove to be very good antioxidants that can be used to prevent several diseases (Alzheimer's disease, neoplastic diseases, cardiovascular diseases, diabetes mellitus), and for photoprotection with a high safety profile and low financial costs. Some of the presented compounds promise wider practical applications in therapy, but clinical trials are still needed. **Keywords:** FERULIC ACID, OXIDATIVE STRESS, ANTIOXIDANT, THERAPEUTIC EFFECTS.

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Reactivity of Imidazolidine-4-thione Derived Enamines and Iminium Ions

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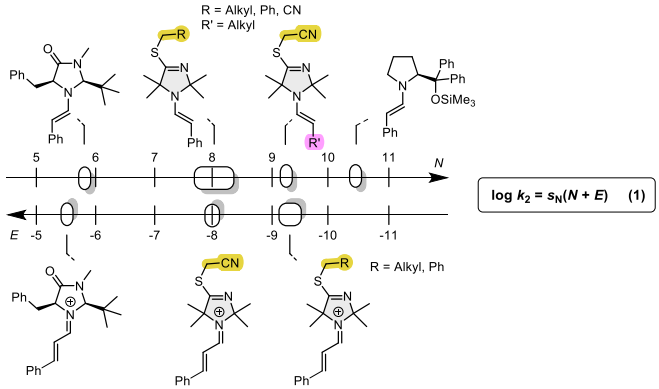
***PO*31**

Imidazolidine-4-thiones are structurally similar to MacMillan organocatalysts, but examples utilizing them as catalysts are rare in the literature.[1,2a] Only recently, it has been discovered that imidazolidine-4-thiones are efficient as catalysts in the alkylation of aldehydes by bromoacetonitrile under prebiotic early Earth conditions.[2] By following the kinetics of reactions between imidazoldinethione derivatives with reference compounds of known electrophilicity parameter *E* or nucleophilicity parameter *N* and s_N, the Mayr-Patz equation (1) can be applied to garner a better understanding of the reactive intermediates generated by these underexplored organocatalysts.



This presentation will be centered around the reactivity of the nucleophilic enamines and electrophilic iminium ions derived from imidazoldine-4-thiones, which will be compared to those derived for structurally related imidazolidinones (MacMillan) and proline-based systems (Hayashi-Jørgensen), whose reactivities have previously been characterized.[3] Quantification of the reactivity parameters of imidazolidinethiones will provide insight into how these organocatalysts promote organic reactions under both prebiotic and modern lab conditions.

Acknowledgement: This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 101024710.

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Mineral composition of some aromatic and medicinal plants used in Morocco

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***PO*32**

Abstract

Recently aromatic and medicinal plants (AMPs) have gained a lot of research interest. However, most of the works have been devoted to bioactive compounds and related biological activities; consequently, little is known about Moroccan AMPs mineral composition. Hence the originality of this work, which aiming at investigating the mineral composition of twenty AMPs belonging to 10 botanical family obtained from various Moroccan regions. Mineral composition was determined using an inductively coupled plasma optical emission spectrometer in various plant parts. Large variations were found in mineral content among the studied samples. Potassium, Calcium, Phosphorus, Magnesium and Sodium were found to be major elements. Iron, Manganese, Boron, Zinc and Copper were detected at minor levels. Most of the investigated plants were shown to be a good promising source of minerals. Important correlations were found among different minerals. These outcomes were confirmed by principal component analysis, which separate among studied plants and minerals through the first two principal components. According to obtained results, the studied plants could provide a new promising source of necessary minerals for human diet and other various applications.

Keywords

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In vitro photodynamic activity against Staphylococcus aureus of functionalized gold nanoparticles with pheophorbide α.	
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The aim of the study was to obtain novel gold nanoparticles (AuNPs) that were coated with PEG or SiO_2 and were used as vehicles for photosensitizer (PS) molecules - pheophorbide α. These complexes were then evaluated photochemically and also underwent antimicrobial activity tests against reference strain of Gram-positive bacteria *Staphylococcus aureus.* The potential additive effect was also examined between AuNPs and the pheophorbide dye.

The absorption spectra of the functionalized AuNPs with PEG and pheobride showed two maximas at 410 nm and 667 nm wavelength and a smaller peak at 525 nm caused by AuNPs alone. The longer end of the absorbed electromagnetic wave being within the therapeutic window, meaning that the 667 nm wavelength can efficiently penetrate human tissues and excite PS without causing harmful effects. (Diagram 1) Photochemical evaluation indicated that the type of polymer attached to AuNP had influence on singlet oxygen efficiency. The maximum being 65% for the PEG 10k polymer and the minimum was 62% for the PEG 2k. In the antimicrobial activity tests researched systems were illuminated by 3 different wavelengths 405, 525 and 660. The best performance of the developed PSs systems was observed after irradiation at a wavelength of 660 nm. The hybrid mixture Au-NPs@PEG-SH with pheophorbide α indicated the highest bactericidal effect exceeding 5.8 log reduction in growth. The dye alone had a slightly lower reduction effect around 5 log. The highest reduction upon illumination at 525 nm was only 2 log suggesting that photochemical processes were significantly more contributed than photothermal ones in the antimicrobial effectiveness of the researched complexes.

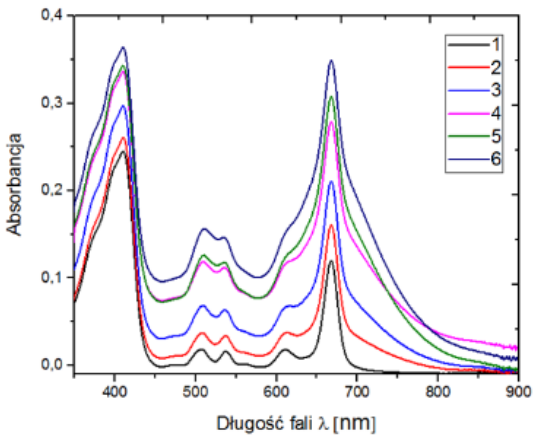

Fig. 1 Absorption spectra of hybrid mixtures consisting of pheophorbide α (constant concentration 1.65 · 10^{-6} M) with different concentrations Au-NRs@PEG-SH 10 k ((0, 1.33, 2.66, 4.00, 5.33, 6.66) · 10^{-11} M listed as spectra 1-6)

According to evaluation the obtained systems may predispose as worth developing candidates in medical treatment of superficial, nosocomial infections.

Synthesis and anticancer activity of new ivermectin derivatives

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***PO*34**

Ivermectin (**IVR**) is a 16-membered lactone belonging to the group of avermectins, i.e. compounds isolated in 1967 from the *Streptomyces avermitilis* strain (**Figure 1**)[(a)]. **IVR** exhibits a broad spectrum of antiparasitic properties and is used to treat a wide variety of diseases (e.g. river blindness, elephantiasis, or scabies)[(b)]. Satoshi Ōmura and William Campbell were awarded the 2015 Nobel Prize in Physiology/Medicine for the discovery and development of **IVR**.

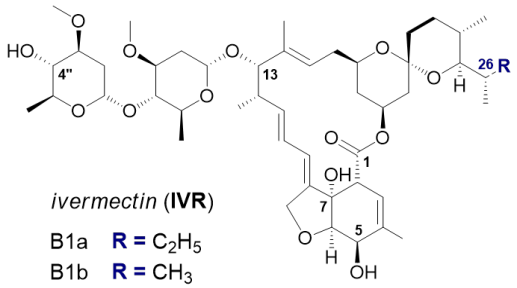

Figure 1. Chemical structure of ivermectin.

Recent studies have shown that **IVR** exhibits high anticancer activity against various cancer cell lines, including glioblastoma, leukemia, pancreatic cancer and colorectal cancer, making it an interesting drug to be repurposed for anticancer therapy[(c, d)]. The anti-cancer mechanism of action of **IVR** is very complicated and involves many different biochemical processes[(d)]. However, the literature lacks reports on the anticancer activity of **IVR** derivatives. Therefore, a series of derivatives of **IVR** was synthesized. Designing new analogs was focused on the C13 position of the **IVR** to determine how the presence or absence of a sugar substituent would affect the anticancer activity of this compound. Then, in cooperation with biologists, the antiproliferative activity of the obtained derivatives was determined on various cell lines.

The research was funded by the Polish Ministry of Education and Science as part of the Diamond Grant project, number 0159/DIA/2020/49.

