Group for the Promotion of Pharmaceutical chemistry in Academia

GP_2A 2024 – 32nd Annual Conference

28th– 30th August 2024

University of Coimbra

Coimbra, Portugal

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Welcome message from Prof. Pascal Marchand (Nantes Université - France, President of the GP2A Committee)

At the beginning of the GP2A, the Universities of Coimbra and Porto were involved in the network but, unfortunately, we never had the chance to organise the conference in Portugal. That is why we are delighted to welcome you to this beautiful country for the **32nd Annual GP2A (Group for the Promotion of Pharmaceutical Chemistry in Academia) Conference**.

The last edition in Marseille France was a real success and, this year, we are so happy to meet you in **Coimbra – Portugal from August 28th to 30th, 2024**.

The Olympic Games in France have been nothing short of spectacular! The competition has been fierce, with athletes from around the world delivering unforgettable performances and pushing the boundaries of human achievement. The French hosts have truly outdone themselves, creating a warm and friendly atmosphere that embodies the spirit of the Olympics. We are looking forward to the Paralympics!

I am sure that Assoc. Prof. Vânia M. Moreira and her team will pursue the "Scientific Games" by setting up this meeting with an excellent line-up of keynote speakers and very attractive social events, including guided tours and a Fado show. I would like to thank the Local Organising Committee for their huge involvement.

We have aimed to embrace the multidisciplinary nature of drug discovery and chemical biology including topics that cover a broad range of interest in both medicinal chemistry and interfacing disciplines. These comprise infectious and neurodegenerative diseases, chemoprevention of cancer, protein degradation, approaches to target identification, hit identification and optimisation for drug candidate, natural products, inflammatory diseases/pain, and the application of structural cheminformatics, machine learning, artificial intelligence and new synthetic concepts. We are delighted with our invited speaker line-up of **8 internationally recognised experts**, who will highlight recent advances in the field of applied chemistry towards novel health solutions.

The annual GP2A symposium host city alternates between France and another country and provides a rich 'cultural broth' for new ideas, network growth and collaboration, both for established scientists

and earlier career researchers. We are pleased to see a large student contingent at the conference this year, who represent the future of our discipline and ensure the continuity of our activity. With this in mind, **12 young researchers** will have the opportunity to present their work to the delegation and be considered for the oral presentation prizes. In addition, we look forward to **poster sessions** which will also be considered for the conference poster prizes. They won't win any medals, but they will ll have our deepest respect.

Finally, we would like to express our gratitude to all the speakers and sponsors for their support of GP$_2$A 2024.

So, we wish you to enjoy the GP$_2$A 2024 Conference! We are so proud to have built such a great network, from the “Atlantic” to over Europe, dedicated to Pharmaceutical Chemistry. Over years, all the conferences were organised in a friendly atmosphere with a high scientific level of the exchanges. We will continue to give the opportunity to young researchers to give talks and to share the floor with senior researchers since we consider such approach as the identity of GP$_2$A network.

On a personal note, this edition marks the end of my Presidency after 7 years. Thank you for everything, dear colleagues and friends. It has been a very rich experience, both scientifically and humanly, with a wonderful team to whom I owe a great deal. It has been a wonderful time, but "the show must go on" and I have no doubt about the future of this great network, which is in good hands with competent and motivated people.

SAVE THE DATE! The **33rd Annual GP$_2$A Medicinal Chemistry Conference** will be taking place at the **Nantes Université – France, June 11th to 13th, 2025**. We will have the fantastic opportunity to organise a joint conference with the **Paul Ehrlich Euro-PhD Network** aiming to provide an in-depth research training and mobility of PhD students in the area of Medicinal Chemistry at European level.

Prof. Pascal Marchand
Nantes Université (France)
GP$_2$A President

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GP2A 2024 Schedule

Wednesday 28th August 2024 *Venue:* ***Auditório da reitoria, UC***	
Time	
13:30 – 17:00	Registration open
	Session I *Session chairs*: **Assoc. Prof. Vânia M. Moreira** **Prof. Jorge A. R. Salvador** Faculty of Pharmacy, University of Coimbra, Portugal
14:00 – 14:20	Opening of 32nd GP2A Conference **Prof. Pascal Marchand** Chairman of the GP2A committee Nantes Université, France **Assoc. Prof. Alfredo Dias** Vice-Rector of the University of Coimbra **Assoc. Prof. João José Simões de Sousa** Vice-Dean, Faculty of Pharmacy, University of Coimbra
14:20 – 14:55	**KN**: Chemical neuroscience for Alzheimer's disease – Hybrid molecules and photopharmacology **Prof. Dr. Michael Decker**, Julius-Maximilian-University Würzburg, Germany
14:55 – 15:15	**OC**: A MTDL's approach against Alzheimer's disease: deconstruction of a tricycle **Thomas Guiselin**, University of Caen Basse-Normandie, France
15:15 – 15:35	**OC**: Advances in the development of synthetic allosteric modulators of protein kinase C **Katia Sirna**, University of Helsinki, Finland
15:40 – 17:15	**Welcome Reception** *Venue:* ***Auditório da reitoria, UC***
17:30 – 18.30	**Optional Activity 1** (*prebooking only*) **Guided Tour to Palace of Schools**. Enjoy a visit to the Palace of Schools (Baroque Library, Saint Michael's Chapel and Royal Palace) of the University of Coimbra, accompanied by a UC Guide

Thursday 29th August 2024 *Venue:* ***Auditório da reitoria, UC***	
Time	**Session II** *Session chairs:* **Dr. Jean-Jacques Hélesbeux**, Université d'Angers, France **Assoc. Prof. Emília Sousa,** University of Porto, Portugal
8:30 – 16:00	Registration open
09:00 – 09:35	**KN**: The One Health concept in antiparasitic drug discovery, what matters? **Prof. Maria Paola Costi**, University of Modena and Reggio Emilia, Italy
09:35 – 09:45	**SPECANALÍTICA**
09:45 – 10:20	**KN**: Fighting against multiresistant fungal infections a state-of-the-art update and the beginning of a chemical biology study of synthetic antifungal drugs **Prof. Line Bourel**, University of Strasbourg, France
10:20 – 10:40	**OC**: Synthesis and evaluation of thio-linked pyrimidine-based compounds against *Leishmania donovani*: *In silico* and *in vitro* assessments **Inês Costa**, University of Algarve, Portugal
10:40 – 11:40	*Coffee Break, Sponsor Exhibitions and Poster Session*
	Session III *Session chairs:* **Prof. Christophe Rochais, University of Caen Basse-Normandie, France** **Prof. Vittorio Pace, University of Turin, Italy**
11:40 – 12:15	**KN**: Machine learning to accelerate the chemical sciences **Assist. Prof. Tiago Rodrigues**, University of Lisbon, Portugal
12:15 – 12:35	**OC**: Development of new antivirals using a high throughput fragment merging strategy **Dr. Hadia Almahli**, University College London, UK
12:35 – 12:45	João Pedro Nogueira **CEM/QLABO**
12:45 – 13:20	**KN**: Accelerating medicinal chemistry by Flow-Enhanced Synthesis **Assoc. Prof. Antimo Gioiello**, University of Perugia, Italy
13:20 – 14:30	*Lunch, Sponsor Exhibitions and Poster Session*
	Session IV

	Session chairs: **Assoc. Prof. Niamh O'Boyle, Trinity College Dublin, Ireland** **Prof. Maria-João Queiroz, University of Minho, Portugal**
14:30 – 15:05	**KN**: Novel inhibitors of the endocannabinoid's catabolic enzymes as potential therapeutics for epilepsy and neuroinflammatory conditions **Prof. Stefania Butini**, University of Siena, Italy
15:05 – 15:25	**OC**: Lighting up bleeding control – Photopharmacology on factor Xa **Eva Schaller**, University of Würzburg, Germany
15:25 – 15:45	**OC**: Development of novel sirtuin-1 activators: promising therapeutic tools against neurodegenerative diseases **Rodrigo F. N. Ribeiro**, University of Coimbra, Portugal

16:15 – 17:45	**Optional Activity 2** (*prebooking only*) Guided ***tour to the Old Cathedral of Coimbra*** *PLUS* "***Fado ao Centro*****" show** - Includes 2 short videos about the history of Fado in Coimbra, a Fado concert with Port wine tasting

18:30 – 19:50	GP_2A committee meeting (committee only) *Venue:* Quinta das Lágrimas, Coimbra Rua António Augusto Gonçalves, 3041-901 Coimbra
20:00	**Conference Dinner** (*prebooking only*) *Venue:* Quinta das Lágrimas, Coimbra Rua António Augusto Gonçalves, 3041-901 Coimbra

Friday 30th August 2024 *Venue:* ***Auditório da reitoria, UC***	
Time	**Session V** *Session chairs:* **Assoc. Prof. Shailesh Mistry, University of Nottingham, UK** **Prof. Susan Matthews, University of Sheffield, UK**
09:00 – 09:35	**KN**: Working with degradation and protein instability in drug discovery **Dr. Mikael Altun**, Karolinska Institute, Sweden
09:35 – 09:55	**OC**: From inhibitors to degraders: Application to the design of innovative compounds for the treatment of chemoresistant ovarian cancer **Thomas Lemaitre**, University of Caen Basse-Normandie, France
09:55 – 10:15	**OC**: A versatile conjugation platform for the development of PROTACs and molecular probes for their characterization **Lucía González**, University of Santiago de Compostela, Spain
10:15 – 11:15	*Coffee Break, Sponsor Exhibitions and Poster Session*

	Session VI *Session chairs:* **Dr. Florence McCarthy, University College, Cork, Ireland** **Dr. Laura Carro, University College London, UK**
11:15 – 11:35	**OC**: Benchmarking traditional and deep learning models for protein target activity prediction **Ana Laura Dias**, University of Lisbon, Portugal
11:35 – 11:45	**Dr. Sara Pinto** Sociedade Portuguesa de Química (SPQ)
11:45 – 12:05	**OC**: Development of new nature-inspired synthetic flavonoids for marine biofouling prevention **Daniela Pereira**, University of Porto, Portugal
12:05 - 12:25	**OC**: Design and synthesis of novel allosteric modulators for the prostaglandin EP2 G protein-coupled receptor **Constance Dalton**, University of Nottingham, UK
12:25 – 13:30	*Lunch, Sponsor Exhibitions and Poster Session*
	Session VII *Session chairs:* **Prof. Pascal Marchand, Nantes Université, France** **Assoc. Prof. Vânia M. Moreira, University of Coimbra**
13:30 - 13:50	**OC**: 4-Anilinoquinazoline derivatives as new potent and selective NOD1-RIPK2 inhibitors for the treatment of inflammatory diseases **Morgane Rivoal**, University of Lille, France
13:50 – 14:25	**KN**: Serendipity and drug-unlikeness in the discovery of a new antimalarial agent **Prof. Dr. Diego Muñoz-Torrero**, University of Barcelona, Spain
14:25 – 15:00	**Prize Announcements** (early career presentations and poster presentations) **Other Announcements** Conference Close

Keynote Lectures

Chemical Neuroscience in Alzheimer's Disease: Hybrid Molecules and Photopharmacology

Michael Decker[a]

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Alzheimer's disease (AD) is still uncurable and next to its pathophysiological hallmarks of βamyloid plaques and τ-protein hyperphosphorylation, neuroinflammation is observed. It is observed that counteracting neuroinflammation is effectively reversing cognitive decline in animal models of AD. Such anti-neuroinflammatory action can be effectively mediated by inhibiting the enzyme human butyrylcholinesterase (BChE),[1] by activating the human muscarinic acetylcholinesterase receptor subtype 1 (*h*ACh$_1$R or *h*M$_1$R), and/or by activating the human cannabinoid receptor subtype 2 (*h*CB$_2$R).[2] We report on novel ways to selectively inhibit BChE by carbamates and thereby improve both short- and long-term memory using pseudo-irreversible inhibitors with tunable duration of action, which directly correlate with dosage necessary *in vivo*.[3] Following this approach, BChE inhibition was combined with concomitant agonist activity at the *h*CB$_2$R. Despite lower activity (at both targets) in the micromolar range, compounds represent "small molecules" and were very potent *in vivo* proving synergistic mode of action.[2]

"Photopharmacology" uses molecular photoswitchable moieties that are incorporated into bioactive molecules to control pharmacological activity by light, achieving unprecedented spatio-temporal control of bioactivity. The challenges of this approach are illustrated for photoswitchable BChE inhibitors enabling light control of each step of carbamoylation BChE and yielding a photoswitchable inhibitor, that was inactive as its *trans*-photoisomer *in vivo*, but active as its *cis*-photoisomer.[4]
Furthermore, photoswitchable *h*CB$_2$R agonists were developed representing "*cis*-on" affinity switches, as well as a compound that is a "*trans*-on" efficacy switchable photo-agonist.[5] This compound used novel benzimidazole-based photoswitches, which require visible, but not UV-light for switching.[6] Furthermore, the latter compound represents the first-in-class light-controllable class-A GPCR biased agonist.[5]
Finally, the most recent developments regarding photoswitchable *h*M$_1$R agonists are reported, which includes red-shifted orthosteric agonists as well as the first photoswitchable class-A allosteric modulator ("Photo-BQCA") enabling light-control of *h*M$_1$R action.[7]

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The One Health concept in antiparasitic drug discovery, what matters?

Maria Paola Costi

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Nearly 75% of emerging human infections worldwide originate from animals. Current drugs for both human and animal (H&A) vector-borne diseases (VBD) are in short supply and have limited efficacy, potential toxicity, and limited resources. Emerging environmental issues in pharmaceutical use/manufacturing are increasing attention in this area. Collaboration and research between different expertise involving human and animal medicines are essential to define how new drugs can be developed using a more sustainable approach[1]. All the drug discovery process can include the greener principles[1]. OneHealth*drugs* (www.onehealthdrugs.com) is a COST Action dedicated to the development of innovative strategies for the supply of drugs with an environmentally friendly profile. The new drugs should combat H&A VBD while maintaining the principles of an optimal profile for both organisms, improving their quality by also implementing delivery technologies. With these aims, we have developed different concepts. We highlight the scarcity of ecotoxicological data for commonly used antiparasitic drugs and stress the urgent need for considering the One Health concept; then we advocate for employing predictive tools and nonanimal methodologies such as New Approach Methodologies at early stages of antiparasitic drug research and in subsequent development[3]. In one representative case we have investigated the biochemical mechanisms of resistance to antimonials, paromomycin, and miltefosine in three drug-resistant parasitic *Leishmania infantum* strains from human clinical isolates, using a whole-cell mass spectrometry proteomics approach. We identified 14 differentially expressed proteins that were validated with their transcripts. Next, we employed functional association networks to identify parasite-specific proteins as potential targets for novel drug discovery studies[4]. We used SeqAPASS analysis (Sequence Alignment to Predict Across Species Susceptibility, EPA tool) to predict susceptibility based on the evolutionary conservation of protein drug targets across species. 5 proteins were identified at the end of the process emerged as top candidates. SeqAPASS Among them calpain-like cysteine peptidase was the best selected protein. Overall, this work identifies new biological targets for designing drugs to prevent the development of Leishmania drug resistance, while aligning with One Health principles that emphasize the interconnected health of people, animals, and ecosystems. Other cases will be presented showing the interconnection between One Health approaches and drug discovery process.