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Elucidation of structure-fonction relationships of LRRK2/phosphatase complexes in Parkinson's disease	***PO*35**
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Neurodegenerative diseases represent a major public health issue that needs to be addressed. Among them, Parkinson's disease (PD) is considered as the most common motor pathology. Recently, the gene coding for leucine-rich repeat kinase 2 (LRRK2) has emerged as one of the major determinants of PD in both sporadic and familial forms.(a) Under physiological conditions LRRK2 is a multiphosphorylated protein associated with neuroprotective effects and involved in cell morphology and vesicular trafficking. In contrast, under pathological conditions, LRRK2 mutations lead to an underphosphorylated protein associated with neurologic detrimental effects. Targeting LRRK2 cellular pathways is currently considered one of the most promising strategies for the development of PD modifying therapies. (b)

Preliminary work of our team has shown that this process is mediated by the protein phosphatases such as PP2A (c), (d), (e), (f). Our goal is therefore to target the LRRK2/phosphatase interaction in order to restore the basal, neuroprotective threshold of LRRK2 phosphorylation. Thus, our studies allowed us, thanks to a PEPSCAN strategy carried out in collaboration with UTBS of Paris, to identify several PP2A peptides ligand of LRRK2. My work was to develop, characterize and confirm the binding affinity of these peptides from PPP2CA and PPP2R2A with LRRK2 full lengh recombinant, by microscale thermophoresis as biophysical method of interaction.

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Targeting Ribosomal Maturation to Develop Inhibitors for Antitumor Purposes

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***PO*36**

Ribosomes are the cell's huge ribonucleic machinery in charge of synthesizing protein from mRNA. Ribosome synthesis increases in cancer cells to cope with a rise in protein synthesis and sustain unrestricted growth. Ribosome biogenesis has recently emerged as an effective target in cancer therapy. Fap7 (also named hCINAP for human species), which is an assembly factor could engage in the cytoplasmic cleavage of small ribosomal subunit by interacting with Rps14. Depletion of Fap7 causes the defect of small ribosomal rRNA maturation which suggests the indispensable role of Fap7/Rps14 complex in ribosome synthesis [1]. Additionally, Fap7 also regulate the degradation of tumor suppressor p53 by directly binding Rps14 through RP-HDM2-p53 pathway. The disrupting the interaction of Fap7 and Rps14 could activate p53 to suppress the growth of tumor [2].

Based on the structural information of Fap7/Rps14 complex, the C-terminus of Rps14 is crucial for their interaction. In order to disrupt the interaction of Fap7/Rps14 complex, a series of peptide analogues of C-terminus of Rps14 is designed to bind Fap7 competitively. In addition, there is a ADP binding site nearby the C-terminus of Rps14 binding pocket [3]. Therefore, bisubstrate inhibitors that connecting ADP analogue and Peptide analogue were designed for the better activity and specificity. HTRF assay was utilized for the affinity test for all the inhibitors.

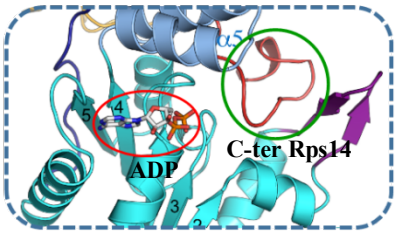

Fig 1. ADP bind Pocket & C-terminal Rps14 binding site in aFap7

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Novel Bioactive Xylofuranosyl Isonucleoside Analogs Containing Triazole and Guanidine Motifs

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***PO*37**

The development of structures analogous to nucleosides and nucleotides has attracted a significant interest in (bio)organic and in medicinal chemistry due to their propensity to interfere with nucleos(t)ide-dependent biological events that are crucial for life as well as for the progress of various diseases. The anticancer and antiviral efficacies of nucleos(t)ide analogs are demonstrated by the various examples of such compounds approved as anticancer and antiviral drugs,[(a)] while their antimicrobial potential has been well reported.[(b)]

Strategies for the design of nucleos(t)ide analogs include simple modifications at purine, pyrimidine or at ribose/2-deoxyribose moieties, the use of other nitrogenous heteroaromatic systems or other glycosyl units, the installation of phosphate group mimetic motifs or modification on the type or location of the bond connecting nucleobase and sugar.

In this communication the synthesis and biological evaluation of a variety of 5′-isonucleoside analogs constructed on xylofuranosyl templates and comprising a 1,2,3-triazole moiety and/or a guanidine group is reported. The triazole motif was envisaged as a surrogate of a nucleobase and it was also connected to a phosphonate, phosphoramidate, or a phosphate moiety to establish new potential and rather stable neutral mimetics of the diphosphate system. The synthetic methodologies used azido xylofuranoses as precursors and employed key steps such as azide-alkyne 1,3-dipolar cycloaddition, phosphorylation, Arbuzov reaction, N-glycosylation, or guanidinylation.

Biological assays revealed the therapeutic interest of some molecules, with compounds showing significant inhibition of acetylcholinesterase, potent antiproliferative activity in a breast cancer cell line or potent effects against the Gram-positive bacterial pathogen *Streptococcus pneumoniae*, with activities comparable to those of reference drugs.

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Targeting phenotypic variation to enhance tuberculosis treatment	
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Mycobacterium tuberculosis is the bacterium responsible of the tuberculosis. It is very resistant and can adapt fast to its environment making it one of the most dangerous bacterium[(a)]. Thus, it is appropriate to find a countermeasure to face this resistance by targeting proteins which are involved in these processes[(b)]. It has been demonstrated, through the literature and bio-assays realized by our collaborator in Pasteur Institute, that the protein TBNAT (TuBerculosis arylamine N-AcetylTransferase) is associated to the deactivation of Isoniazid (INH) in resistant bacteria, one of the four drugs from the actual treatment, by acetylation of the terminal amine. Various antibacterial drugs are based on quinolones and more precisely on fluoroquinolone scaffold (Ciprofloxacin, Moxifloxacin) which were a basis for our choice of structure[(c)]. Thus, several novel 1,10-phenanthrolinone derivatives were synthesized, tested and have shown some interesting activity on the bacterium[(d)]. Those phenotypic assays were completed by molecular modelling with docking of our molecules of interest in TBNAT to better understand the mechanism of the protein and compare it with INH. Results from this study will allow us to refine our structure to get better activity and physical properties.

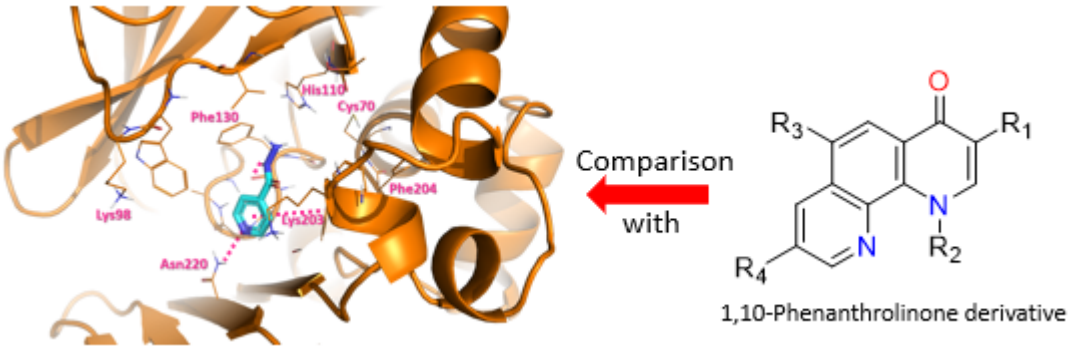

Figure 1: *Docking of INH on TBNAT (left) and general structure for 1,10-Phenanthrolinone (right)*

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Design and synthesis of 11β,13-dihydrolactucopicrin and lactucopicrin analogues and their biological evaluation against *Mycobacterium tuberculosis*

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***PO*39**

Sesquiterpene lactones (STLs) are a large group of naturally occurring terpenoids characterized by a fifteen-carbon (C15) backbone. They are most commonly found in plants of the Asteraceae family, especially in chicory, that accumulate these secondary metabolites mainly in their roots[a]. Of particular interest is that several biological activities have been reported for some chicory derived STLs, including antimicrobial and antifungal activities for lactucopicrin (Lp)[b], anti-adipogenesis effect for lactucin (Lc)[c] and analgesic and sedative properties for lactucin, 11β,13-dihydrolactucin (DHLc) and lactucopicrin[d]. Further studies on the biological potential of chicory derived STLs and analogues are however challenging as only four of these molecules (Lc, DHLc, Lp, DHLp) are commercially available (as analytical standards), and to date there are no published or patented simple extraction-purification processes capable of large scale STLs isolation. Our presented work describes a novel three-step large scale extraction and purification method for the simultaneous purification of both 11β,13-dihydrolactucin and lactucin, as well as isolation of STL-rich fractions containing 8-deoxylactucin, 11β,13-dihydro-8-deoxylactucin, lactucopicrin and 11β,13-dihydrolactucopicrin. The two pure STLs are subsequently used in the context of semi-synthesis to generate analogues for biological evaluation as antitubercular agents. In addition, other described chicory STLs that are not commercially available were also synthesized to serve as analytical standards, including lactucin-oxalate and 11β,13-dihydrolactucin-oxalate. Together, this work will help facilitate the evaluation of the biological potential of chicory derived STLs and their semisynthetic analogues.