Acknowledgment

COST Action CA21111. One Health Drugs against Parasitic Vector-Borne Diseases in Europe and Beyond

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Fighting against multiresistant fungal infections – a state of the art update and the beginning of a chemical biology study of synthetic antifungal substances

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Among the microbial causes for nosocomial infections, multiresistant fungi are frequently incriminated, but researches thereon are somehow left behind.[1] Yet, worldwide, >1.6 million immunocompromised hospitalized patients die annually of invasive fungal diseases (IFDs) notably due to *Candida spp*, against which none of the 4 approved antifungal (AF) drug families is active.[2] The AF arsenal is composed of very toxic Amphotericin B, weakly selective 5-Fluorocytosine and of the Azole class, increasingly inefficient against IFDs. In the 2000s, Echinocandins (ECs) were introduced as semisynthetic lipopeptides (LPs) inhibiting β-(1,3)-D-glucan synthase (GS), an enzyme involved in the biosynthesis of the fungal cell wall. ECs trigger its disruption, which is lethal for yeasts like *Candida spp*. As this enzyme is absent in mammal cells, ECs were initially developed as safe AF drugs against IFDs. Unfortunately, nowadays, more and more *Candida* strains encountered in intensive care units exhibit a low EC susceptibility.[3] So for this class and its target, mechanistic investigations are really urging. In the near future, the identification of new AF scaffolds active on this relevant target would be of great importance for public health. [4]

The University of Strasbourg Institute for Advanced Study (USIAS) funds original research in all scientific domains and serves as a place of intellectual brainstorming and innovation. USIAS is a flagship project of the Excellence Initiative (IdEx) of the University of Strasbourg and supports researchers from any disciplines by kicking off their new scientific projects. Thus the present research program has just begun.

First, a state of the art update regarding fungal pathologies and antifungal substances will be presented. Second, we propose to implement the antifungal arsenal with original ECs-based synthetic LPs that can be more easily sourced and purposely chemically-modified. In this project, their activity will be continuously assessed against fungal strains originating from patients hospitalized at the Hopitaux Universitaires de Strasbourg in low throughput screening EUCAST-grade conditions. In parallel, a medium throughput screening is planned and librairies of alternative original substances will be tested on whole *Candida albicans.* Finally, we will expose the beginning of a chemical biology study. To this purpose, fluorescent ECs have synthesized and the bioproduction of a traceable β-(1,3)-D-glucan synthase has just started, to permit the imaging of their interaction and the structural analysis of the target. If successful, such bioproduction could be extended to the GS of other strains that are also responsible for life-threatening IFDs. By all these pathways, we hope to understand the intimate mechanism of action of synthetic ECs on GS and in parallel, to contribute to the identification of original AF substances.

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Machine learning to accelerate the chemical sciences

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Machine learning and artificial intelligence (ML/AI) are reshaping the chemical sciences by changing research paradigms and enabling new discoveries. Provided enough quality data, ML/AI algorithms can identify hidden patterns that would remain unnoticed otherwise.[1,2] *A central dogma in ML/AI is that performance is tightly connected to the amount of training data. However, recent reports challenge this concept.*[3,4]

In several chemistry use cases, data is typically scarce, heterogeneous and/or unstructured, which poses important challenges to the implementation of discriminative ML/AI tools.[1] *Herein, we show that small amounts of high-quality data are viable starting points for ML/AI, in particular when active learning approaches are pursued. We discuss how smart experiment prioritization can efficiently unravel meaningful patterns in chemical reaction data, in the identification of false positive hits in screening assays and in the design of nanomaterials.*[5–8] *We discuss the impact that low data ML/AI might have in next generation discovery sciences.*

T.R. acknowledges all collaborators who contributed to the execution of the presented work.

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Accelerating medicinal chemistry by flow-enhanced synthesis

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In the target-rich post-genomics era, the competitive arena of the pharmaceutical industry requires constant innovation and accelerated timelines to foster drug discovery pipelines.[1,2] Despite decades of ground-breaking research, compound synthesis is still considered the rate-limiting factor in the pace of drug discovery.

In medicinal chemistry, the preparation of pure compound collections represents the bottleneck of the 'design-make-test-analyse' cycle, as the conventional bench synthesis is a labor-intensive and time-consuming work. Moreover, there exists a persisting need to develop enabling syntheses that can facilitate compound development addressing the process scalability and optimization challenges for large scale production.

The goal of this lecture is to introduce concepts and potential of continuous flow technology in medicinal chemistry, and to showcase the efforts made by our group with the aim to improve synthetic capabilities and expedite the medicinal chemistry learning cycle.[3] A particular attention will be devoted on case studies that have shown the utility of flow chemistry to simplify usual batch operations and, in turn, the synthesis of compound libraries readily available for screenings, as well as to realize sustainable synthetic approaches for lead discovery and development.

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Novel inhibitors of the endocannabinoids' catabolic enzymes as potential therapeutics for epilepsy and neuroinflammatory conditions

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The endocannabinoids (ECs) anandamide (AEA) and 2-arachidonoylglycerol (2-AG), by stimulating cannabinoid CB1 and CB2 receptors (CB1R and CB2R), regulate relevant signaling pathways. The key enzymes involved in ECs catabolism are fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL). Their unique role in terminating ECs signaling and regulating the intracellular levels of AEA, 2-AG and other ECs supports their potential as therapeutic targets. Selective or dual inactivation of ECs degrading enzymes represents an attractive approach for eliciting the desirable effects of CBR activation, while avoiding the negative (psychotropic, among others) effects of CB1R stimulation.

Epilepsy is the second most common neurological disorder with an incidence rate of 0.3-0.5% worldwide. Most of conventional anti-epileptic drugs have narrow therapeutic margin and require therapeutic drug monitoring. Despite the introduction of many II-generation anti-epileptic drugs, pharmacoresistant epilepsy has not been significantly reduced. A reduction of AEA in patients affected by temporal lobe epilepsy (TLE) has been clearly documented. Similarly, the neuroprotective role of AEA was confirmed by the kainic acid induced increase of AEA in hippocampus, which, without affecting 2-AG, provides “on demand” protection against acute excitotoxicity. Seizure activity at the cellular level initiates significant influx of calcium. Over time, impaired neuronal calcium homeostasis increases the activity of pro-oxidant cellular systems. The enocannabinoid system can delay or prevent excitotoxic damage by re-balancing the main excitatory/inhibitory systems and directly modulating mitochondrial function, thus preventing oxidative stress–related epileptogenesis. This rationale led to the proposal of FAAH inhibitors as therapeutic option for the prevention of epileptic disorders. To strengthen this hypothesis we demonstrated that our potent and selective FAAH inhibitor (NF1245, Ki=160 pM [1]) ameliorated the acute epileptic behavior and prevented hippocampal oxidative damage in rat model of pilocarpine-induced epilepsy when tested at 10 mg/kg.[2] The same dose was also effective in TLE generated by electric kindling. Based on our recent results,[3] rational structural modifications produced improved analogues that were able to reduce the oxinflammation state by decreasing DNA-binding activity of NF-kB p65, devoid of cytotoxic effect and unwanted cardiac effects while being able to reduce the severity of the pilocarpine-induced status epilepticus. [2]

Neuro-inflammation, mainly regulated by microglia and astrocytes, is a common feature of several neurodegenerative diseases amyotrophic lateral sclerosis, and multiple sclerosis. In fact, neurological disorders can be triggered by chronic neuro-inflammatory conditions that, through different mechanisms in which the oxidative stress is involved, may lead to neuronal cell death. Oxidative stress is caused by increased levels of reactive oxygen species (ROS) deriving from mitochondrial dysfunctions. Elevating endogenous levels of the ECs through FAAH and MAGL inhibition is a valuable approach to enhance the anti-inflammatory, anti-nociceptive [4, 5] and neuroprotective effects mediated by the ECs. On these bases, we have recently designed a new library of FAAH inhibitors of nanomolar potency embedding ionizable functions, for improving water solubility and the chemical stability. [6] For these compounds, effective in reducing ROS production in 1321N1 astrocytes, the anti-inflammatory activity was evaluated ex vivo in hippocampal slice cultures. New and exceptionally potent irreversible MAGL inhibitors were recently developed for attaining brain permeability.[7] The exploration of different polypharmacological profiles will be also discussed.[8]

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Serendipity and drug-unlikeness in the discovery of a new antimalarial agent

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All of us, medicinal chemists, have very interiorized the notion that our hits, leads, and candidates must feature a number of general attributes or properties, which directly derive from their chemical structure and would give them more chances to become a drug. Thus, we expect that our compounds align with a sort of "structural beauty pattern" that we call drug likeness. Starting with the working hypothesis by Xavier Fernàndez-Busquets (Head of the Nanomalaria group, at Institute for Bioengineering of Catalonia (IBEC) and ISGlobal Barcelona) that protein aggregation, which seems to be abundant in *Plasmodium falciparum*, has a functional role, and, hence, that inhibition of protein aggregation might be a new way to treat malaria, he serendipitously found that a dye used to monitor protein aggregation was indeed able to kill the malaria parasite with nanomolar potency. This compound, YAT2150, is everything but a "beautiful" drug-like molecule. Notwithstanding this, we initiated a joint project to deepen into the physicochemical and biological properties of YAT2150 and to perform a lead optimization campaign to establish a first-in-class family of antimalarial agents based on the inhibition of protein aggregation.
This has resulted in very interesting findings on the profile of YAT2150: i) it has nanomolar potency on chloroquine- and artemisinin-resistant *P. falciparum* lines; ii) it arrests asexual blood parasites at the trophozoite stage; iii) it interferes with sexual and hepatic forms of the parasite; iv) it reduces the amount of aggregated proteins in *P. falciparum* cultures; v) it fluoresces when it accumulates in its main localization in the parasite cytosol, thereby being useful as a theranostic agent; and vi) it is active against the leishmaniasis parasite *Leishmania infantum*.[1,2]

Moreover, after modifications at different points of the chemical structure of YAT2150, we have developed new analogs with improved antiplasmodial potencies, selectivity indexes, and DMPK properties. Overall, these compounds, featuring a novel chemical scaffold and mechanism of action, might be the spearhead of a new generation of antimalarial drugs in the post-artemisinin era and pave the way for the single-drug treatment of the geographically overlapped malaria and leishmaniasis, the two most deadly parasitic diseases.

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Oral Communications

A MTDL's approach against Alzheimer's disease: deconstruction of a tricycle

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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$_6$R 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. 5-HT$_6$R antagonists are also able to promote the 5-HT concentration in the brain. As a result, 5-HT$_6$R antagonists have shown positive effects against the memory disorders affecting these animals. The serotonin transporter (SERT), 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 amyloid deposition and senile plaques in transgenic AD mice and also in humans.

The objective of this project is to design a multi-target directed ligand both able to inhibit 5-HT reuptake and selectively to antagonize 5-HT$_6$R. (**Figure 1, left part**)

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, right part**)

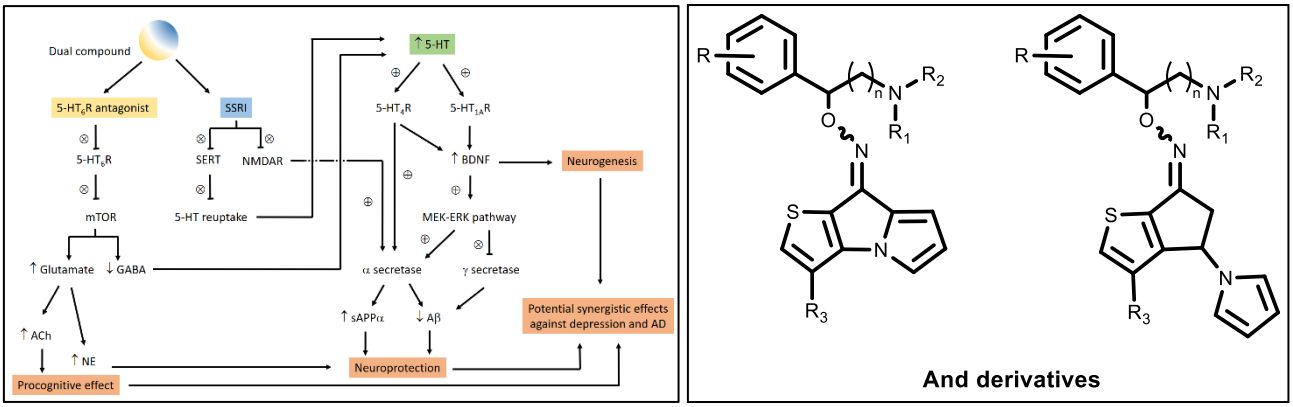

Figure 1. Left: Hypothetical mechanisms of a dual SSRI/5-HT$_6$R antagonist; **Right**: MTDL's scaffolds

Advances in the development of synthetic allosteric modulators of protein kinase C

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Protein kinases C (PKCs) are a family of serine/threonine kinases implicated in several cellular processes, such as modulation of gene expression, cell division, migration, proliferation and differentiation, cell survival, and apoptosis, and therefore, they are involved in different pathologies. Thus, the development of PKC targeted compounds represents a highly promising strategy to identify new drug candidates.[1] We have previously developed 5-(hydroxymethyl)isophthalate derivatives (HMIs) (Figure 1), which demonstrated binding to the C1 domain of PKCs and exhibited anticancer, antifibrotic, and neuroprotective effects.[2-4] However, their high lipophilicity negatively affects their

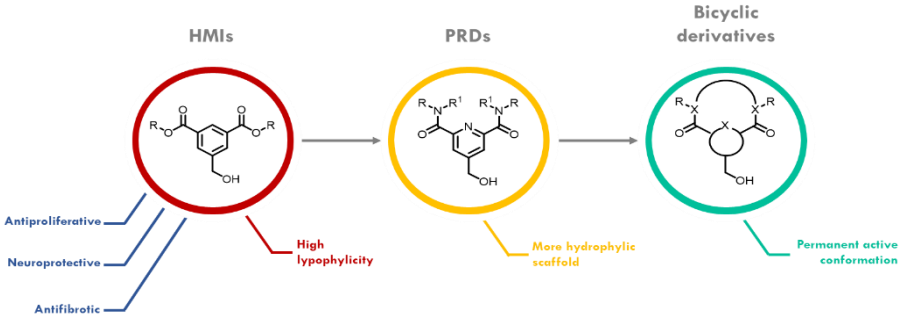

Figure 1. Pros and cons of previous (**HMIs** & **PRDs**) and current (**Bicyclic derivatives**) allosteric modulators of PKC.

drug-like properties. To improve the solubility of HMIs while retaining the activity, several nitrogen-containing cores had already been considered. The last generation of compounds, pyridines (PRDs), showed comparable affinity to the C1 domain while reducing the overall lipophilicity compared to the HMIs.[5] Using the PRDs as a starting point and considering the molecular structure of some of the natural and synthetic ligands of the C1 domain,[6] we designed bicyclic derivatives, bearing a hydroxymethyl group and alkyl/phenyl substituents, as new potential allosteric modulators of PKC (Figure 1). The new small molecules were tested for the binding to the C1 domain, revealing higher affinity than the HMIs. Moreover, a preliminary biological evaluation suggested that the new compounds are able to activate PKC.