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STUDY ON MOLECULAR MODELING OF SOME NEW ADENOSINE MONOPHOSPHATE ACTIVATED PROTEIN KINASE (AMPK) ACTIVATORS

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***PO*40**

AMPK acts as a sensor that detects energy levels inside the cell. It consists of three subunits in eukaryotic cells; α is the catalytic subunit, β and γ are the regulatory subunits. The catalytic module contains a typical eukaryotic kinase domain (KD) and β subunit known as the carbohydrate-binding module (CBM) (1,2). Between these two modules there is a site for AMPK activators (3).

With AMPK activation, catabolic pathways such as fatty acid oxidation, glucose uptake, glycolysis, autophagy, and mitophagy are activated, anabolic pathways such as protein synthesis, fatty acid synthesis, sterol synthesis, glycogen synthesis, gluconeogenesis are inhibited (4). While AMPK is allosterically activated by AMP, it is also activated in various conditions such as starvation, hypoxia, intoxication, and inhibition of the mitochondrial respiratory chain, where cellular energy is consumed (5).
These important roles in cell metabolism have made AMPK a target for small drug molecules, from metabolic diseases to cancer.

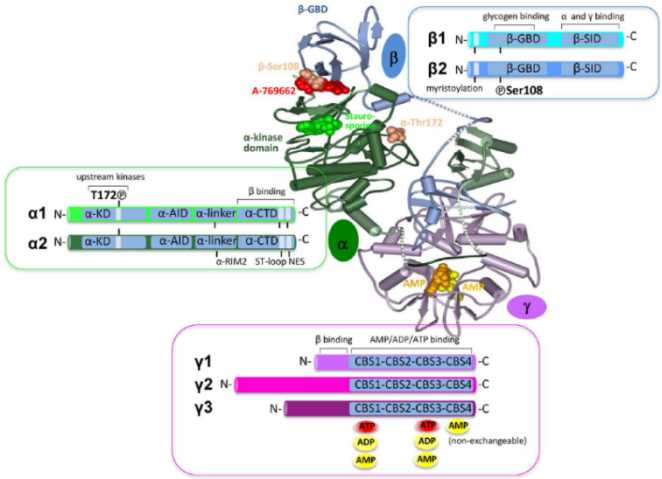

Figure. Structure of AMPK (2)

Some molecules have been discovered that will allosterically activate AMPK (1) and also mediate the CBM-KD interaction, thus providing active conformation for KD. Biphenyl ring system draws attention in these compounds (6,7). Inspired by the importance of AMPK in cell metabolism, design and molecular docking studies of new AMPK activators bearing chromone core and biphenyl pharmacophore was carried out in this study.

Acknowledgements: This study was supported by a grant of TUBITAK (220S193)

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Hit-to-Lead development of brain-permeable IRE1 inhibitors for an adjuvant therapy in glioblastoma

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***PO*41**

Glioblastoma (GB) is the most frequent and malignant primary brain tumor. Its highly infiltrative nature and aggressiveness leads to systematic failure of currents therapeutics with a median survival of 15 to 18 months post-diagnosis. Signaling by the inositol-requiring enzyme 1 (IRE1), a bifunctional serine/threonine kinase, has been identified **as a pro-survival adaptative mechanism** playing an instrumental role in several cancers[(a)]. This pointed toward IRE1 as an appealing therapeutic target in oncology as an adjuvant treatment and as such, studies have reported promising results when IRE1 inhibitors are used alongside standard chemotherapies[(b, c)]. Our group established the relevance of targeting IRE1 in GB and we showed in GB mouse models that **IRE1 inhibition results in reduced tumor aggressiveness and increased sensitivity to temozolomide** (TMZ), the reference chemotherapy agent in this cancer[(d)].

However, known IRE1 inhibitors are incompatible with passive permeation of the blood-brain barrier (BBB)[(c)], which is a significant concern to treat GB. This observation led us to identify and develop a new inhibitors series (Z4P) which display a good BBB permeability and showed very promising results *in vivo* on a xenograft mice model (Fig. A)[(e)]. **The structure-activity relationships (SAR) study and the hit-to-lead process around our hit compound represent the core of this medicinal chemistry project**.

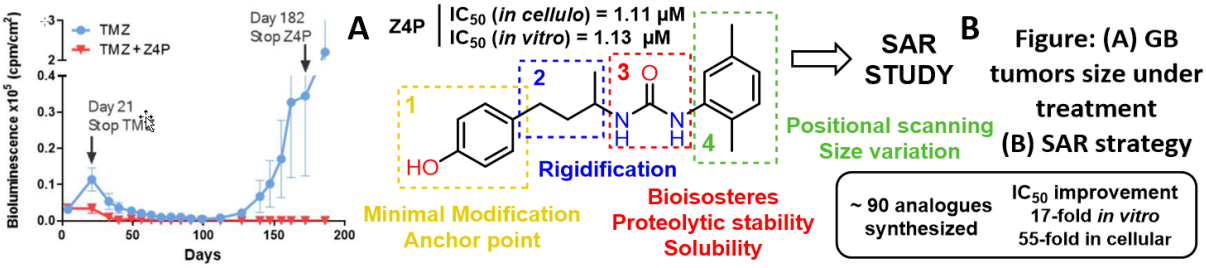

Figure: (A) GB tumors size under treatment (B) SAR strategy

Supported by molecular modelling and cheminformatics tools, we initially synthesized a first library of analogs to define the SAR (Fig. B). This allowed us to access active molecules at the nanomolar range both in *in vitro* and in cellular models. Our current aim is now **to develop lead-like compounds displaying improved binding affinity, kinase selectivity and ADMET properties.** The crystal structure of the best leads in complex with IRE1 cytosolic domain is also ongoing.

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A new avenue to fight Alzheimer's Disease: Playing the serotonergic piano with pleiotropic compounds

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***PO*42**

Alzheimer's disease (AD) has been described for the first time more than a century ago and its molecular causes are now the subject of a relative consensus around the hyperphosphorylation of the TAU protein and the aggregation of the ß-amyloid (Aß) peptide into neurotoxic oligomers.

5-HT_6R is a valuable target of therapeutic interest in AD. The inactivation leads, in particular, by inhibition of the mTOR pathway, to procognitive effects observed in rodents (Figure 1). 5-HT_6R antagonists are also able to promote, via a decrease of GABA levels, the 5-HT concentration in the brain. As a result, 5-HT_6R antagonists have shown positive effects against the memory disorders affecting these animals. The serotonin transporter (5-HTT), on the other hand, has also demonstrated its interest as a target in the treatment of AD. Indeed, its antagonists, which selectively inhibit serotonin reuptake (SSRI) at the pre-synaptic level have also demonstrated their ability to reduce, after chronic administration, amyloid deposition and senile plaques in transgenic AD mice and also in humans. The increase in serotonin levels, that they otherwise induce in animal models of AD, allows them to exert a positive effect on the memory disorders these animals suffer.

The objective of this project is to design a pleiotropic drug candidate both able to inhibit 5-HT reuptake and selectively to antagonize 5-HT_6R. To our knowledge, such a compound has never been described before.
Starting from a hit, selected from the CERMN's chemical library, a first set of derivatives has been synthesized in order to establish the structure-activity relationships and improve the expected activities.