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Synthesis and evaluation of thio-linked pyrimidine-based compounds against *Leishmania donovani: In silico and in vitro assessments*

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Leishmaniases are a cluster of syndromes recognized by WHO as neglected tropical diseases, caused by *Leishmania* parasites. Available chemotherapy for treating these infections is unsatisfactory, mainly due to emerging resistance. There is thus a huge need for novel drugs, with better efficacy, safety and reduced tendency to resistance development.[1] In the search for novel biomolecular targets, trypanothione reductase (TR) becomes attractive due to its vital role in maintaining the parasite's redox machinery. TR reduces the disulfide bridge of trypanothione disulfide (TS_2) into the reduced trypanothione $T(SH)_2$, a di-thiol responsible for eliminating reactive species for *Leishmania.*[2,3] Moreover TR owns several advantages, namely its structural similarity among all *Trypanosomatidae* parasites and its absence in the mammalian host.[4] Among the search for better antileishmanial options, a pilot study identified the potential of aryl sulfides in inactivating TR.[3,5] Considering these results, we disclose the synthesis of a library of novel thio-linked pyrimidine-based compounds based on the Buchwald–Hartwig methodology. Different products were formed by changing the reaction time, some of them being confirmed by X-ray crystallographic studies. The results of our computational studies indicate that all compounds from our library interact with residue Arg222, thus restricting the interaction between the enzyme and its cofactor NADPH. Finally, we also disclose results of the *in vitro* antileishmanial activity of all compounds against *L. donovani axenic and intramacrophage amastigotes,* as well as their cytotoxicity against Raw 264.7 cells. Compounds **IC69** and **IC90** proved to be the most active against both forms of *Leishmania*, exhibiting IC_{50} values *on a nanomolar scale (Figure **1**).*

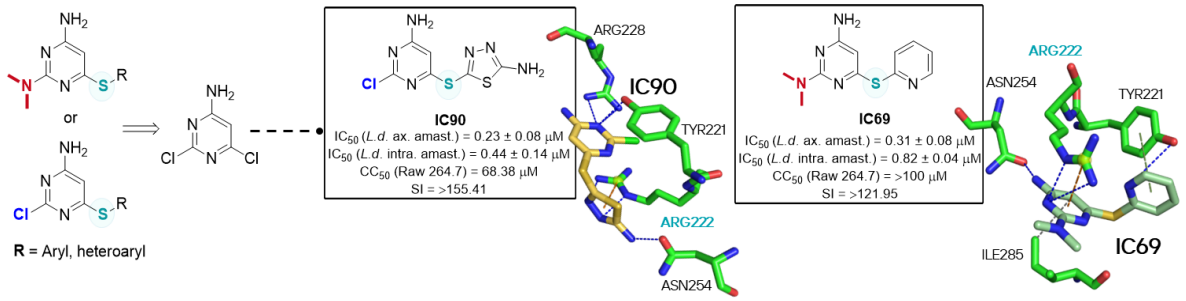

Figure 1. Representation of the research approach followed, with indication of best performing thio-linked pyrimidine-based conjugates among those synthesized and studied within the presented work.

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Development of new antivirals using a high throughput fragment merging strategy

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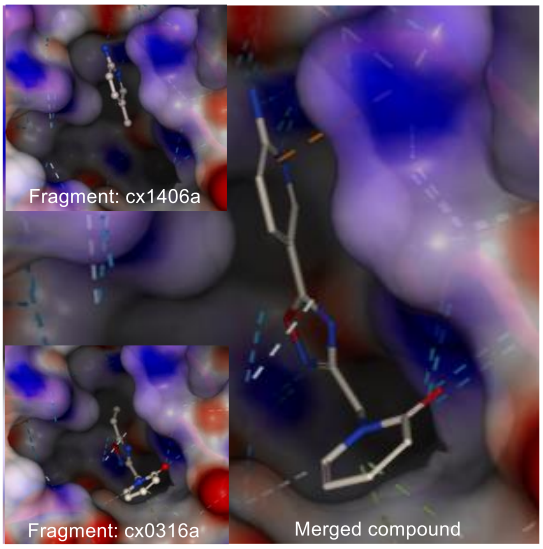
Viral infections continue to pose health risks coupled to major healthcare costs. A broad range of viruses including SARS-CoV-2 (Severe Acute Respiratory Syndrome COronaVirus 2) and CHIKV (CHIKungunya Virus)[1] continues to evolve and pose a pandemic threat. The dawn of this decade witnessed how SARS-CoV-2, responsible for the COVID-19 pandemic caused more than 774 million infections and led to more than 7 million deaths[2]. Developing effective antivirals with new mechanisms of action is essential for pandemic preparedness. In the READDI-AViDD consortium, we focus on the development of new small molecule antivirals based on hits derived from *in silico*, fragment and high throughput screening. For hits validated through orthogonal assays, hit to lead campaigns are conducted. All data and ideas are placed in the public domain for others to use. In READDI-AViDD project, we carry out the design, synthesis and biological evaluation of broad-spectrum antivirals targeting different viral proteins: SARS-CoV-2-RdRp, SARS-CoV-2-nsp14/10, SARS-CoV-2-nsp14, CHIKV-nsp2- protease and CHIKV-nsp3-MD.



Here we describe the Fragment Based Drug Discovery (FBDD) approach that we are using in the development of new inhibitors targeting CHIKV-nsp3-Macrodomain and the most promising *in vitro* methodologies that can expedite this process. Fragmestein[3] is used in this project to develop fragment merged compounds and we also used Fragalysis[4] which allow us to study the binding interactions of the merged compounds with the target protein (CHIKV-nsp3-Macrodomain) based on their original fragments and then to follow up with the synthesis of these compounds aiming to explore new antivirals which could also assist with the elimination of other viral pathogens[5].

Figure 1. Fragment merged compound designed by Fragmenstein showing binding interactions with CHIKV-nsp3-MD at the adenine binding site.

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Development of novel sirtuin-1 activators: promising therapeutic tools against neurodegenerative diseases

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Machado-Joseph disease is a fatal neurodegenerative disorder characterized by the expression of the toxic mutant ataxin-3 protein. Importantly, our group found that resveratrol, through sirtuin-1 (SIRT1) activation, is effective in alleviating the phenotype of transgenic MJD mice.[1] Moreover, similar positive effects have been described in other neurodegenerative disorders.[2] To overcome the low potency, low bioavailability, and lack of SIRT1 specificity of resveratrol, diverse synthetic activators were developed.[2] Despite high expectations, clinical trials with novel sirtuin-activating compounds (STACs) were disappointing mainly due to pharmacokinetic (PK) issues. Therefore, the present study aimed to take advantage of state-of-the-art computer-aided drug design to discover an improved potent and safe STAC.

All the available 3D structures of SIRT1 were analysed and prepared (Pymol; Jalview; AlphaFold). The two models containing the STAC-binding domain (PDB ID: 4ZZJ / 5BTR) were further optimized and subjected to 1 microsecond molecular dynamics (MD) simulations to explore the behaviour of SIRT1-ligand complexes (Desmond, Schrödinger). After extensive examination, trajectory frame clustering was performed, according to the protein backbone or loops deviations, and the top 5 clusters for each analysis were retrieved. This resulted in 20 representative structures of SIRT1. A comprehensive compound database comprising near 5 million structures, including our own virtual library, was created and virtual screening simulations were performed using Glide (Schrödinger). The compounds were ranked based on their docking score, and, more importantly, the number of times each was present in the top molecules per cluster, allowing us to predict not only the possibility of a strong binding but also the consistence across SIRT1 dynamics. Ligand optimization and redocking were performed with Glide (Schrödinger) and SeeSAR (BioSolveIT). Hits were defined as molecules with good docking scores (Glide) and binding affinities (SeeSAR), when present in the top compounds of most of the 20 clusters. Specialized ADME and toxicity prediction modules were used to filter our compounds to ensure drug-likeness properties and surpassing the limitations of existing STACs (QikProp; SwissADME; pkCSM; Optibrium). Moreover, MD are being performed providing crucial insights into ligand-protein interactions and stability profiles.

We obtained a set of virtual STACs with promising activity and PK profile. This study has the potential to bridge the gap between our previous work and a future pharmacotherapy, also providing proof-of-principle for treatment of high-burden neurodegenerative disorders.

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From inhibitors to degraders: Application to the design of innovative compounds for the treatment of chemoresistant ovarian cancer.

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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. The standard treatment consists of cytoreduction surgery combined with chemotherapy but resistance to platinum salts, constituting the primary cause of therapeutic failure. Escaping apoptosis is a key feature of the tumour process, partly due to the overexpression of anti-apoptotic proteins from the Bcl-2 family, including Bcl-2, Bcl-x_L and Mcl-1. These proteins are privileged targets to be inhibited to overcome resistance, and their simultaneous inhibition restores apoptosis.[1] However, inhibition of both proteins leads to cardiotoxicity and thrombocytopenia due to on-target/off tumor effects.

In order to restore apoptosis, achieve tissue selectivity and avoid toxicity, we chose to develop compounds that simultaneously degrade these proteins by hijacking the UPS (Ubiquitin Proteasome System) pathway. The UPS is one of the main pathways responsible for protein degradation *in vivo* and is involved in almost 80% of protein degradation in the cell. It is a quality control process that uses E3 ligases to identify damaged or misfolded proteins so that they can be degraded via the proteasome, also known as the "cell's trash-disposal machinery".[2]

Our work is therefore to design and synthesise new degraders, and more precisely PROTACs and Molecular Glues[3], directed against two Protein Of Interest (POI): Mcl-1 and Bcl-x_L. Molecular scaffolds used to start this work have been studied in previous work of the research team and have shown interesting inhibition activities.[4] The synthesis of 25 degraders will be presented in this study, including *In silico*, *in vitro* and *in vivo* results for some of them.

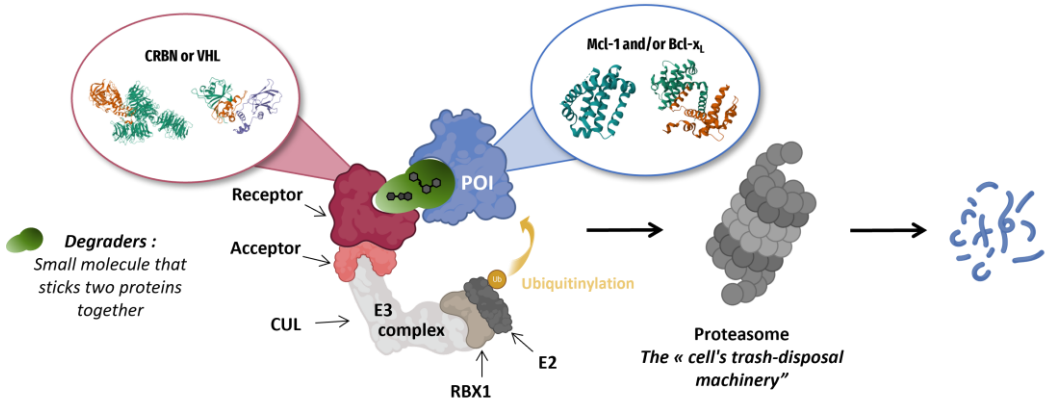

Figure 1. Schematic representation of a degrader ternary complex with the POIs and E3 Ligases (CRBN and VHL).

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A versatile conjugation platform for the development of protacs and molecular probes for their characterization

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PROTACs (PROteolyisis TArgetting Chimeras) are heterobifunctional molecules capable of hijacking E3 ligases in order to degrade a specific protein of interest (PoI). This unique mechanism of action has led to the development of a vast number of PROTACs targeted towards different PoIs, always using a limited pool of E3 ligases. Indeed, most PROTACs developed so far hijack CRLCRBN and CRLVHL, using thalidomide derivatives and VH 032 variants.[1,2]

The limited expansion of the E3 ligase toolbox has led to a need for pharmacological tools dedicated to screening E3 ligase ligands. In this context, Celtarys Research's expertise in developing fluorescent tools using an efficient and convergent proprietary conjugation technology is a perfect fit for designing and synthesizing new fluorescent probes for different ligases.[3]

Herein, we report the data obtained during a proof-of-concept using Celtarys' technology to obtain a total of 10 PROTACs as well as the process behind the development and synthesis of novel VHL and CRBN fluorescent probes and the preliminary affinity data of 8 VHL fluorescent ligands, developing a TR-FRET assay for the best ligand.

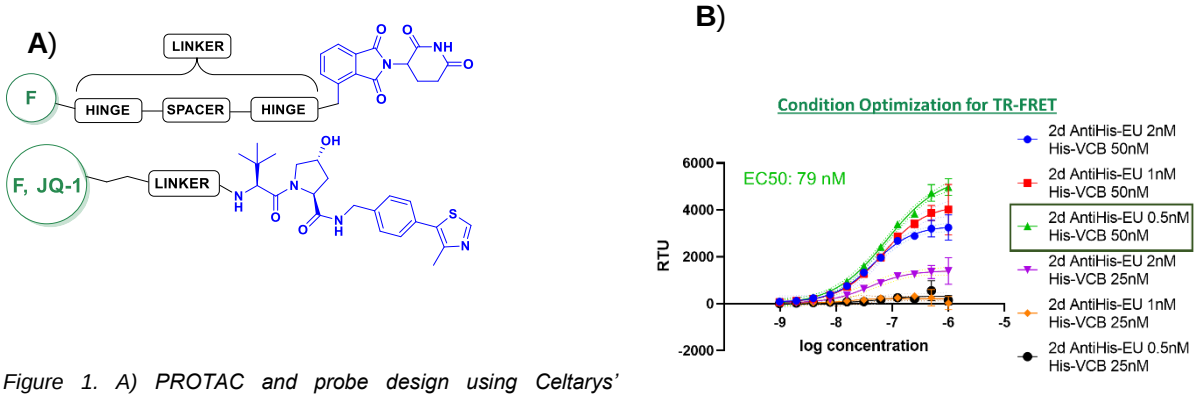

Figure 1. A) PROTAC and probe design using Celtarys' proprietary technology. B) TR-FRET assay concentration optimization.

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Benchmarking traditional and deep learning models for protein target activity prediction

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Machine learning (ML) algorithms can learn subtle, hidden patterns in sparse chemical data and use this knowledge to make predictions on unseen data. Small molecule target discovery, a key step in the drug discovery process, has been accelerated by ML models.[1,2] ML methods, ranging from traditional approaches (*e.g.* Random Forest) to deep learning (DL), such as Transformers, can be exploited for activity prediction and target discovery. Although the success of DL in a wide range of applications suggests its advantage over traditional methods, its performance has shown to be only marginally better or even inferior.[3]

Therefore, we assessed the performance of several ML methods for the activity prediction task. This benchmarking study was conducted on the ChEMBL database (version 31), with 1167 protein targets (50 – 8,000 entries). The algorithms were designed to predict normalized activity values, using CATS2 pharmacophore descriptors for fixed representation and SMILES for representation learning, and were optimized through hyperparameter tuning. Model performance was evaluated using regression metrics such as Coefficient of determination (R^2), Mean Absolute Error (MAE), and Mean Squared Error (MSE). Metrics were obtained from a 10-fold cross-validation with different random state values.

We found that activity predictions for the ChEMBL database were significantly better with traditional methods, specifically tree-based methods which outperformed all DL methods, including representation learning. This difference could be attributed to the data-intensive nature of DL models, which may struggle with smaller, more specific datasets typically associated with biological research. Consequently, our findings emphasize the importance of selecting the appropriate algorithm for activity prediction, with traditional ML methods proving more suitable for activity predictions.

This work was supported by the Fragment-Screen (101094131) project. A.L Dias acknowledges Fundação para a Ciência e Tecnologia (FCT) for the financial support from the PhD studentship 2022.09827.BD.

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Development of new nature-inspired synthetic flavonoids for marine biofouling prevention

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Marine biofouling, caused by the settlement and accumulation of marine micro and macroorganisms on submerged surfaces, namely on boats, is responsible for several economic, environmental and health concerns.[1] Antifouling coatings containing biocides have been used over the past decades to prevent this phenomenon. However, these biocides presented high toxicity for the environment and human health, so more environmentally safe antifoulants are urgently needed.[2] Aiming to discover new sustainable antifouling compounds with low ecotoxicity and considering the potential of some marine flavonoids as antifoulants, our research group has been focused on the synthesis and evaluation of antifouling activity of synthetic flavonoid derivatives.[3,4] Among them, several flavonoids showed promising antifouling activity, namely the prenylated chalcone C1P (Figure 1).[4] Based on these results, and in an effort to develop more effective antifoulants, a series of chemically related flavonoid analogues was prepared using lead optimization strategies of Medicinal Chemistry (Figure 1). The antifouling activity was investigated using the *in vivo* anti-settlement bioassay with *Mytilus galloprovincialis* larvae and marine biofouling microorganisms. Complementary assays with *Artemia salina* were also performed to evaluate their toxicity against non-target marine organisms. These studies resulted in the identification of several flavonoids with antifouling activity and low toxicity against macro- and microfouling species.

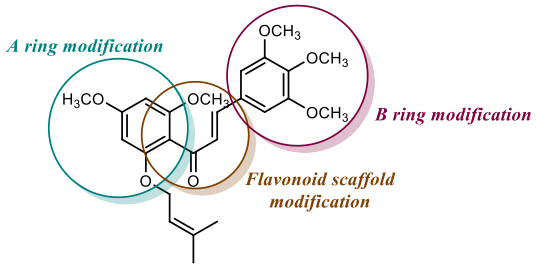

Figure 1. Structure of C1P and synthetic research plan.

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Design and synthesis of novel allosteric modulators for the prostaglandin EP2 G protein-coupled receptor

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The prostagladin EP_2 receptor (EP_2) is a widely expressed G protein-coupled receptor activated endogenously by prostaglandin E_2 (PGE_2), 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] EP_2 antagonism is therefore considered a possible therapeutic approach to treat these diseases. Previously, numerous orthosteric antagonists (i.e. those that bind to the PGE_2 binding site) have been synthesised.[1, 3] In 2020, "**Compound 1**" (Figure 1A) was reported as the first allosteric EP_2 antagonist that demonstrates a reversible, agonist dependent mode of action.

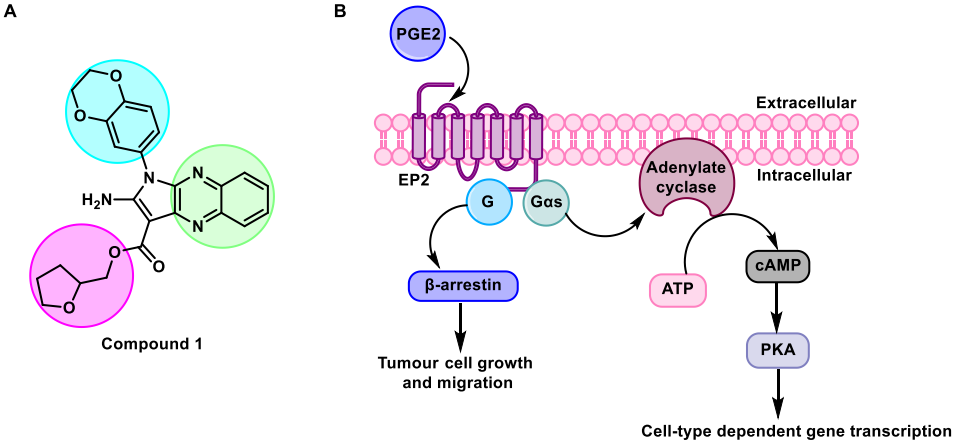

Figure 1. ***A.*** *Structure of "**Compound 1**" highlighting three regions of interest for structural modification; dioxane (blue- where most structural changes occurred in the literature), tetrahydrofuran (pink) and quinoxaline (green).* ***B.*** *PGE_2 binds and activates EP_2, $G_{\alpha s}$ -mediated induction of adenylate cyclase to increase cytoplasmic cAMP levels. Downstream events are then mediated through protein kinase A. EP_2 activation also induces ß-arrestin2 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*) moiety. Initial work has identified novel analogues of "**Compound 1**" displaying improved affinity and potency for EP_2 compared to the literature compound whilst demonstrating an insurmountable mode of action indicitive of a negative allosteric modultor. Pharmacological characterisation was using conducted using both a NanoBRET competition binding study employing the G protein mimetic peptide TMR-Gαs19cha18 and a NanoBiT complementation assay demonstrating selectivity at the hEP2 receptor compared to the closely related hEP4 receptor.[3, 4]

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4-Anilinoquinazoline derivatives as new potent and selective NOD1-RIPK2 inhibitors for the treatment of inflammatory diseases

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Inflammation is a defense mechanism with the function to restore tissue damages and to eliminate pathogens. Inflammation can be triggered by danger signals (DAMP: Danger Associated Molecular Pattern) or pathogenic signals (PAMP: Pathogen Associated Molecular Pattern) recognized by immune cells present in tissues, through Pattern Recognition Receptors (PRR). Among these PRR, Nucleotide Oligomerization Domain 1 and 2 (NOD1/2) have been identified to play an important role in innate immunity responses. It has been reviewed that inhibition of NOD1 could be interesting to treat severe infections and inflammatory diseases. In this work, we identified the first selective NOD1 *vs* NOD2 inhibitors at the nanomolar range based on a 4-anilinoquinazoline scaffold.[1,2] We demonstrated that NOD1 inhibition occurs through the inhibition of Receptor Interacting Protein Kinase 2 (RIPK2), a serine/threonine kinase, involved in its downstream signaling pathways (Figure 1).[2] Our best inhibitors, demonstrate no cytotoxicity, selectivity for RIPK2 over EGFR and VEGFR and a capacity to reduce pro-inflammatory cytokine IL-8 secretion in HEK-Blue™-*h*NOD1. Moreover, two of our compounds showed promising *in vivo* activity on a DSS-induced colitis murine model.[2] The 4-anilinoquinazoline scaffold offers novel perspectives to design NOD1-RIPK2 inhibitors, potentially useful to treat inflammatory diseases.

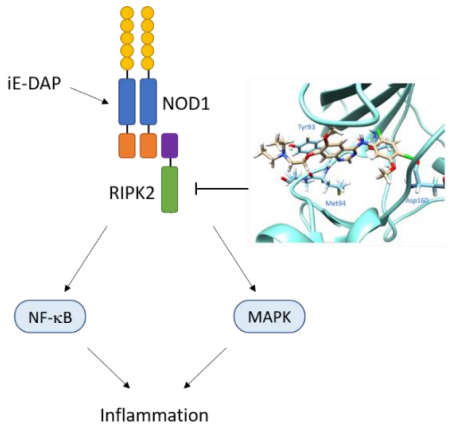

Figure 1. Representation of our compounds' mode of action in inhibiting NOD1 inflammatory signaling pathways.

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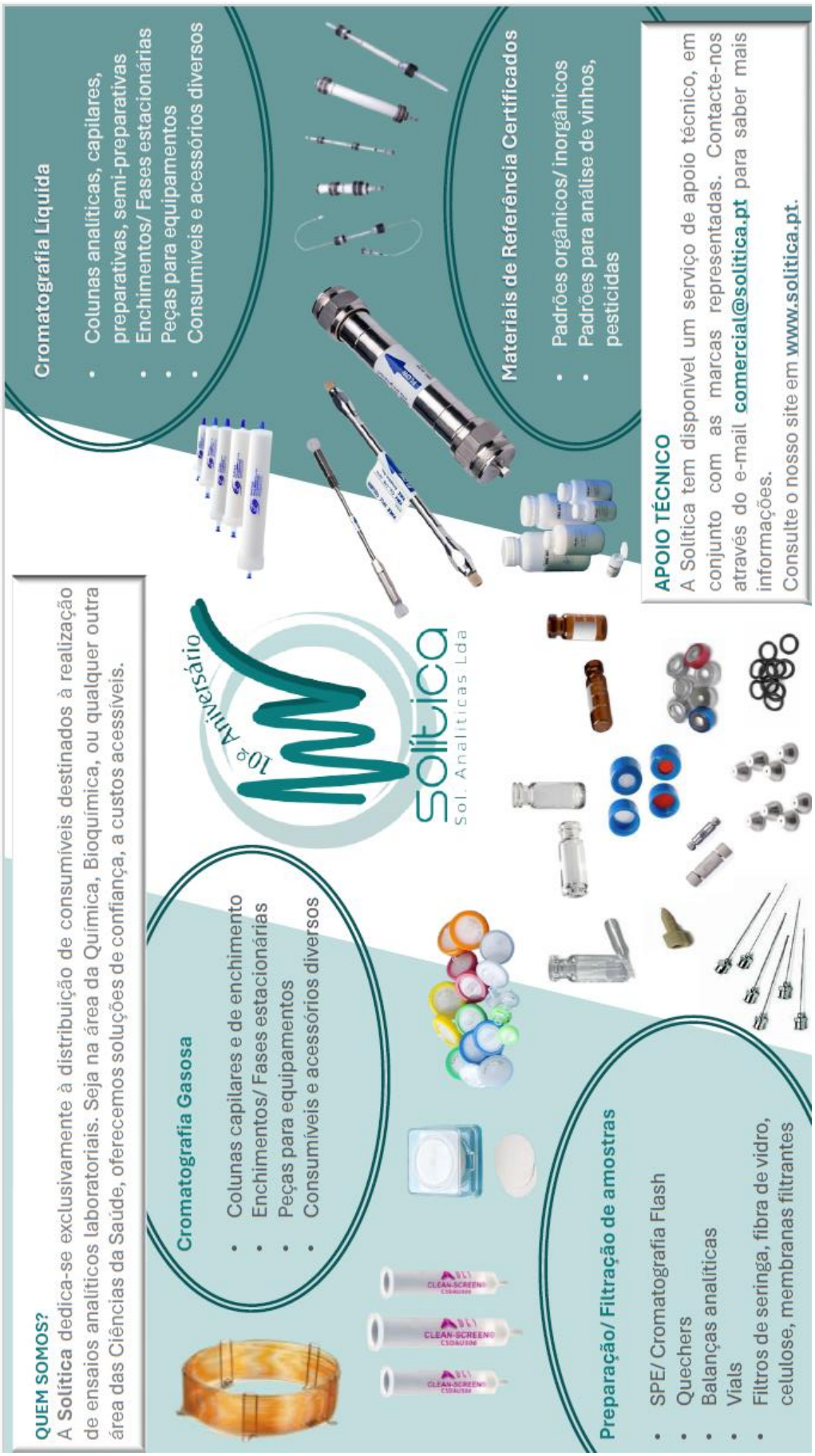
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Posters Abstracts

P01: Use of machine learning methods and pharmacophore screening to search for compounds with dual antiparasitic and anticancer activity among different thiazolidinone and pyrazoline derivatives

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Thiazolidinone ring derivatives, such as 2,4-thiazolidinedione, rhodanine (2-thioxo-4-thiazolidinone), 2-alkyl(aryl)-substituted and 2-amino(imino)-substituted 4-thiazolidinones are widely used as privileged structures and sub-structures for the design of "drug-like" molecules, including those with anticancer and anti-parasitic properties [1]. The analysis of sub-libraries of compounds based on the synthesized various thiazolidinones from the "in-house" library of the Department of Pharmaceutical, organic and bioorganic chemistry with the anticancer activity on Leukemic cell line HL-60 (NCI protocol) and anti-parasitic activity against *Trypanosoma brucei brucei* (*in vitro* studies) were chosen for the ML studies. To classify the compounds with the antitrypanosomal activity as an independent variable an IC_{50} calculated in the growth inhibition assay towards *Tb brucei* was selected. The classes were divided as follows: i) class 1: IC_{50} <5 μM or inhibition > 90% at 10 mg/mL; ii) class 2: IC_{50} 5-10 μM or inhibition < 90% > 50% at 10 mg/mL; iii) class 3: IC_{50} > 10 μM or inhibition < 50% at 10 mg/mL.

Compounds from the class 1 (with the highest inhibition rates towards *Tb brucei*) were selected in one cluster when applying both the agglomerative hierarchical clustering and k-means clustering algorithms. Selecting compounds from the same classes into the same clusters when applying above mentioned ML techniques testifies the robustness of the algorithms. The agglomerative hierarchal clustering is based on dendogram creation. An unsupervised ML algorithm k-means clustering aims to minimize *the sum of distances between the points and their respective cluster centroid.*

Pharmacophore screening was carried out for 5 compounds (from the 1st class) identified in one cluster: 3,5-arylidene-1*H*-pyrazol-thiazol-2-one and 3,5-arylidene-1*H*-pyrazol-isatine hybrid molecules, 5-enamine-rhodanine-3-phenylpropionate, 5-ene-2-amino-4-thiazolidone derivatives to a pharmacophore merged from a series of BCL-2 complexes with antagonist venetoclax (PDB codes: 6O0K, 6O0M, 6O0P), which is used for the chronic lymphocytic leukaemia and acts via promoting apoptosis. The results of pharmacophore modeling (LigandScout 4.4 Software) characterized all studied molecules as active (pharmacophore-fit scores 38-58.7). Obtained pharmacophore model was then used for the screening of a set of hybrid molecules bearing combination of 4-thiazolidinone or thiazole core and phenyl-indole or 6-phenyl-imidazo[2,1-*b*][1,3,4]thiadiazole fragment with the *in vitro* studied submicromolar levels of IC_{50} on *Tb brucei and Tb gambiense* [2]. All 19 tested compounds fit the pharmacophore model with pharmacophore-fit scores within the range of 36.01-55.55.

Conclusions. A set of thiazolidine derivatives with the established dual antitrypanosomal and anticancer activity had been analyzed by clustering methods resulting in selecting a group of highly active antitrypanosomals with good anticancer properties. The latter underwent pharmacophore screening (BCL-2-venetoclax complexes). The same pharmacophore model when applied to a set of highly active antitrypanosomals – indole and imidazothiadiazole thiazolidinone hybrids had also showed high pharmacophore-fit scores suggesting they might possess antiproliferative properties as well.

Acknowledgment. We are grateful to the LigandScout developers for the providing free academic license.

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P02: Synthesis of Indeno[1,2-b]indoles: Challenges and Insights from Literature to Experiment

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Indeno[1,2-*b*]indole has been demonstrated to be a key scaffold for the design of new bioactive molecules in oncology (e.g. inhibitors of protein kinase CK2, inhibitors of the *breast* cancer resistance protein ABCG2). Depending on the synthetic route chosen, a large possibility of specific functionalizations can be achieved.[1] Initially, we focused our SAR study on substituents (from R_1 to R_5) in order to develop new indeno[1,2-*b*]indoles as CK2 inhibitors.

Four functionalized indeno[1,2-*b*]indoles were synthesized using the two-step reaction described by Hemmerling *et al.*[2] and Gozzi *et al.*[3] (Figure 1).

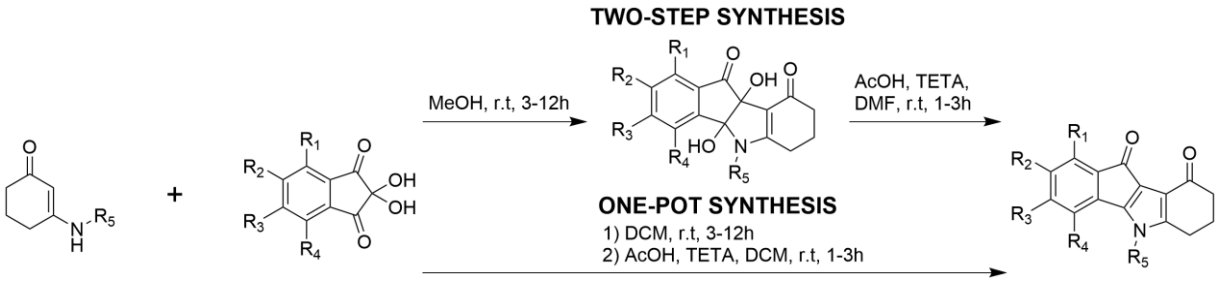

Figure 1. Comparison of two-step synthesis from Gozzi *et al.*[3] and one-pot synthesis.