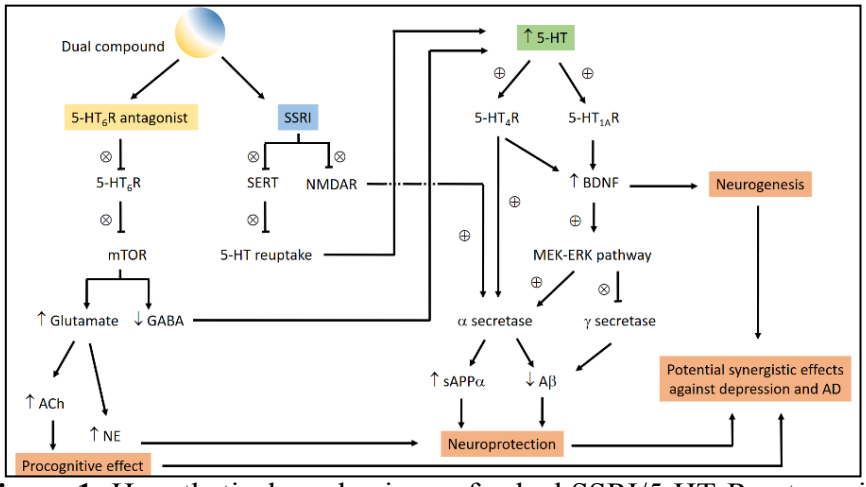

Figure 1: Hypothetical mechanisms of a dual SSRI/5-HT_6R antagonist

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Molecular modeling, design and synthesis of PROTACs as a new therapeutic approach for chemoresistant ovarian cancer.

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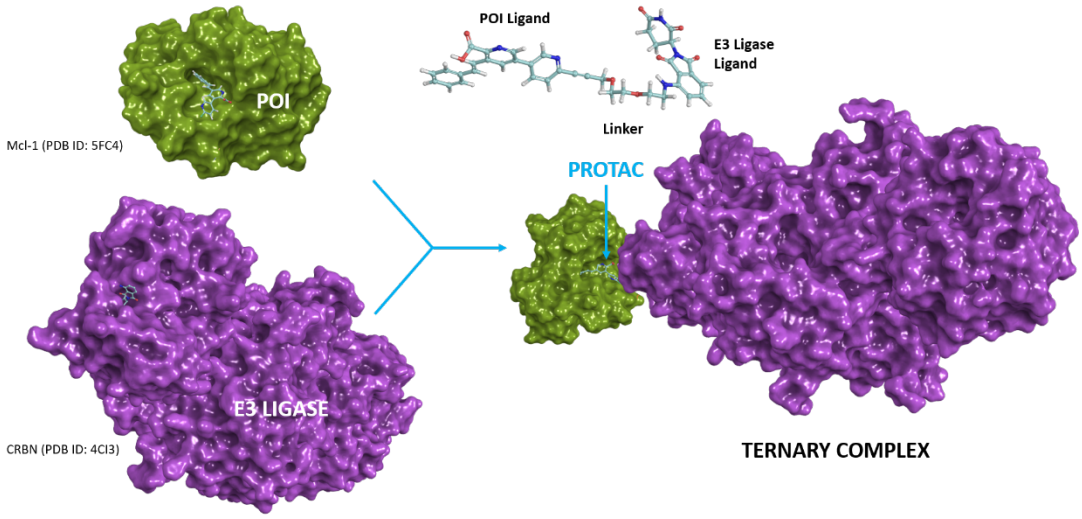
***PO*43**

Ovarian cancer is one of the most common gynecologic cancers that has the highest mortality rate. The diagnosis is often late and the cancers are thus at a too advanced stage, making therapeutic strategies ineffective. “Silent killer” is a name that has been given to this cancer.[(a)] Resistance to standart treatments constitutes the primary cause of therapeutic failure. It has been shown that cell survival depends largely on the overexpression of Bcl-x_L and Mcl-1. These two proteins are privileged targets to be inhibited to overcome resistance, and their simultaneous inhibition restores apoptosis.[(b)]

In order to achieve tissue selectivity and avoid toxicity, we chose to develop compounds that degrade concurrently these two proteins using PROTAC (PROteolysis TArgeting Chimeras) technology.[(c)] The pharmacodynamic activity is thus no longer linked to the number of occupied receptors, but is the consequence of the degradation of the target proteins. This effect is manifested at lower doses without non-tumor toxicity.

Our work is therefore to design and synthesise new PROTACs directed against Mcl-1 and Bcl-x_L. Molecular scaffolds used to start this work (analogues of Pyridoclax[(d)] and derivatives of azetidine molecules) have been studied in previous work of the research team and have shown interesting activities. Structure-activity relationship approaches and molecular modeling studies are carried out on these ligands to obtain the best synchronous activity. On the other hand, ligands of E3 ligases and different linkers of variable nature and length will be used to promote the formation of the ternary complex.



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Synthesis and biological evaluation of 6-substituted quinolines as *Escherichia coli* efflux pump inhibitors

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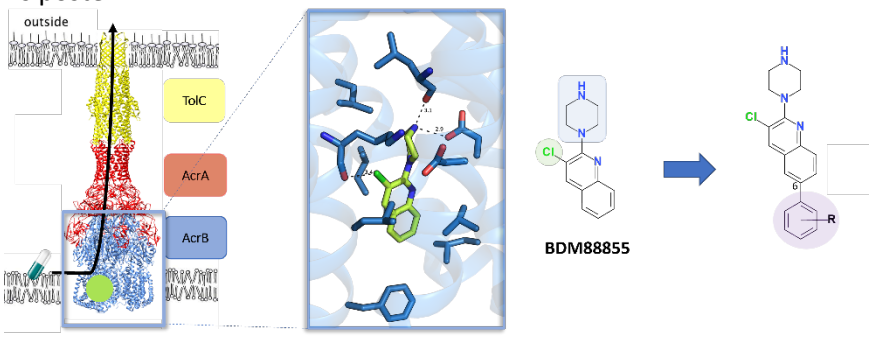
***PO*44**

Antimicrobial resistance (AMR) has become a major public health priority leading to 4.95 million deaths in 2019 and estimates predict 10 million annual deaths by 2050.[(a)] One of the most common resistance mechanism is the (over)expression of efflux pumps. The active transport of several classes of antibiotics from the bacteria to outside is mediated by these efflux pumps, in particular AcrAB/TolC which is mainly expressed by Enterobacteriaceae such as *Escherichia coli*.

To overcome AMR, the aim of the project is to develop AcrB inhibitors in order to potentiate the activity of a large panel of antibiotics. For this purpose, a screening of 1280 fragments was performed on *E. coli* in combination with a substrate of this pump and allowed the identification of a hit (BDM73185).[(b)]

The hit was then optimized to a more potent analogue with a quinoline ring (BDM88855). This compound was co-crystallized with AcrB and was shown to bind to a unique site on the transmembrane domain of this protein. The crystallographic structure confirmed also that the piperazine in position 2 is essential for activity, as well as the presence of a halogen atom (Cl, Br, I) in position 3. An unexploited region was observed at the bottom of the crystallographic structure, therefore, a phenyl ring, diversely substituted by electro-withdrawing or donating groups, and pyridine rings were introduced in order to improve the potency. The synthesis of these analogues and the corresponding biological results will be presented in this poster.



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Synthesis and biological evaluation of butyrylcholinesterase inhibitors to treat Alzheimer's Disease: a comparison of equine and human models.

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***PO*45**

Background

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder (ND) leading to the most common form of age-related dementia. Current drugs against AD are mostly acetylcholinesterase (AChE) inhibitors with only symptomatic effects along non-negligible side ones. Less affected by the neurodegeneration, butyrylcholinesterase (BuChE) is a new alternative target for the treatment of AD.[(a)] Considering AD multifactorial causes, the pleiotropic strategy which aims for multiple therapeutic actions within only one compound is intensely investigated nowadays.[(b)]

Aim

Pseudo-irreversible aryl-carbamate inhibitors like rivastigmine[(c)] act through transient carbamylation of BuChE. Our project is to dig deeper into this concept and design novel pleiotropic prodrugs[(d)] mimicking rivastigmine[(e)] and activated by BuChE to release a secondary active substance (AS) against AD. Such strategy would lead to a synergetic double therapeutic effect for the treatment of ND.

Enzyme models

The tools for this study are *h* and *eq*BuChE. These enzymes have a 90% sequence homology and considering the poor availability and high cost of *h*BuChE, *eq*BuChE has been widely used as a surrogate to evaluate the inhibition potency of AD drug candidates. It has already been showed on a few classical BuChE inhibitors that using *eq*BuChE can lead to biased results.[(f)] This work is aiming to identify the possible impact of BuChE form on the evaluation of pseudo-irreversible inhibitors.