It has been observed that the reaction conditions described become inappropriate depending on the substituents used. Indeed, unexpected results have been observed: incomplete reaction progress, very low yields, significant formation of by-products.

In this presentation, we will discuss the optimization work concerning the quantities of reagents and the selection of solvents used in the synthesis process. Based on the optimal reaction conditions determined, a one-pot synthesis method has been developed to improve yields and make the synthesis more convenient and straightforward.

This work was supported by ANR-DFG (XPLOR_CK2, ANR-22-CE92-0081).

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P03: Fragment-based drug design: an effective approach for aiming at challenging targets to discover new anti-inflammatory agents

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Various methods can be used to discover new drug candidates. These include the fragment-based drug design method. We report the successful use of this method in the development of a both selective and affine compounds for the BIR2 domain of XIAP protein. X-chromosome-linked inhibitor of apoptosis protein (XIAP) is a protein involved in various signalling pathways, in particular thanks to its different baculovirus IAP repeat (BIR) domains, which are involved in different protein-protein interactions. XIAP is implicated in a pro-inflammatory pathway: *via* its BIR2 domain. XIAP interacts with receptor-interacting protein 2 (RIP2), ultimately leading to pro-inflammatory signalling.[1] Therefore, blocking selectively the XIAP-BIR2 domain could reduce this inflammatory signalling. The main problem in developing compounds that disrupt this protein-protein interaction is the high homology between the BIR2 and BIR3 domains of XIAP and other members of IAP family (in particular cIAPs) leading to off target effects.[2] In order to avoid them, it is crucial to develop compounds that are selective for XIAP-BIR2. The aim of the "XIAP project", currently developed in CERMN, is to design molecules that interact specifically with XIAP-BIR2, in order to disrupt the XIAP-RIPK2 interaction and obtain potentially anti-inflammatory molecules.

To achieve this, we embarked on a chemoinformatics-assisted "*de novo drug design*" process, using a fragment-based drug design method. This first stage enabled us to explore the domains of interaction between XIAP-BIR2 and RIPK2 and, among other things, to determine the differences between XIAP-BIR2 and XIAP-BIR3. Thanks to these data, we synthesised an initial library of 50 fragments. *In vitro* affinity evaluation of fragments for both XIAP-BIR2 and XIAP-BIR3 was carried out using AlphaScreen® and Fluorescent Polarization Assay (FPA) technologies. The modulation of best fragments led to the obtention of a hit molecule, affine and selective for XIAP-BIR2. Validation of the inhibitory activity of XIAP in cellular models was carried out using 'HEK-Blue NOD' cell lines, which specifically control the expression of the NOD1 and NOD2 signalling pathways (figures 1A). Thanks to this proof of concept, we are now continuing our pharmacomodulation work to improve the affinity of the hit while maintaining selectivity for XIAP-BIR2, such as shown in Figure 1B.

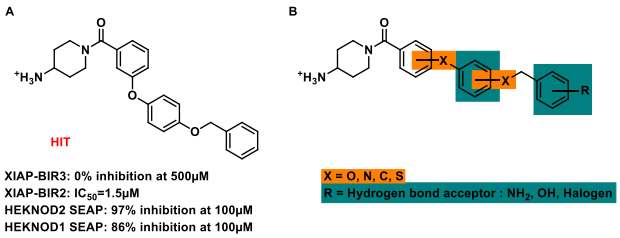

Figure 1. Current results and objectives of the "XIAP project"

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P04: Semisynthetic Anti-cancer Halimane Derivatives from *Plectranthus ornatus* Codd.

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Natural products have long been a cornerstone in drug discovery, providing a vast array of bioactive compounds with therapeutic potential. The *Plectranthus* genus is widely recognized for its medicinal benefits. *Plectranthus ornatus* Codd., in particular, is traditionally used in Africa to treat gastric and liver ailments, with its leaves known for their antibiotic properties[1]. The primary component of *P. ornatus* is the halimane compound, 11 *R**− acetoxyhalima− 5,13*E*− dien− 15− oic acid (**Hal**), which is noted for its anticancer effect [2]. This study aimed to enhance the efficacy of the halimane lead compound and additional physiochemical characterization of **Hal** was conducted. To our knowledge, this research is the first to publish data on the absolute configurations using SCXRD and the thermal stability of **Hal**. Reactions of **Hal** with various amines were performed to create new semi-synthetic derivatives and their structures were elucidated. The cytotoxicity of these derivatives was tested against three leukemia cell lines (CCRF-CEM, K562 and HL-60). Their antioxidant activity was examined using H2O2-induced HGF-1 cells, and anti-inflammatory activity was studied using RT-PCR and ELISA. The findings revealed that the amide derivatives of **Hal** exhibited moderate cytotoxicity and more potent activity compared to the parent molecule, providing insights into the structure-activity relationship (SAR) of **Hal**. These derivatives also showed protection against DNA oxidative damage. Furthermore, they demonstrated anti-inflammatory properties by modulating gene and protein expression of cytokines IL-1β, TNF-α, and IL-6, induced by LPS in normal HGF-1 cells. Overall, this study offers valuable insights into the improved biological activities of semi-synthetic **Hal** derivatives, laying the groundwork for novel cancer therapy drug formulations.

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P05: Modifying positions 2 or 8 of the imidazo[1,2-*a*]pyrazine lead compound CTN1122 affects its antileishmanial activity, L-CK1.2 kinase inhibition, and safety profile.

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Leishmaniasis is a parasitic disease classified as a neglected tropical disease by the WHO. It manifests in various forms—cutaneous, mucocutaneous, and visceral—and poses a serious public health issue, with 12 million people infected globally and over 40,000 deaths annually. The disease is endemic in many regions worldwide, with its emergence in Europe attributed to global warming. Current treatments are far from ideal due to their high toxicity, significant costs, and administration methods that limit accessibility for disadvantaged populations. Additionally, increasing parasite resistance to these treatments is diminishing their effectiveness in some areas. Consequently, there is an urgent need to develop new treatments that are safer, more effective, and target novel proteins to overcome these resistances. A promising recent discovery is **CTN1122**[1], which targets a specific *Leishmania* Casein Kinase 1 protein (L-CK1.2)[2,3] and demonstrates strong antileishmanial properties. In this context, we have decided to synthesize **CTN1122** analogues to enhance the pharmacological activity profile. (**Figure 1**)

IC_{50} (amastigotes *L. major*) = 0.80 µM
IC_{50} (amastigotes *L. donovani*) = 2.74 µM
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

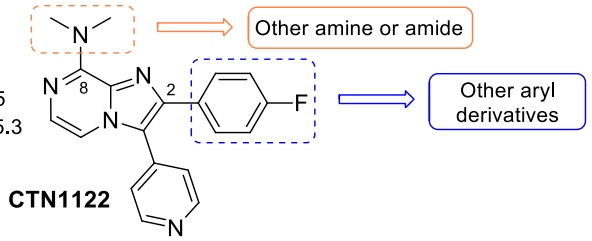

Figure 2: Modulations from the hit compound **CTN1122**

Two types of pharmacomodulation on the imidazo[1,2-*a*]pyrazine ring of the lead compound **CTN1122** will be presented and compared. One by modifying the substituent in position 8 with various amines and amides and the other by modifying the substituent in position 2 with variously substituted aryls. The study of these analogues will enable us to discuss the structure-activity relationship concerning their antileishmanial properties, their ability to inhibit the target protein L-CK1.2 and to consider their toxicity profile.

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P06: *In Vitro* Evaluation of Potential Substance P Antagonists Designed for Dermatological Applications

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Chronic pruritus has been linked with the activation of neurokinin 1 receptor (NK1R) by substance P (SP), making the design of SP antagonists an upcoming strategy to alleviate this dermatological condition.[1] The identification of a natural SP antagonist, along with the disclosure of NK1R crystallographic structure, facilitated the design of new SP antagonists. Given the common association between pruritus and inflammation, our objective was to utilize structure-based drug design to develop novel SP antagonists inspired by a promising marine natural product and evaluate them *in vitro* in representative skin cell lines. This approach seeks to create innovative compounds suitable for the topical treatment of inflammatory skin diseases associated with pruritus.

Seventy designed ligands were evaluated for their binding affinity to NK1R (PDB 6E59, AutoDock Vina) together with their pharmacokinetic properties, using *in silico* methods. Eighteen compounds were selected and evaluated *in vitro* (keratinocytes, macrophages, and fibroblasts) to assess both cytotoxicity and potential anti-inflammatory activity. A significant reduction in the pro-inflammatory mediator nitric oxide (NO), together with a significant decrease in inducible nitric oxide synthase (iNOS) protein levels, and the absence of NO-scavenging potential, suggest the inhibition of inflammatory pathways upstream of the synthesis of iNOS. The presence of an aromatic moiety appears crucial for the observed activity, prompting further design studies and new synthetic approaches. A total of ten new potential substance P antagonists were obtained and structurally characterized for further studies.

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P07: Synthesis and anti-tumor evaluation of thieno[2,3-*b*]pyrazine derivatives

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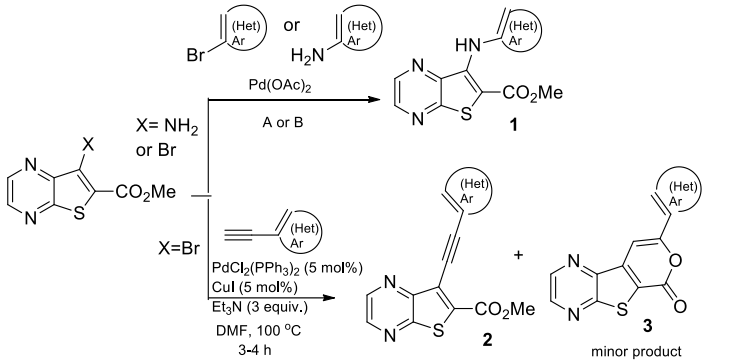
The thieno[2,3-*b*]pyrazine skeleton has been found in natural products such as urothion and its derivatives, and in biologically active synthetic compounds useful in the prevention or treatment of inflammation, cell proliferation and immune-related conditions and disease.[1a,b]

Herein we present the synthesis and preliminary antitumor evaluation of thieno[2,3-*b*]pyrazine derivatives obtained by Pd-catalysed C-N Buchwald-Hartwig (compounds **1**),[2] and Pd/Cu-catalyzed Sonogashira (compounds **2**) couplings, starting from the methyl 3-amino or 3-bromothieno[2,3-*b*]pyrazine-2-carboxylate. Furthermore in the Sonogashira coupling reaction, compounds **3,** resulting from 6-*endo-dig* cyclization, were also obtained as minor products (**Scheme 1**).



Scheme 1- Synthesis of thieno[2,3-*b*]pyrazine derivatives **1**, **2** and **3**

The series of compounds **1**, **2**, and **3** were evaluated for their cytotoxic activity in several human tumor cell lines (Caco-2, MCF-7, AGS, HeLa and NCI-H460) and, in Vero Cells or in a porcine liver primary cell culture (PLP2) as toxicity models. For the most promising compounds, characterized by low GI_{50} values and no toxicity in non-tumor cells, further studies on apoptosis induction and cell cycle profile were conducted to gain insights into their mechanisms of action.

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P08: Targeting tuberculosis: exploring dual-action terpenoid derivatives as promising agents

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Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*Mtb*), remains a significant global health threat with substantial morbidity and mortality rates. The efficacy of first-line anti-TB drugs, isoniazid (INH) or rifampicin (RIF), was compromised by the development of chromosomal mutations in *Mtb* over recent decades. However, the amount of new anti-TB drugs entering clinical trials is insufficient. Alternatively, semi-synthesis or structural modifications of well-known first-line antitubercular drugs offer a versatile approach to yield effective medications. Thus, the aim of the present study is to employ the prodrug/codrug strategy to optimize the INH structure in order to enhance its efficacy against *Mtb*.

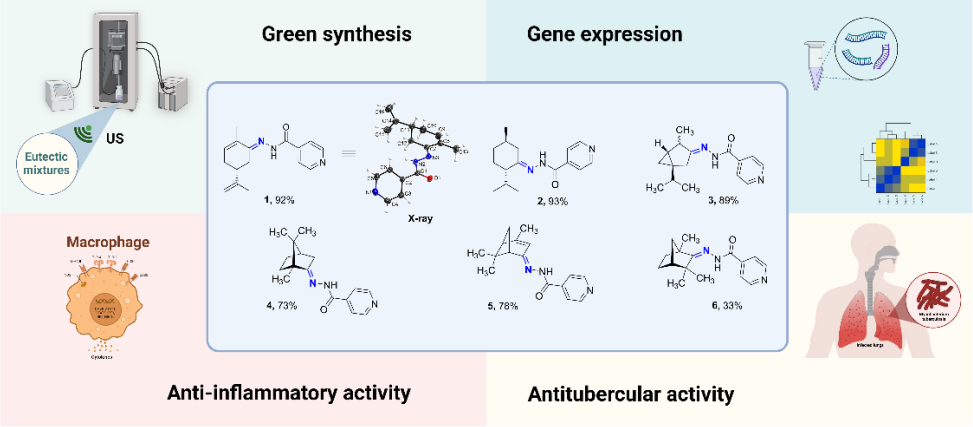

Figure. Investigation of terpenoid derivatives with dual action.

Terpenoid derivatives exhibited significant activity against the virulent *Mtb* strain H37Rv, with MIC_{90} values ranging from 0.5 to 8 µM. Given the intracellular nature of *Mtb* growth, the synthesized compounds attenuated the expression of pro-inflammatory cytokines TNF-α and IL-6 in LPS-induced THP-1-derived macrophages. Additionally, qRT-PCR analysis revealed downregulation of IL-6, IL-10, TNF, CCL3, and CCL4 gene expression in macrophages upon treatment with INH derivatives. The most promising candidate exhibits activity against *Mtb*-infected human monocyte-derived macrophages at a concentration of 0.5 µM. Furthermore, we conducted *in vitro* ADME profiling, assessed cytotoxicity against HepG2 cells and THP-1 macrophages for the most active terpenoid derivatives.
Thus, terpenoid-based INH derivatives are active against the virulent *Mtb* strain H37Rv, modulate pro-inflammatory cytokine expression, downregulate specific gene expression, and exhibit promising efficacy against *Mtb*-infected human macrophages, suggesting them as anti-TB agents with favorable *in vivo* ADMET.

P09: Translational Approach to Combat RNA Viral Infections in Horses: A Pathway Towards Equine and Human Health Protection

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RNA viruses present significant challenges to animal health, particularly in equine populations, where infections like Equine Arteritis Virus (EAV) and Equine Infectious Anemia Virus (EIAV) have become increasingly prevalent.[1] Despite advancements in veterinary medicine, the arsenal against these viruses remains limited, urging innovative strategies for effective disease management. Our interdisciplinary research initiative is aimed at integrating veterinary virology with medicinal chemistry to address the pressing need for novel antiviral therapies against EAV and EIAV. After some successful preliminary tests exploring this hypothesis[2], we have employed cutting-edge technologies, including *in silico* screening of CERMN's library of compounds and structure-based drug design, to identify and develop new antiviral molecules. Also, our approach encompasses drug repurposing strategies, leveraging the diverse chemical space of existing compounds to expedite the discovery of potential therapeutics, that would enable us to rationally design and optimize drug candidates, targeting essential viral proteins and host cell factors critical for viral replication and pathogenesis.

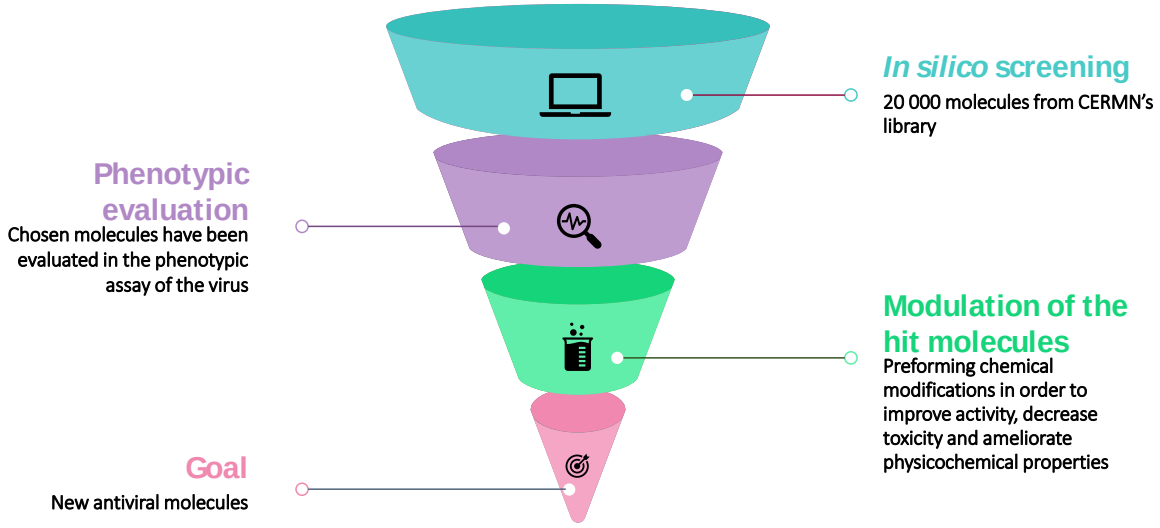

Figure 1. Representation of the research process.

Finally, we want to explore the translational potential of our research by investigating structural and functional similarities between equine and human viral infections, offering insights into the development of therapeutics against human pathogens such as HIV and coronaviruses like SARS-CoV-2.[3]

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P10: Covalent modification of wild-type p53 with a tryptophanol-derived oxazoloisoindolinone

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The protein p53 has a crucial role in cells, preventing genome mutations. Mutations in the *TP53* gene are present in about 50% of human tumours, and in these cases p53 is unable to carry out its tumour-suppressing functions. The presence of mutated forms of p53 is linked to the development of more aggressive tumours with increased metastatic potential.[1] Consequently, there is growing interest in developing small molecules able to modify mutant p53 to wild-type (wt) p53 functional form. Until now, few mut-p53 activators have been developed and entered clinical trials, and none has yet reached clinic use. Over the last few years, our research group has been involved on the development of tryptophanol-derived oxazoloisoindolinones as p53 activators.[3] Optimization of one hit compound led to the development of a more active and more selective derivative for colon cancer cells expressing p53. In this communication, we will disclose our latest results on the study of the mechanism of action of this new derivative. The lead compound was tested against wt-p53, R273H and R280K mutant p53 using a differential scanning fluorimetry (DSF) assay, showing that it stabilizes the proteins. Mass spectrometry-based covalent binding assay with wt- p53 protein, showed that the compound can react and covalently bind to cysteines in the wt p53 DNA binding domain (Figure 1).

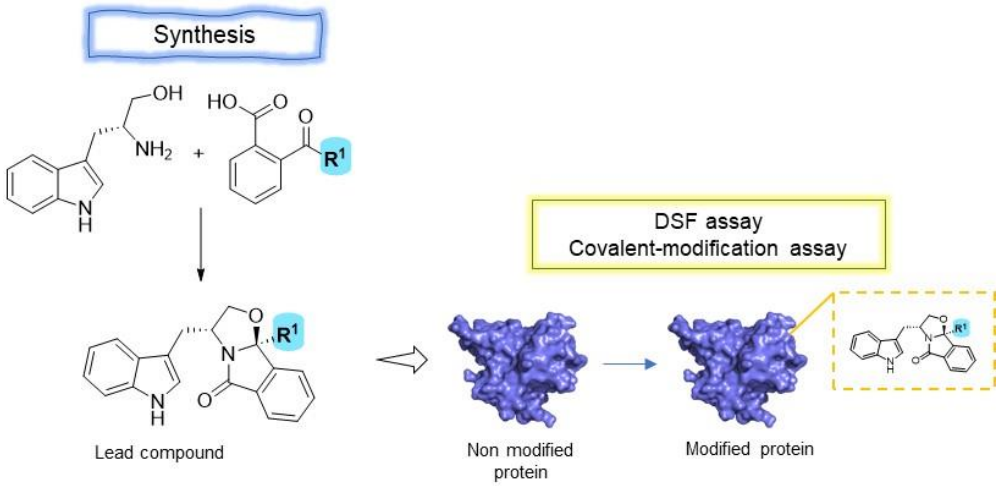

Figure 3. Overview of the assays.

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P11: Synthesis of Glycosyl-Triazole-Phthalimides as Antiviral Agents

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus responsible for causing coronavirus disease 2019 (COVID-19).[1] Since its discovery, research has rapidly advanced to develop treatments for patients and combat the virus's spread. However, the need for updated drugs persists due to the emergence of new variants and severe cases that are more difficult to treat. Using a click reaction,[2] 12 molecular hybrids were synthesized by combining azido-phthalimide derivatives and 2,3-unsaturated alkynyl-*O*-glycosides, resulting in the formation of 1*H*-1,2,3-triazole-based compounds with excellent yields (54-99%). Cytotoxic activity on Vero cells and activity against the SARS-CoV-2 virus were investigated *in vitro*. The compounds exhibited 20% cytotoxic concentrations (CC_{20}) ranging from 208.5 µM to over 1000 µM. Following screening, all compounds showed significant differences in statistical analyses against the SARS-CoV-2 virus. Compound **3e** had a selectivity index (SI) value of 195.8, and compound **3f** had an IC_{50} value of 11.2 µM. *In silico* analyses, including docking and molecular dynamics, were also performed to elucidate the mechanism of action and interactions between the synthesized compounds and the target proteins of SARS-CoV-2.[3] The computational results indicated that 3CLpro could be the plausible target for these analogs, with compound **3f** emerging as the best candidate.

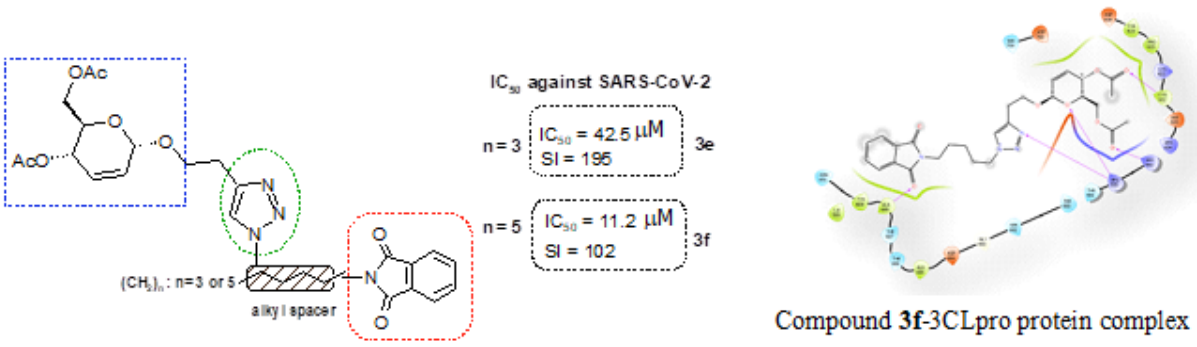

Figure 1. Results of the post-infection assay of compounds **3e** and **3f** against the SARS-CoV-2 virus

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P12: Effect of LUSO's thermal water on LPS-induced macrophage inflammation

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Ingestion of natural mineral water (NMW) contributes to important mineral intake, which might explain their extensive use in human nutrition with acknowledged health benefits, particularly related to an anti-inflammatory effect[1,2]. NMW's therapeutic properties are empirically recognized but lack scientific validation, particularly in Portugal. In this study, we focused on LUSO NMW, a hyposaline water, mainly composed by chlorine, sodium and potassium, with relevant traces of magnesium, calcium and bicarbonate. LUSO NMW-based therapies (indicated primarily for the Circulatory, Nephro-Urinary and Respiratory system diseases, and Rheumatic and Musculoskeletal disorders), are often directed to inflammatory-associated pathologies. Hence, we investigated the effect of LUSO NMW in an in vitro model of inflammation, specifically the murine macrophage cell line (RAW 264.7) cultured in normal culture medium or LUSO NMW-containing medium, for 48 h, in the absence or presence of Lipopolysaccharide (LPS; 100 ng/mL). In these cells we evaluated: 1) cellular metabolism (Resazurin assay); 2) M1 (pro-inflammatory) and M2 (anti-inflammatory) profile (Flow cytometry); 3) Phagocytic capacity (Flow cytometry); 4) NF-kB nuclear translocation (Immunofluorescence); 5) Gene expression (real-time RT-PCR); 6) Protein levels (Western-blotting); 7) Nitric oxide (NO) (Griess assay) cytokines secretion levels (ELISA). The results showed that LUSO NMW increased macrophage metabolism and phagocytosis. Moreover, the expression of the M2 marker, CD163, was significantly higher in cells exposed to LUSO NMW. In an inflammatory context (with LPS), LUSO NMW decreased *Il6* and *Tnfa* gene expression, pro-IL-1β protein levels, and IL-1β, IL-6 and TNF-α secretion levels. In contrast, cells exposed to LUSO NMW exhibited higher mRNA and protein levels of the antioxidant enzyme HMOX1. Overall, these results validate the anti-inflammatory effect of LUSO NMW, and support its antioxidant potential. In conclusion, LUSO NMW therapeutic effect should be deeply explored, including as an adjuvant in immune- and anti-inflammatory-based therapies.

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P13: Discovery and SAR exploration of novel a_{2a} antagonists as anticancer agents

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Adenosine is a key immunosuppressive metabolite that regulates one of the major mechanisms supporting immune tolerance in tumors[1]. In normal cells, A_{2A} and A_{2B} receptors are engaged in the regulatory mechanisms that protect tissues against excessive immune response[1,2]. However, in the tumor microenvironment, an elevated adenosine concentration hijacks this protective pathway and obstructs anti-tumor immunity[2].

Adenosine inhibits the biological functions of T lymphocytes, infiltrating the cancer tissue by binding to the A_{2A} receptor. Similarly, activation of A_{2A} receptor on NK cells leads to a loss of their effector capacity, and therefore hinders the elimination of cancerous cells[2]. In this regard, A_{2A} and A_{2B} receptor antagonists constitute an emerging family of immunotherapeutic agents for cancer treatment. Accordingly, we herein document the design, synthesis, and SAR studies of a large collection of A_{2A} receptor antagonists.

Inspired by the Lundbeck 28 ligand[3], we carried out a pharmacomodulation process with the aim to improve the potency and selectivity of the series by introducing new diversities that potentiate non-orthosteric interactions. The classical UGI-4CR and several of its variants were employed for library synthesis, thus enabling to identify new ligands with excellent A_{2A} affinity/selectivity profiles. The antiproliferative and antimetastatic effect observed for selected A_{2A} antagonists will be presented.

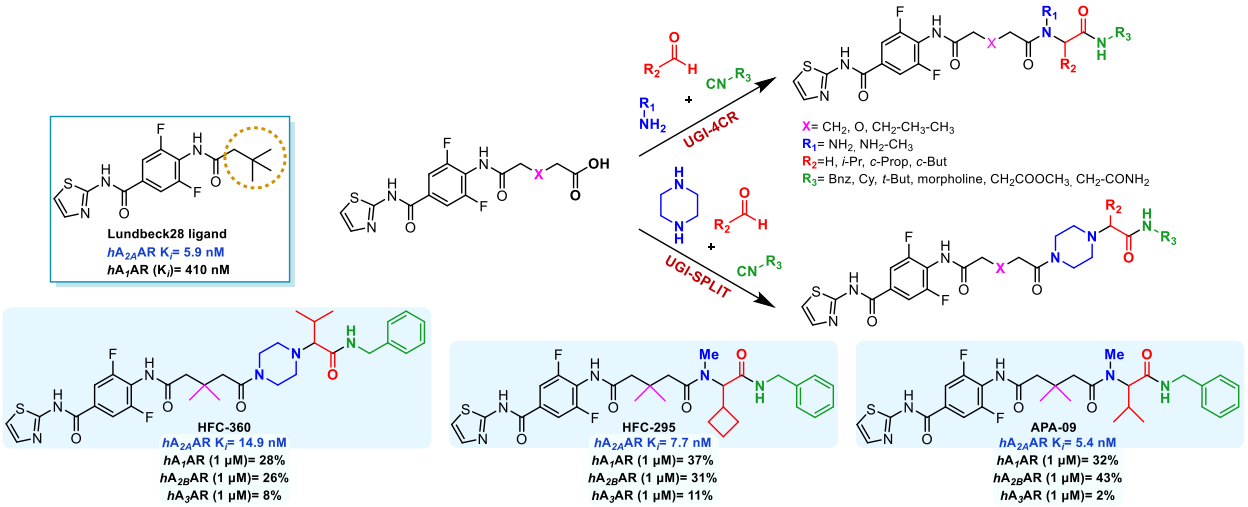

Figure 1. Selected compounds obtained from the MCR-assisted pharmacomodulation of *Lundbeck28* ligand

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P14: Marine-derived cyclodepsipeptides: synthesis though an emerging alternative to conventional peptide cyclization

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Unnarmicins A and C are cyclodepsipeptides produced by marine bacteria *Photobacterium* sp.,[1] that can inhibit the fungal ABC transporters whose overexpression is the cause of the highest levels of multi-drug resistance of pathogenic fungi.[2] Structurally, they comprise a tetrapeptide and a hydroxy aliphatic chain linked by an ester bond, differing only in the length of the aliphatic chain (**Figure 1**). Current methods for the chemical synthesis of cyclodepsipeptides in solution is a great challenge, particularly the head-to-tail cyclization step due to the formation of dimers or oligomers that reduces overall yields and restricts chemical diversity of cyclic molecules.[3] Therefore, the trend is to explore other synthetic approaches.[4]

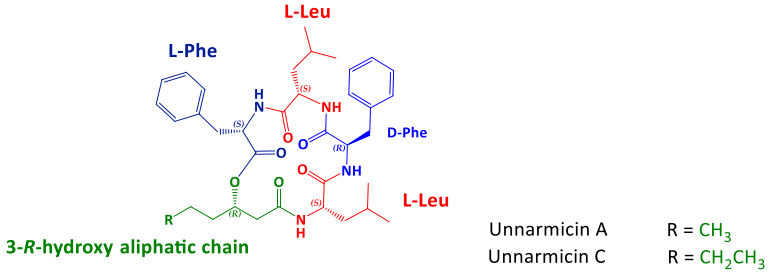

Figure 1. Structures of cyclodepsipeptides, unnarmicin A and C.