Methods

The study consists in the *in vitro* evaluation on both BuChE of selected compounds. The inhibitory activity (IC_{50}) of these molecules are determined and their mode of action is investigated through the measurement of the enzyme stability by mass spectrometry and adapted enzyme kinetic studies that describe all aspects of the interactions. The results will be discussed displaying the differences between the two enzymes and giving our thoughts on the pending adequation of the *eq* model.

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Selenoether derivatives of 1,3,5-triazine in search of selective 5-HT$_6$ receptor ligands

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***PO*46**

In recent years, 1,3,5-triazine was established as promising chemical scaffold for development of potent serotonin 5-HT$_6$ receptor antagonists with potential application in treatment of neurodegenerative and neuropsychiatric diseases. In this study, a new series of 10 selenoether triazine derivatives (**1**-**10**, Fig.1) was synthesized and tested *in vitro* and *in silico*[(a)].

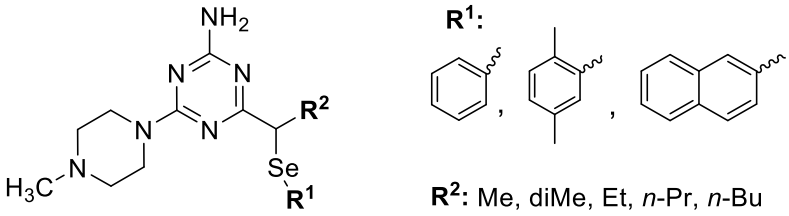

*Fig. 1 Structures of investigated compounds **1**-**10***

The compounds were obtained within 3-step synthesis, including Grignard reaction, alkylation and cyclic condensation. The affinities for 5-HT$_6$ and off target receptors were tested in the radioligand binding assay. Additionally molecular docking toward 5-HT$_6$ receptor was performed. The majority of tested compounds showed significant affinity towards 5-HT$_6$R (*Ki*< 100 nM) and satisfactory selectivity over the off-targets. SAR analysis allowed to identify the types of aryl substituents and linkers (branching) that are beneficial for the required potent action on 5-HT$_6$R.

Partly supported by the National Science Centre (grant UMO-2018/31/B/NZ7/02160). Part of the studies was performed within Student Medicinal Chemistry Club (Studenckie Koło Chemii Medycznej UJ CM w Krakowie).

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INDOLE-BENZIMIDAZOLE DERIVATIVES AS ANTIBACTERIAL AGENTS AND THEIR DOCKING PROFILES

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PO47

Staphylococcus aureus is one of the responsible pathogens causing the hospital infections that is characterised by skin and mucous membrane infections (1). Topoisomerase-II DNA-gyrase and Topoisomerase-IV catalyze the topological modifications in cell thus regulate cell survival. These enzymes become noteworthy targets for antibacterial drug discovery since they exist in bacteria strains and is absent from eukaryotic cells (2). In this study, we implemented design and synthesis of several indole-benzimidazoles (**1-11**) and probed their antibacterial activity on various bacteria strains. Furthermore, we analyzed the docking results of the most potent compound **3** and compared it to the standard compound Ciprofloxacin. The antimicrobial activity of compounds were determined against *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 9027, *Acinetobacter baumannii* ATCC 19606, *Klebsiella pneumonia* ATCC 18883, *Staphylococcus aureus* ATCC 29213, Methicillin Resistant *Staphylococcus aureus* (MRSA) ATCC 43300, *Enterococcus faecalis ATCC* 29212 with using micro-dilution method (3). AutoDock Vina 1.1.2. was used for the docking analysis (4). According to the antibacterial activity results, compound **3** had MIC value of 0.48 µg/mL on *Staphylococcus aureus* ATCC 29213 strain. This value was 31.2 µg/mL for MRSA ATCC 43300 and 62.5 for *Enterococcus faecalis ATCC* 29212, proving that this compound was selective for *S. aureus*. MIC value of Ciprofloxacin was 0.25 µg/mL for *Staphylococcus aureus* ATCC 29213. Using this standard in docking with DNA-gyrase and Topo-IV, higher activity of this derivative was spotlighted. As a result, this compound was able to bind to the active region of these enzymes with higher affinity (-8.1 kcal/mol for DNA-gyrase B subunit and -8.4 kcal/mol for Topo-IV) than that of Ciprofloxacin (-7.9 kcal/mol for DNA-gyrase B subunit and -7.3 kcal/mol for Topo-IV). The results of our study has gifted us a prominent candidate with favorable MIC value and good docking profile. This lead compound **3** has given us an idea for SAR studies and in the future we aim to utilize it for discovering novel agents against nosocomial infections that are caused by *S.aureus* strains.

Acknowledgements: This study was supported by a grant of TUBITAK (grant number: 213S037)

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Synthesis of T20K immunosuppressive cyclotide.	***PO48***

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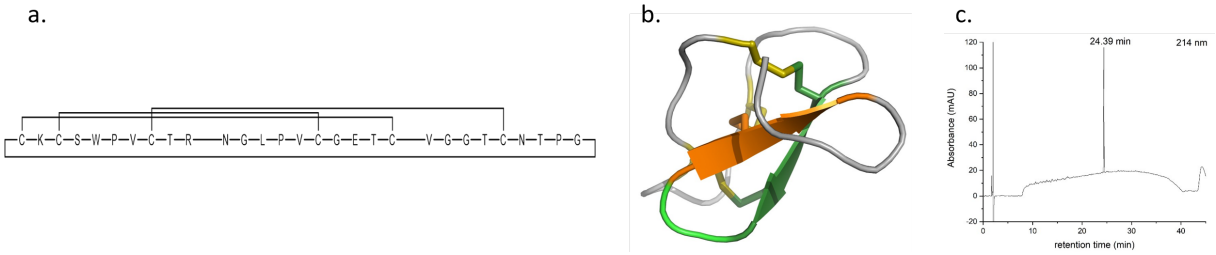
T20K is an immunosuppressive cyclotide derived from the naturally occurring plant peptide katala B1. It has been shown to suppress T-lymphocytes in an IL-2 dependent pathway.1 T20K is currently in phase I clinical trials for the treatment of multiple sclerosis (MS), a neurodegenerative disease driven by autoreactive T-cells.1 Besides interesting bioactivity, cyclotide T20K also features unique chemical features. It is a cyclic peptide composed of 29 amino acid residues, and 3 disulfide bonds, referred to as the cyclic cysteine knot motif (Figure 1) 2. These unique structural features confer a high chemical, enzymatic and thermal stability. This makes them good potential candidates for drug development e.g., molecular grafting and receptor ligand design. Here we describe the comparison of two synthetic strategies to produce T20K in sufficient quantities.



We chose to retro-synthetically disconnect cyclic T20K between Gly11-Gly12 for the first strategy, whereas second strategy involved Gly18-Cys19 retrosynthetic disconnection. For first strategy, side chain protected linear peptide was cyclized between Gly11-Gly12, whereas the second strategy took the advantage of native chemical ligation (NCL) to effect cyclization. Linear peptides were synthesized by Fmoc SPPS on an automated synthesizer. Upon cyclization, the peptides were folded under redox conditions to form thermodynamically stable T20K. HPLC analysis with the natural product confirmed the correct disulfide connectivity. This synthetic access to large quantities of T20K would help us elucidate its molecular mode of action in multiple sclerosis.

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Fingerprint approach using macrocyclic "chemical nose" sensors	PO49

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The biomolecular composition of body fluids are a direct reflection of severity and progression of diseased states. We aim to investigate a non-specific serum-based strategy, which mimics the human olfactory system for differential sensing, thereby generating a unique fingerprint tied back to the serum composition for disease diagnosis.

We developed a sensor array with cross-reactive synthetic receptors based on the host- guest interaction of triphenylamine derivatives(TPA) with the macrocycle Cucurbit[7]uril(CB[7]). The host-guest inclusion complex imposes a structural confinement on the TPA's and enhances their fluorescence intensity, while CB[7] provides diverse binding modes for generation of distinct fluorescent fingerprints upon interaction with biomolecules. This sensing strategy has been extended to a droplet-based microfluidic device to evaluate the array with reduction in sample volumes. Pre-existing cohorts of preeclamptic serum samples have been assessed and the generated fluorescence signatures along with available clinical and biological data will be processed by suitable statistical approaches such as supervised clustering by Linear Discriminant Analysis to obtain classifiers for PE occurrence and outcomes.