Herein, we report the synthesis of new cyclodepsipeptides, analogues of unnarmicins A and C, though an emerging alternative to conventional peptide cyclization. First, the peptide building blocks were synthetized through a solution-phase synthetic strategy by using coupling agents and protecting agents such as *tert*-butyloxycarbonyl (Boc), benzyl ester, and methyl groups. Deprotections were planned according to the labile acid and base groups. In addition, chiral liquid chromatography was used to enantioseparate and determine the enantiomeric purity of chiral building blocks comprising a hydroxy fatty acid chain. The structures of all the synthetized compounds were established by spectroscopic methods. To your knowledge, it is the first report of synthesis of cyclodepsipeptides by this peptide cyclization approach. Further studies will include the evaluation of their antimicrobial activities.

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P15: Introducing chirality into nature-inspired flavones as promising eco-friendly antitumor agents

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Searching for more environmentally friendly drug production and development practices leading to compounds with greater biodegradability and less ecotoxicity is an emerging issue given the negative impact of their improper disposal in the environment.[1] Flavones are an important class of natural products with great interest in Medicinal Chemistry due to their multiple biological activities, particularly antitumour.[2] Frequently, their combination with a chiral moiety, such as amino acids, results in highly biodegradable compounds with greater selectivity for the target.[3] Over the last decades, several reports have focused on the synthesis of chiral flavonoids to evaluate the influence of chirality on their pharmacological profile.[4]

Following the concept of "benign by design"[5] and according to the research group experience, a library of chiral derivatives of flavones (CDF) was prepared by combination of four different flavone skeletons with enantiomerically pure esters of tryptophan and tyrosine to assess the influence of chirality on their antitumor activity. Liquid chromatography using a polysaccharide-based column confirmed the success of the enantioselective reactions, with enantiomeric ratios above 89%. Moreover, biological assays performed on three human tumour cell lines showed that CDF displayed better antiproliferative activity compared to their precursors. Particularly, Trice derivatives conjugated with methyl ester of tryptophan stood out for their lower GI_{50} values. Interestingly, enantioselectivity was proven in most enantiomeric pairs, where usually one enantiomer demonstrated prominent antiproliferative activity towards the other enantiomer. Additional studies to predict the toxicity and evaluate the mechanisms underlying the most promising compounds are being carried out.

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P16: Conjugation of siderophore mimetics with antibiotics/antimicrobial adjuvants as a new approach to overcome antibacterial resistance

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Antibacterial resistance is already a global health emergency.[1] In consequence, the development of innovative strategies to fight antibacterial resistance is now a top priority. Siderophores are metal chelating compounds with a high affinity for iron which are produced by numerous microorganisms as well as some plants.[2] The conjugation of siderophores or their synthetic mimetics with antibiotics constitutes a promising approach to the development of target-directed antibacterial agents, with encouraging results already reported in the literature.[3] Inspired by the vast potential of this strategy, in this work we aimed to synthesize siderophore mimetics and conjugate them with an antibiotic or with an antimicrobial adjuvant, such as an efflux pump inhibitor.

Herein, several siderophore mimetics were synthesized and conjugated with an efflux pump inhibitor, to obtain five novel conjugates (**Figure 1**). The efflux pump inhibitor was first attached to a linker and then combined with the siderophore mimetic through sequential coupling reactions. Efforts in the coupling of the siderophore mimetics with a known antibiotic are currently underway. Additionally, the effect of siderophore mimetics in the growth of a reference strain of *Escherichia coli* and the antibacterial activity of the obtained conjugates against a panel of human pathogenic bacteria was investigated. Future work includes the assessment of possible synergism with antibiotics and investigation of the conjugates' capacity to inhibit bacterial efflux pumps.

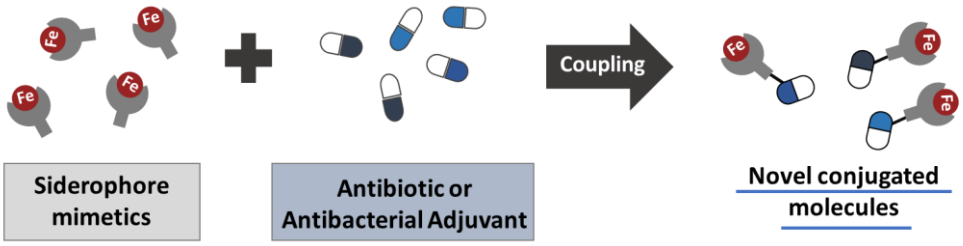

Figure 4 Schematic representation of the main goal of this work.

FCT - UIDB/04423/2020, UIDP/04423/2020, 2021.05224.BD doi:10.54499/2021.05224.BD, 2022.00379.CEECIND/CP1728/CT0001 doi:10.54499/2022.00379.CEECIND/CP1728/CT0001.

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P17: Drug Repurposing to Discover Novel Antibacterial Agents: Our Experience

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Drug repurposing offers significant advantages in the field of drug discovery over traditional approaches. It features shorter development times, reduced costs, and improved safety profiles by utilizing existing drugs or drug candidates for new indications or targets.[1] In early 2022, our colleagues screened an FDA-approved drug library and identified the S1PR modulator fingolimod as a promising antibacterial agent against *S. aureus* and *A. baumannii*.[2] Inspired by this discovery, we screened a selected set of commercially available S1PR modulators, leading to the identification of etrasimod as a promising antibacterial agent against several Gram-positive bacteria, including multidrug-resistant (MDR) strains.[3] In addition to repurposing S1PR modulators, we have structurally optimized them to enhance their antibacterial activity.[4] Concurrently, by combining our experience with S1PR modulators and available in-house data, we have identified the main structural features necessary to achieve antibacterial activity against Gram-positive bacteria. Additionally, as S1PRs are part of the GPCR superfamily, we screened a small set of other GPCR-targeting drugs and clinical candidates. This effort resulted in the identification of AMG837, a well-known GPR40 agonist albeit a previously failed clinical candidate, as a possible starting point for developing antibacterial agent against Gram-positive bacteria (unpublished data).

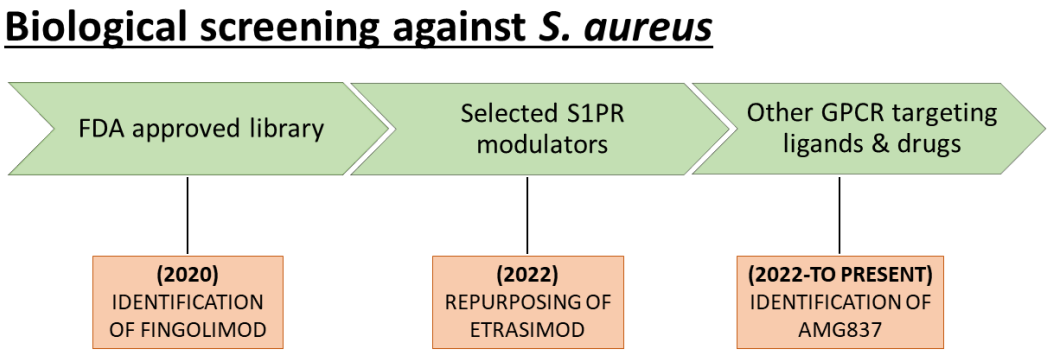

Figure 1. Overview of our research work in antibacterial field using drug repurposing approach.

In summary, our recent success in identifying S1PR-targeting drugs as promising antibacterial agents against Gram-positive bacteria underscores the importance of the drug repurposing approach. Our work also opens new avenues for exploring other GPCR-targeting drugs and clinical candidates as potential starting points for discovering effective antibacterial agents to combat MDR bacteria.

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P18: QN6 as a new ligand for the therapy of diseases of aging and stroke

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We have recently identified (*Z*)-*N*-benzyl-1-(8-hydroxyquinolin-2-yl)methanimine oxide (**QN6**), as a potent hBuChE (IC_{50} = 1.06 ± 0.31 nM) and hMAO-B (IC_{50} = 4.46 ± 0.18 μM) inhibitor, showing antioxidant and biometal chelator properties, able to cross the blood–brain barrier, no cytotoxic, acting as a neuroprotector agent in a 6-hydroxydopamine cell model of Parkinson's disease (PD),[1] as an anti-amnesic ligand in the scopolamine-induced mouse model of Alzheimer's disease (AD), and that chronic treatment of double transgenic APPswe-PS1δE9 mice with **QN6** reduced amyloid plaque load in the hippocampus and cortex of female mice.[1]

Here we report the neuroprotective properties and the antioxidant power of **QN6** for their potential application in stroke. *In vitro* neuroprotection studies of **QN6** in an oxygen-glucose-deprivation model of cerebral ischemia, in human neuroblastoma cell cultures, indicate that **QN6** is a potent neuroprotective agent that prevents the decrease in neuronal metabolic activity (EC_{50} = 3.97 ± 0.78 μM) as well as necrotic (EC_{50} = 3.79 ± 0.83 μM) and apoptotic cell death (EC_{50} = 3.99 ± 0.21 μM),[2] showing high capacity to decrease superoxide production (EC_{50} = 3.94 ± 0.76 μM). Furthermore, in an experimental permanent focal ischemia model, **QN6** treated animals exhibited a very significant reduction (75.21 ± 5.31%) of the brain lesion volume size.

Overall, **QN6** as a unique, single and multivalent agent for the combined therapy of diseases of aging such as PD/AD, and stroke.[1,2]

This research was supported by grants OPTICOMC903 and NACONT from the Camilo José Cela University (Madrid)

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P19: New azole antifungals with a fused imidazopyrimidone scaffold

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Currently, drug resistance observed with many anti-infectives clearly highlights the need for new broad-spectrum agents to treat invasive fungal infections (IFIs).[1] The antifungal *armamentarium* includes the polyenes (amphotericin B formulations), the pyrimidine analogue (flucytosine), echinocandins and the azoles (fluconazole, itraconazole (first generation), voriconazole, posaconazole and isavuconazole (second generation). Isavuconazole, and its structural analogue ravuconazole share a similar 4-(1,3-thiazol-4-yl)benzonitrile moiety (Figure 1), and both are active against clinically important yeasts and moulds including *Candida* spp. and *Aspergillus* spp..[2] These azoles inhibit cytochrome P450-dependent lanosterol 14α-demethylation (CYP51) leading to a depletion of ergosterol (major component of the fungal cell membrane). *As part of our research project* we replace the thiazolyl substituent of ravuconazole by an imidazo[1,2-*c*]pyrimidin-5-one scaffold while retaining the benzonitrile moiety or substituting it by a more hydrophilic pyridine-2-carbonitrile (Figure 1).

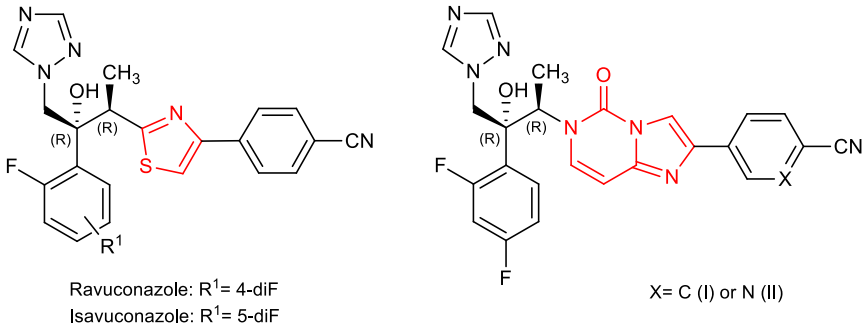

Figure 5. Chemical structures of some antifungal agents and our synthesized compounds.

These compounds were tested against pathogenic *Candida* spp. (fluconazole-susceptible and fluconazole-resistant) and against some filamentous fungi such as *Aspergillus fumigatus,* and the zygomycetes *Rhizopus oryzae* and *Mucor circinelloides*. Compound **I** was also evaluated against two murine models of lethal systemic infections caused by *Candida albicans*.

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P20: Conformational Restriction of Designer Drugs Provides Potent and Selective CB_2 Agonists with Neuroprotective Effect

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Synthetic cannabinoid receptor agonists (SCRAs) are new psychoactive substances that mimic the psychotropic effects of THC. Introduced into the illicit drug market in the 2000s, they are sold over the Internet under names like Spice, K2, or "synthetic marijuana".[1] The consumption of SCRAs is associated with serious adverse effects, including psychosis, seizures, cardiotoxicity, and renal injury, and has led to significant mortality. However, their effects in humans remain largely unknown, posing challenges for scientists, healthcare professionals, and regulatory authorities.[1,2] The first part of this study documents the synthesis and pharmacological characterization of a library of 64 enantiopure SCRAs. Pharmacological data demonstrated that these compounds are highly potent at both CB_1 and CB_2 receptors.[3] The collection was developed to provide standard compounds for enforcement agencies to monitor SCRAs in the illicit drug market. The second part of the study focuses on increasing selectivity for the CB_2 receptor. Designing molecules with a 5- or 6-carbon ring at the amide terminus resulted in 64 new compounds with conformational restriction. This modification preserved their activity and made them highly selective for the CB_2 receptor while maintaining their potency. Biased agonism studies were conducted to understand the specific signaling pathways activated by these compounds. Additionally, a small sample of six compounds was evaluated for neuroprotective effects, revealing promising data.

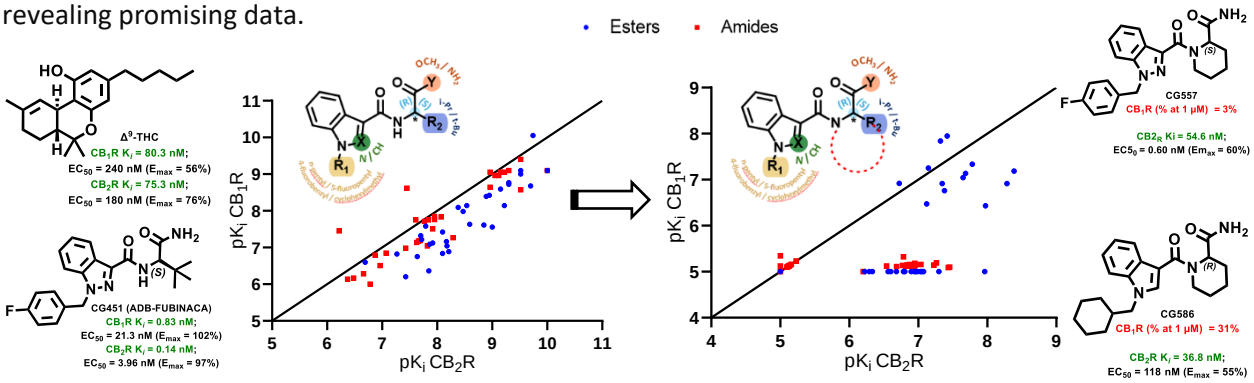

Figure 1. Graphical representation of the pharmacological data of SCRAs and cyclic amides. It shows the transition of compounds from being very potent and non-selective to highly selective for the CB_2 receptor.