We have thus far been able to optimize the photophysical properties of the sensor array and generate fluorescence fingerprints to discriminate a diverse range of 17 protein analytes. The array has been tested for its ability to capture diversity in biofluids like serum and provide successful discrimination of the protein analytes in this complex media. The capacity of the chemical nose to discriminate between preeclamptic and non-preeclamptic patient samples has been evaluated with 17 serum samples to establish a proof of concept with 100% accuracy. The system has further been optimized on a dedicated droplet-based microfluidic platform with minimal utilisation of sample volumes, where the detected fluorescence output signal has been correlated with the initial droplet composition to provide discrimination of selected proteins analytes with 100% accuracy.

Herein, we developed a 'chemical nose' sensor for fingerprinting and pattern recognition of biomolecules. The ability of this system to detect changes in spectral signatures of serum will provide a new diagnostic methodology for complex diseases like preeclampsia and will enable us to propose a strategy for big data analysis based on chemical sensing and machine learning.

Green Suzuki-Miyaura cross-couplings in aqueous media involving O-electrophiles and air-stable nickel precatalysts

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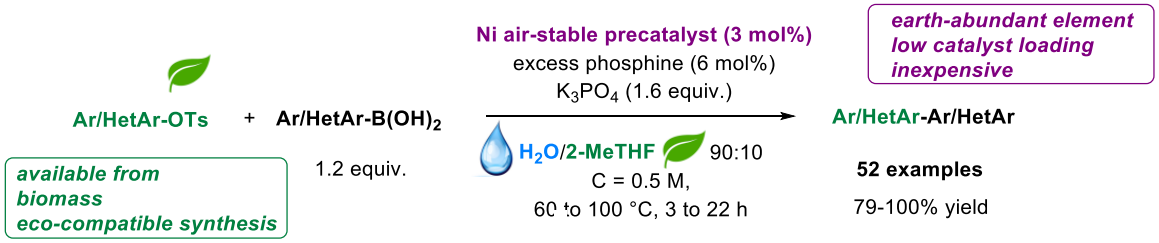
PO50

In the context of the sustainability-focused development plan outlined by the United Nations in 2015, the need for green and sustainable chemistry and engineering has been clearly identified as a major challenge. However, the lack of "green" manufacturing processes is an unsolved problem in major areas especially in organometallic catalysis. Hence, despite their exponential development, cross-coupling (C-C) reactions remain highly polluting by associating toxic organic halides to over-exploited low-abundant palladium (0.015 mg/kg earth crust) and organic solvents, which represent over 80% of the chemical waste of the chemical industry. [a] Although significant advances have been made in the field thanks to micellar systems, these works only focus on organic halides and none of them concern eco-compatible O-based electrophiles.[b]

For this reason, we have developed an eco-compatible Suzuki-Miyaura cross-coupling[c] which allows access to biaryl as well as heteroaryl compounds. The process combines a non-noble metal complex and sustainable O-based electrophiles in a green media composed of 90% water. In details, the association we have targeted gathers the use of:

- Aryl/heteroaryl tosylates, which represent a sustainable alternative to corresponding halides since they are readily available from biomass (phenols) and chemically stable and they can be synthesized in an eco-compatible manner.[d]
- An air-stable catalyst issued from "non-noble" abundant and inexpensive nickel (84 mg/kg earth crust). A low catalyst loading was utilized (3 mol%) and evaluation of residual nickel by atomic absorption spectroscopy (AAS) revealed amounts lower than 10 ppm.
- Aqueous reaction media composed of 90% water and 10% of a biosourced organic solvent (methyl tetrahydrofurane) for solubility issues for a significant reduction of chemical wastes (Scheme 1).



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Organoruthenium complexes as anticancer drug candidates.	***PO51***
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Half-sandwich complexes are of considerable interest in medicinal, material, and nanomaterial chemistry.[1] The design of libraries of such complexes with particular properties and reactivity is therefore a major quest. We have developed a strong interest in 16-electron ruthenium and osmium half-sandwich complexes based on a carborane ligand ([Ru/Os(η^6-*p*-cymene)(1,2-dicarba-*closo*-dodecarborane-1,2-dithiolato)]) and investigated their applications in biology,[2] and in the fabrication of nanomaterials.[3] Inspired by their intriguing chemistry in solution,[4] we have now extended the pool of 16-electron complexes and designed a new family of precious metal organometallics bearing dithiolatoaromatic ligands.[5]

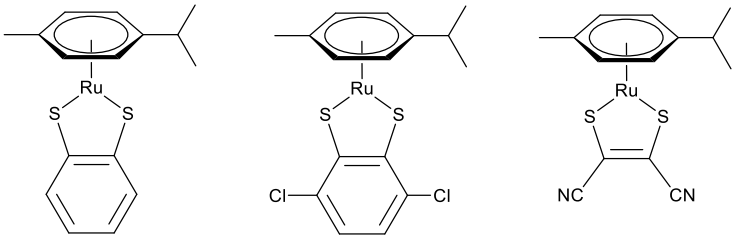

Figure 1. Structure of half-sandwich ruthenium complexes bearing different dithiol ligands.

Here we will discuss the potential of organoruthenium complexes with dithiol ligands as drug candidates for anticancer applications.[6]

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A general procedure for carbon isotope labeling of urea derivatives with carbon dioxide.

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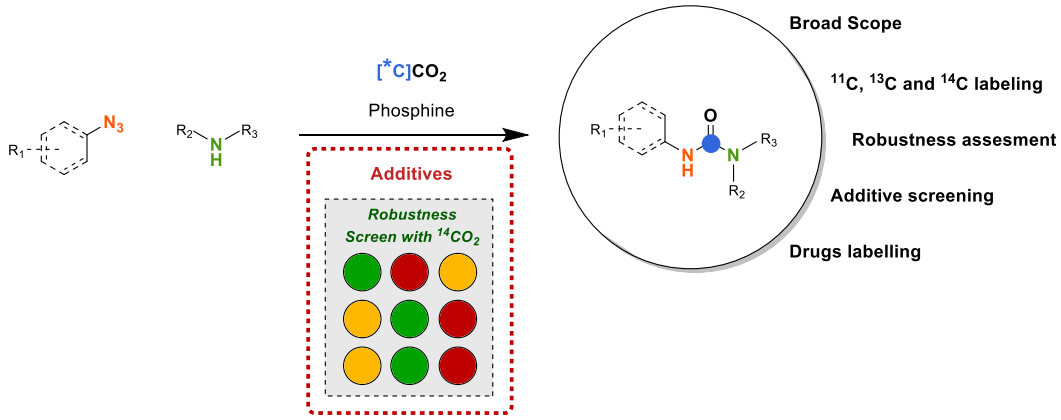
PO52

Carbon isotope labeling is a precious technology, which allows tracking organic compound either in the living organisms or environment. While long-lived β^- isotope carbon-14 (^{14}C, $t_{½}$ = 5730 years) is of paramount importance for the collection of biological data through ADMET studies, short-lived β^+ isotope carbon-11 (^{11}C, $t_{½}$ = 20 min) is routinely employed for PET imaging studies in humans and primates.

Nowadays, traditional multi-step synthesis with ^{14}C generates high amounts of radioactive waste and are extremely demanding in terms of resources and sustainability. On the other hand, ^{11}C is produced in limited amounts and requires fast and efficient reactions for its valorization in a radio-synthetic process [1].

In order to overcome such limitations, our group developed a Staudinger/ aza-Wittig cascade reaction using stoichiometric amounts ^{13}C, ^{14}C and ^{11}C-labeled-CO_2, that allows a rapid and straightforward access to different radio-labeled carbonyl derivatives, minimizing the generation of radioactive waste [2a, 2b].



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Dual synergy of photodynamic and sonodynamic therapy in the eradication of methicillin resistant *Staphylococcus aureus*	***PO53***

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Antibiotic resistance is currently a major problem in treatment of many diseases. Every year another strains are found resistant to antibiotics, and there is a possibility that most popular therapies based on those medications will no longer be effective. Thus, the presence of strains such as methicillin-resistant *Staphylococcus aureus* (MRSA) is becoming particularly important. MRSA causes either systemic or superficial infections of skin and soft tissues, with significantly higher mortality rate than other *S. aureus* isolates. Those infections are often acquired in hospitals, particularly affecting elderly and immunocompromised patients, but healthy people can be affected as well. The main problem with MRSA is that those strains can develop resistance to many beta-lactam antibiotics[(a)]. Some strains of MRSA were also found to be resistant even to glycopeptide-based antibiotics, such as vancomycin and teicoplanin, what constitutes a great difficulty in antibiotic-based treatment[(b)]. Therefore a great interest is put to overcome this phenomenon. The promising alternatives are photodynamic therapy (PDT) and sonodynamic therapy (SDT), as well as their combination. Those methods rely on the excitation of certain compounds, during light and/or ultrasound exposition, what results in generation of cytotoxic Reactive Oxygen Species (ROS), such as hydroxyl radicals, superoxide radicals and singlet oxygen[(a)]. Interestingly, some compounds are more potent in PDT, while others can undergo SDT approach. It appears that combination of PDT and SDT is often effective than particular approaches, as thanks to their compatibility, drawbacks of both methods (high concentrations of sensitizers, poor tissue penetration or low energy outside the ''therapeutic window'' – 600-800 nm in PDT, easier affecting of the neighbouring tissues in SDT) can be overcome[(a)]. During the studies, the combination of Rose bengal (xanthene dye) as photosensitizer and Chlorin e6 (Ce6) as sonosensitizer was investigated. The compounds appeared to be stable during sonication and irradiation, and their interactions were assessed by Job method. Their combinations in different molar ratios were then used for combined PDT/SDT treatment of MRSA *in vitro*, reaching up to 5 log reduction, despite not increasing the dark toxicity of compounds.

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Bioinspired lipidic alkynylcarbinols as anticancer agents	**PO54**

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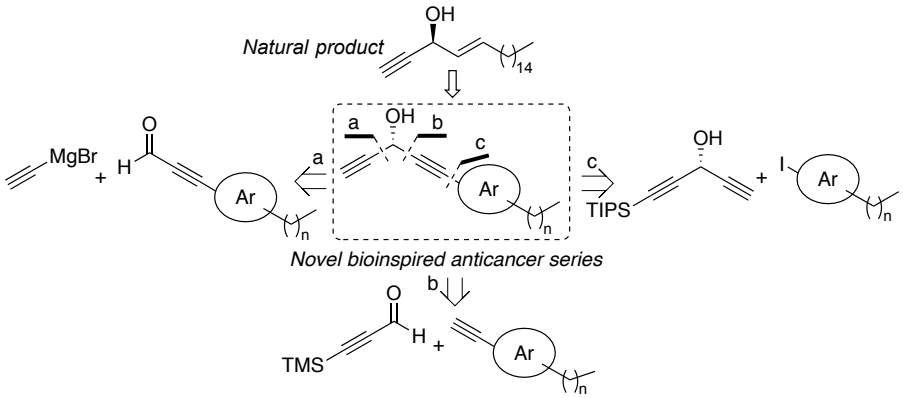
Cytotoxic natural acetylenic lipids embedding a chiral alkynyl carbinol unit at the terminal position of a linear aliphatic skeleton represent a potential source of anticancer agents.[i] We showed that chemistry-driven evolution of such lipidic alkynyl carbinols (LACs) could lead to an up to 1000-fold increase in potency for enantioenriched synthetic analogues.[ii] We also recently demonstrated that cytotoxic LACs behave as prodrugs upon *in situ* enantiospecific oxidation by SDR enzymes (Short-chain Dehydrogenases/Reductases): the resulting ynones react as Michael acceptors with multiple proteins, including a proteasome subunit, thus inducing apoptosis.[iii]



A new series of anticancer molecules will be described, in which the alkynylcarbinol pharmacophore is conjugated with an (hetero)aromatic ring, itself bearing the lipophilic chain.[iv] In order to ensure optimal efficiency and flexibility, complementary synthesis routes were studied. More than 30 synthetic analogues, as well as in cellulo-clickable probes, were obtained under racemic or enantioenriched form. Biological data of cytotoxicity, cell imaging and modification of cellular proteins using clickable probes show that this potent anticancer series displays the same mechanism of action as the one recently uncovered for related non-aromatic LACs[c], thus confirming their pharmacological potential.

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Development of new inhibitors of SK3 channel to prevent metastasis occurrence	***PO55***

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Currently, there is no treatment able to prevent bone metastasis. We discovered that while the abnormal expression of the SK3 channel by cancer cells promotes cancer cell migration and bone metastasis development, its suppression reduces them. Here, we propose to develop SK3 channel inhibitors as a new class of anti-metastatic drugs in targeted and personalized cancer therapy (targeted to SK3 channel and dedicated to patients with cancer cells expressing the SK3 channel).

Lead compound **NS8593** is currently one of the SK negative modulator inhibitor. However, the selectivity is current limitation in order to use this compound as anti-metastatic agent.

Our team is developing new synthetic strategies in order to provide novel polyfunctionalized pyridopyrimidines to explore structure-activity relationships and to improve the selectivity of final compounds. To achieve these objectives, we have developed efficient and modular strategies using S_NAr and palladium-catalyzed coupling reactions to modulate the main scaffold.

Among all the 25 compounds tested using patch clamp technique we identified **GF495**, a chiral compound, as strong inhibitor of SK3 channel with an IC_{50} = 18.4 nM (n=12). This compound was also found to inhibit the SK2 channel with an IC50 of around 1nM (n=7). In vitro experiments showed that this compound was not toxic until 10 µM. Our results show that **GF495** (100nM) significantly reduces the migration of five cancer cell lines, expressing SK3 channel including the MDA-MB435s. Furthermore, **GF495** has on effect on the migration of breast cancer cells that do not expressed SK3 (MDA-MB231) or in which SK3 channel were knockdown (MDA-MB435-shSK3). In vivo experiments showed that GF495 was not toxic until 20 mg/Kg (i.p. 5 times a week for 2 weeks). Finally, **GF495** was tested on a murine model of metastatic breast cancer (i.p.1 mg/kg, 3 times a week for 15 weeks). **GF495** treatment reduces dramatically bone metastasis (88.8%) and suppresses uterine and ovarian metastases,

To conclude, **GF495** is a new and potent inhibitor of SK3 channel, that show a capacity to reduce the development of metastasis. These promising results encourage us to develop analogues of **GF495** molecule, with at least a better selectivity (no effect on SK2 channel). In addition, it seems necessary to characterize the role of SK2 channel in cancer cell biology.

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Diversity-oriented strategies around mannopyranoside

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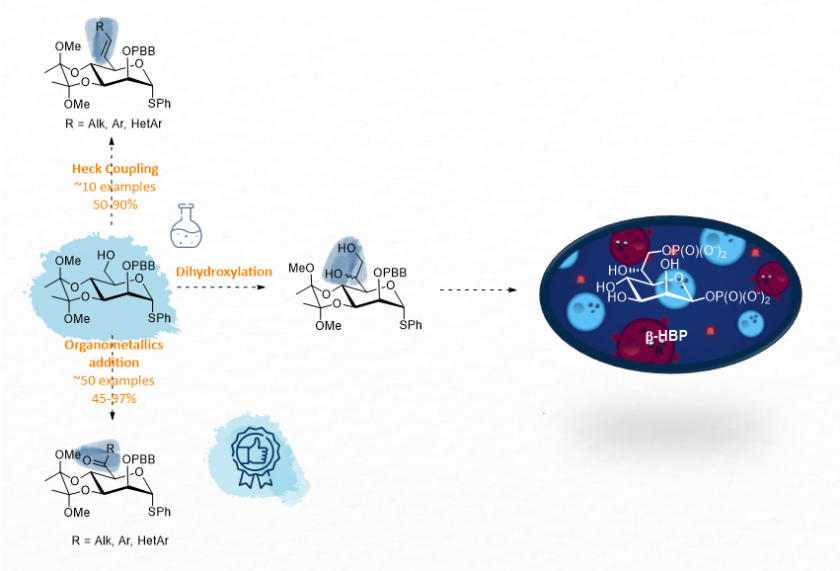
PO56

Among the various roles of carbohydrates in biology (virulence, structural components, energy storage and so on…), we focused, in the laboratory, around the use of polysaccharides as mediators of immunoprotection through vaccination.[1] As such, the development of a polyssacharidic vaccine against shigellosis,[2] one of the most important diarrheal disease, led us to understand the role of carbohydrates in Gram negative bacteria, especially in a highly-alarming context around AMR (Antimicrobial Resistance).[3] Heptoses, known as seven-carbon-chain-containing sugars,[4] are bacteria-specific, and as such target-interesting, carbohydrates, incorporated in the inner core of their membrane, and are involved in various metabolic processes, such as inflammation triggering in shigellosis.[5]



We firstly designed several routes to access heptommanosides, in large-scale, with emphasis towards efficiency and ecocompatible methods, starting from commercially available mannose scaffolds. As part of a collaboration with Institut Cochin, we applied those methods to the synthesis of β-HBP (heptose-1,6-biphosphate), a hypothesized PAMP (Pathogen-Associated Molecular Pattern).[6]

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Applying the new GLI reference values for DLCO in patients with pulmonary arterial hypertension

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PO57

ABSTRACT

Background: The diffusion capacity of the lung for carbon monoxide (DLCO) is widely used as a diagnosis and prognosis variable for patients with pulmonary hypertension (PH). While the ECSC reference values have been commonly used for interpretation of DLCO, implementation of new equations has been proposed by the Global Lung Initiative (GLI). We aim to evaluate the impact of such change on the interpretation of DLCO in patients with two subtypes of PH, namely idiopathic pulmonary hypertension (IPAH) and pulmonary veno-occlusive disease (PVOD).

Methods: Data were collected from the French PH registry. IPAH and PVOD patients initially evaluated by the reference center between April 1st, 2017 and April 1st, 2022 were included. DLCO values at inclusion were expressed as percentages of predicted value (% pred) using both ECSC and GLI equations, which were then compared within each group (PVOD and PAH) using a paired sample non-parametric test. Spearman correlation (ρ) was used to assess the correlation between quantitative variables. Frequency differences between groups were tested using chi^2 test.

Findings: A total of 74 PH patients were included, 37 being diagnosed with PVOD and 37 with IPAH. As compared with PVOD, IPAH patients were more often female (78.4 % vs 35.1 %, $p<10^{-2}$). with lower age (55.4 vs 67.2 years, $p<10^{-2}$) and higher DLCO value (15.2 vs 8.1 mL/min/mmHg, $p<10^{-3}$). Among both IPAH and PVOD patients, the use of GLI vs ECSC equation increased the value of % pred DLCO (73.8 vs 64.1, $p<10^{-3}$) and (33.4 vs 31.6, $p<10^{-3}$) respectively, a higher difference being observed among patients with IPAH as compared to PVOD (9.8 vs 1.8, $p<10^{-3}$). The magnitude of the difference between DLCO % pred with GLI and ECSC equation, was negatively correlated with age ($\rho= -0.66$). and positively correlated with DLCO raw value ($\rho = 0.68$).

Conclusion: Switching from ECSC to GLI equations have separate effects depending on which subtype of PH is considered. Physicians and researchers should be aware that it significantly increases the % pred DLCO in a clinically relevant manner among patients with IPAH.

Keywords: pulmonary hypertension, diffusion capacity of the lung for carbon monoxide, reference values

Discovery of a novel blood brain barrier-permeable IRE1 kinase inhibitor for adjuvant glioblastoma treatment.	***PO58***

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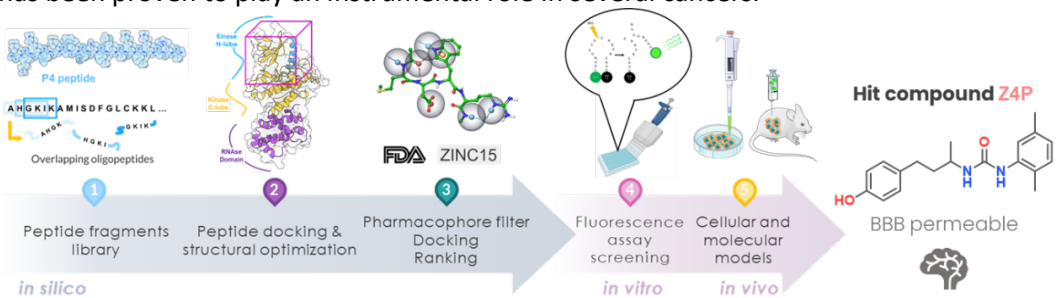
The Inositol-requiring enzyme 1 (IRE1) is a bifunctional serine/threonine kinase and endoribonuclease that is a major mediator of the unfolded protein response during endoplasmic reticulum (ER) stress. IRE1 signals through the non-canonical splicing of XBP1 mRNA and/or through regulated IRE1-dependent decay (RIDD) of RNA. It is involved in several diseases such as immune, metabolic and degenerative disorders as well as cancer. Tumour cells experience ER stress due to adverse environmental cues such as hypoxia or nutrient shortage as well as high metabolic/protein folding demand. To cope with those stresses, **cancer cells utilize IRE1 signalling as an adaptive mechanism** and it has been proven to play an instrumental role in several cancers.



Together, **this makes of IRE1 inhibition an attractive therapeutic option in oncology** as monotherapy or as adjuvant therapy alongside established treatments[(a)]. Several preclinical studies have successfully showcased it as such in multiple myeloma, prostate cancer, acute myeloid leukemia and triple negative breast cancer (TNBC). We recently demonstrated through local intracerebral inhibition that IRE1 is a highly relevant target for adjuvant treatment in glioblastoma[(b)], the most frequent and malignant form of primary brain tumors. However, known modulators of IRE1 activity[(c)] cannot cross the blood-brain barrier (BBB) and are therefore incompatible with concomitant systemic administration as adjuvant. In this context, we developed a structure driven drug discovery pipeline[(d)] to identify novel inhibitors able to cross the BBB. This study led to the discovery of Z4P, a BBB-permeable and kinase site-bound ligand showing inhibitory activities in GBM cell models, sensitization of tumor cells to Temozolomide (TMZ), and more strikingly prevents tumor relapse in mice when used in combination with TMZ[(e)].

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The development of a photoluminescent probe of basophilic protein kinases

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PO59

Protein kinases (PKs) are enzymes that catalyze the phosphorylation of proteins in organisms and thereby regulate many cellular processes. Their overexpression and dysregulation is associated with severe diseases, such as cancer and diabetes, therefore PKs have become one of the most studied targets in pharmaceutical research. Various inhibitors are being developed for the regulation and analysis of protein kinases.

Bisubstrate inhibitor design, wherein the inhibitor binds simultaneously to the ATP-binding site and peptide-binding area, provides higher affinity and selectivity compared to inhibitors that only bind to one of the aforementioned binding sites[(a)]. The bisubstrate PK inhibitors (ARCs) developed in the medicinal chemistry workgroup of the University of Tartu are conjugates of an adenosine analogue and a peptide, connected by a linker. ARCs labelled with fluorescent dyes can be used as photoluminescent probes of PKs.

ARCs comprising a selenium heterocycle have exhibited intense long-lifetime photoluminescence when bound to PKs[(b)]. In the present work an ARC-type inhibitor containing 7-deazapurine and selenophene moieties was developed, which binds strongly to the catalytic subunit of cAMP-dependent protein kinase (PKAc) with a K_D value in the low nanomolar range. Such probes can be used for the development of assays for protein kinases that are based on the quantification of time-gated luminescence intensity (TGLI). These assays find applications for the biochemical characterization of novel protein kinase inhibitors as well as in diagnostic methods based on the detection of disease-related protein kinase biomarkers.

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Photoinduced isotope equilibration between formate salts and CO_2 : application to carbon labeling

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PO60

Carbon radioisotope labeling has a remarkable impact on public health. Long lived β^- isotope carbon-14 (^{14}C, $t_{1/2}$ = 57300 years) is of paramount importance for the collection of biological data such as absorption, distribution, metabolism, excretion (ADME) studies.[1] Unfortunately, traditional ^{14}C-radiosynthesis is marred by multiple pitfalls, including lack of available starting materials ([^{14}C]CO_2 being the universal building block), high costs of reagents and generation of considerable amounts of radioactive waste, which are poorly sustainable and difficult to dispose of.

We have explored a photocatalytic approach for the synthesis of labeled carboxylic acids, based on the hydrocarboxylation of alkenes (*i.e.* the Giese reaction).[2,4] Based on a dynamic isotopic equilibration between formate salts and [^{13}C, ^{11}C and ^{14}C]CO_2, C-labeled radical anion $CO_2^{\bullet-}$ could be accessed for the first time,[3] under extremely mild conditions and low photocatalyst loading (0.5 mol%). This methodology was employed for labeling drug derivatives and the late-stage carbon isotope labeling of complex substructures and pharmaceutically relevant compounds.

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