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P21: Development of novel small molecules to reactivate R273H mutant p53

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The tumour suppressor protein p53 is often referred in the scientific community as the "guardian of the genome". In almost 50% of tumours the p53 gene, *TP53*, is mutated.[1] These mutations preferentially occur in the DNA-binding domain of the protein and can be classified as structural (e.g., R175H, Y220C) or DNA contact (e.g., R273H, R280K).[2] Cancers that harbour mutant (mut) p53 R273H are currently one of the most difficult to treat, since this mutation enhances cell proliferative and metastatic properties.[3] Only a few small-molecules have been developed to treat mut p53 tumours by restoring its wild-type (wt) conformation, and inhibiting cell proliferation and tumour growth. However, none of them act on the R273H mutation, and the molecular mechanisms underlying the action of these compounds remain obscure. Nevertheless some have entered clinical trials, *i.e.* APR246 against mut p53 R175H, reaching Phase I and/or II as monotherapy.[1] Enantiopure tryptophanol-derived isoindolinones were previously identified as direct reactivators of wt-p53 and mut p53, and some derivatives showed p53-dependent *in vivo* antitumor activity.[4] In this communication we will disclose our results on the hit-to-lead optimization of this chemical scaffold with the goal of obtaining novel reactivators of mut p53 R273H able to restore the p53 wt-conformation. New substituents were inserted to explore the chemical space and to improve solubility, Figure 1. The synthesized compounds were evaluated against mut p53 R273H using a Differential Scanning Fluorimetry (DSF) assay, and the most promising compounds were also tested against several cancer cell lines expressing different p53 status.

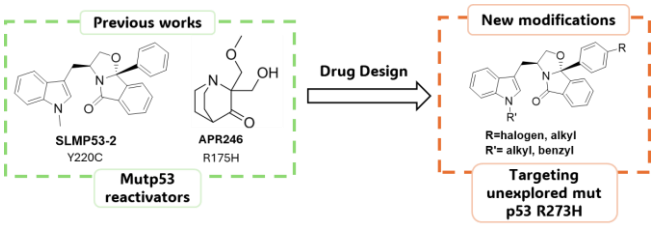

Figure 1. Hit-to-lead optimization on the Tryptophanol-derived scaffold to target mut p53 R273H.

Acknowledgments

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P22: Design, synthesis and biological evaluation of new MT5-MMP inhibitor as potential therapeutic interest in Alzheimer's disease

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Alzheimer's Disease (AD) is one of the most common senile dementia in the world and a global issue in health care. Though several efforts to find therapeutics, most of them broke down in clinical trials with 98% fails since 2003.[1] This pushed scientists to a better understanding of the physiopathology which is still not totally known nowadays. Even though AD is a multifactorial disease, the main hypothesis is the aggregation of Amyloid β peptide (Aβ) from amyloid precursor protein (APP) cleavage which results in the formation of senile plaques in the brain cortex. Finding a way to prevent this aggregation has always been a goal since the discovery of Aβ. Recently MT5-MMP was discovered as a new target playing a role in Aβ formation.[2] MT5-MMP is a metalloproteinase which acts as η-secretase and releases a neurotoxic Aη-α fragment from APP cleavage and in a second time is also proamyloidogenic that promotes production of Aβ. The inhibition of this protein can so become an interesting new therapeutic strategy to treat AD. In this context we have recently identified a new family of MT5-MMP inhibitors possessing an amide linker. In order to explore new analogs, several sulfonamides and triazoles linkers have been introduced and the structure of the ligand (Figure 1) have been compared using X-Ray analysis with the goal to develop potent and selective inhibitors.

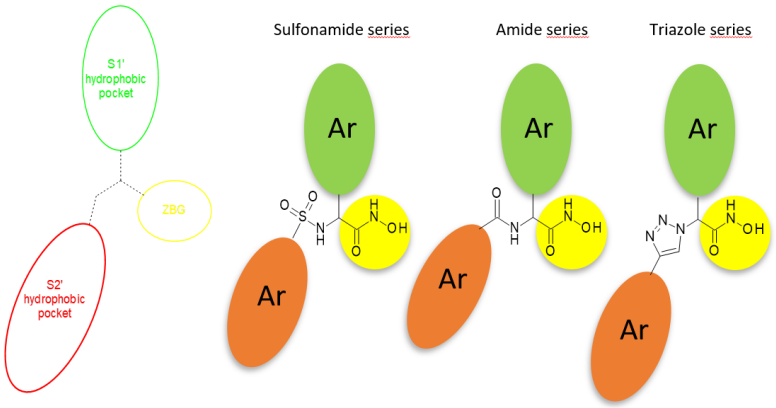

Figure 1 : General structure of the designed inhibitors.

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P23: Targeting IRE1 for an adjuvant therapy in gliobastoma

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Glioblastoma (GB) is the most frequent and malignant primary brain tumor. Its highly infiltrative nature and heterogeneity 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.[1] This makes of IRE1 inhibition an appealing therapeutic strategy in oncology, either as monotherapy or as adjuvant therapy alongside established treatments.[2,3] Our group established the relevance of targeting IRE1 in GB and showed in GB mouse models that IRE1 inhibition resulted in reduced tumor aggressiveness and increased sensitivity to temozolomide (TMZ), the reference chemotherapy.[4] Using a structure driven drug discovery pipeline, we identified Z4P, a blood brain barrier permeable and kinase site-bound ligand showing inhibitory activities in GB cell models, sensitization of tumor cells to TMZ, and more strikingly preventing tumor relapse in mice when used in combination with TMZ.[5] We will disclose here our results concerning the structure-activity relationships (SAR) on the Z4P series.

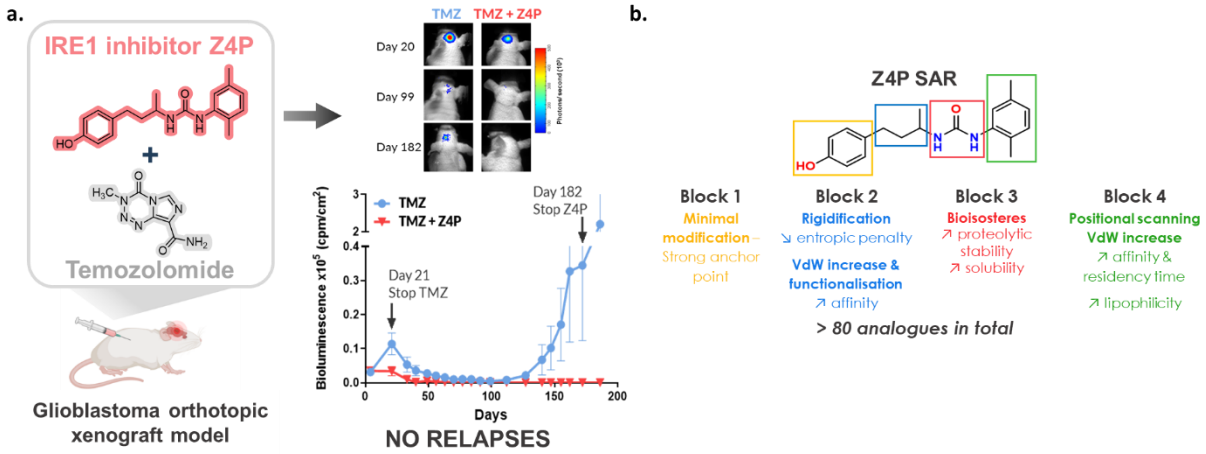

Figure 6: a. Quantitative analysis of bioluminescence imaging signal across 200 days of experiment with temolozomide alone (blue) and the combination temolozomide/Z4P (red). b. Structure-Activity Relationships (SAR) strategy around the Z4P scaffold.

Financial support from La Ligue Contre le Cancer, Plan Cancer and Fondation pour la Recherche Médicale is acknowledged.

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P24: Approaches to the Synthesis of Isatin-based Molecules as Inhibitors of BACE-1 and Cholinesterases

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Alzheimer's disease (AD) remains a significant neurodegenerative disease with limited therapeutic options. Some of the targets involved in AD are considered undruggable, meaning that these biomolecules do not respond to conventional small molecules.[1] Consequently, larger molecules have begun to be considered potential therapeutics for these targets. Macrocycles for a long time have a privileged status for the treatment of various disease, particularly cancer (Dolastatin, Laulimalide A, Peloruside), anti-microbial (Erythronolide B) and immunosuppressants (Rapamycin, FK-506), showing favorable pharmacological properties.

Our interest has been the development of novel oxindole-based macrocycles, which show a large spectrum of biological activities against neurodegenerative diseases, particularly Alzheimer's.[2,3]

In this study, we report our efforts on synthesizing a series of isatin-based macrocycles and their precursors, and evaluating these precursors against some key AD targets. The compounds were tested for inhibitory activity against beta-secretase 1 (BACE-1) and cholinesterases (ChE), both crucial enzymes implicated in AD pathology. Molecular docking studies have been carried out providing further insights. Additionally, we assessed the cytotoxicity and neuroprotective effects of these compounds using the N2A-APPswe cell line, a well-established *in vitro* model for AD.

We thank FCT for funding through the strategic project UIDB/00313/2020|UIDP/00313/2020 to CQC-IMS.

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P25: The Bucherer-Bergs Multicomponent Reaction for Accesing Chiral spiro-oxindole-hydantoins: Screening against *Leishmania donovani*

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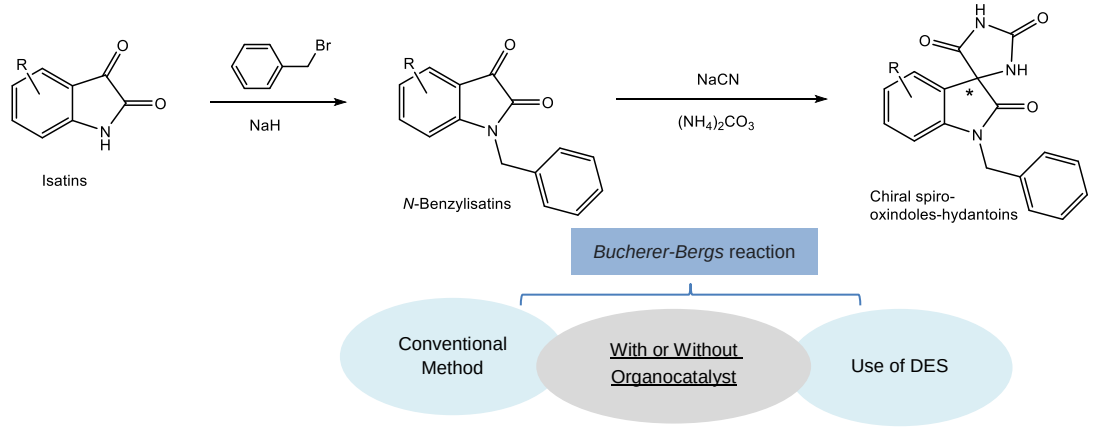
Leishmaniasis is a neglected tropical disease (NTDs), being the second biggest cause of death for a parasitic disease in, after malaria.[1] According to the World Health Organization, it is estimated that 700,000 to 1 million new cases are reported every year. Current treatments include antimony compounds, amphotericin B, pentamidine, miltefosine, among others.[2] However, these pharmaceuticals show toxicity, and require prolonged usage as well as being expensive.[3]
Interestingly, several spiro compounds have already demonstrated antileishmanial activity.[4] The oxindole unit is a well-known pharmacophore [5] and, in fact, compounds containing oxindole have been reported for their antileishmanial activity.[6] Hydantoins (imidazolidine-2,4-ones) are also biologically active.[7] In this communication we will discuss our results on the multicomponent synthesis (*Bucherer-Bergs* reaction) of a library of spiro-oxindole-hydantoins. Our studies included the use of Natural Deep Eutectic Solvents (NADES) and organocatalysts (Scheme 1).
We are currently evaluating these compounds for their antileishmanial activity in *Leishmania donovani*, and gratifyingly some of these compounds were found to be active.



Scheme 1: Synthesis of Chiral spiro-oxindoles-hydantoins.

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P26: Leveraging the identification of novel ubiquitin specific protease 7 (USP7) inhibitors through a structure-based virtual screening protocol

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Ubiquitin-specific protease 7 (USP7) is a member of one of the most largely studied families of deubiquitylating enzymes, which are proteases in control of the dynamics of ubiquitination. It plays a key role modulating the levels of multiple proteins, including tumor suppressors, transcription factors, epigenetic modulators, DNA repair proteins, and regulators of the immune response. The abnormal expression of USP7 is found in various malignant tumors and a high expression signature generally indicates poor tumor prognosis. This suggests USP7 as a promising prognostic and druggable target that offers interesting new avenues for cancer therapy. Wherefore, the main goal of this study was the identification of promising small molecules that could potentially inhibit USP7 enzymatic activity. The work was conducted according to an integrated molecular modelling protocol, including structure-based pharmacophore and molecular docking virtual screening. Such protocol disclosed new USP7 hit compounds, highlighting the utility of computer-aided drug discovery in the early steps of the drug discovery process, and paved the way for the identification of promising USP7 inhibitors that might represent a steppingstone for cancer treatment.

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P27: Design, synthesis and biological evaluation of novel madecassic acid derivatives with anticancer potential

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Madecassic acid (**1**) is a pentacyclic triterpenoid found in the traditional medicinal plant *Centella asiatica* (L.) Urban that has various pharmacological activities.[1] In particular, this natural compound demonstrated anticancer activity by inducing apoptosis in an *in vivo* mouse model bearing the CT26 cancer cell line.[2] There are a limited number of **1** derivatives, and few of them have been explored for their anticancer activity.[3,4] Thus, a series of new derivatives of **1** was synthesized and screened for cytotoxicity against the NCI-60 panel of cancer cell lines. All the tested derivatives exhibited superior antiproliferative activity compared to that of **1**. Among them, compound **29** showed GI_{50} values ranging from 0.3 to 0.9 µM against 26 different tumor cell lines, demonstrating more selectivity for one colon (COLO 205) and two melanoma (SK-MEL-5 and UACC-257) cell lines at the TGI level. The mechanism of action of compound **29** was predicted using CellMiner bioinformatics analysis and validated by biochemical assays. These studies demonstrated that treatment with **29** induced cell cycle arrest at the G1/S transition and disrupted the mitochondrial membrane potential in tumor cells. Concluding, derivative **29** shows promise as a lead compound for the development of new anticancer drugs and merits further research.[5]

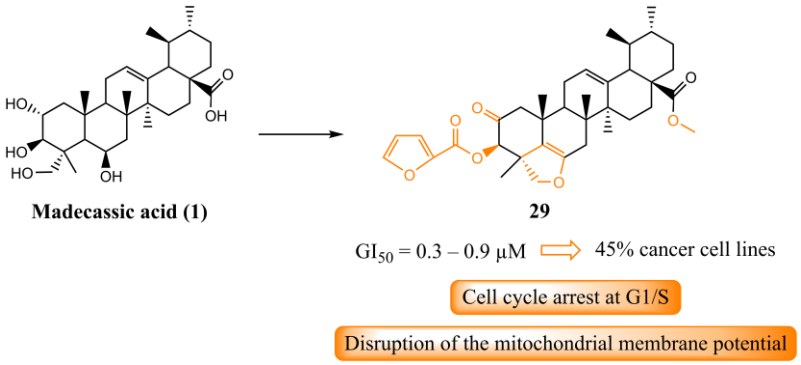

Figure 1. Structure of madecassic acid (**1**) and its derivative **29** with potential anticancer activity.

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P28: Development of emerging strategies to target the Ser/Thr kinase RIPK2

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Inflammation is a defense mechanism designed to repair tissue damage and eliminate pathogens. Receptor-interacting serine/threonine-protein kinase 2 (RIPK2) is a crucial mediator of innate immune signaling pathways, and particularly those initiated by pattern recognition receptors (PRRs) such as NOD-like receptors (NLRs) NOD1 and NOD2.[1] RIPK2 plays a central role in the regulation of inflammatory and immune responses by activating signaling cascades leading to the production of pro-inflammatory cytokines. It functions by recruiting and activating downstream signaling molecules, including the IκB kinase (IKK) complex and mitogen-activated protein kinase (MAPK) pathways, resulting in the activation of transcription factors such as NF-κB and AP-1. Given its pivotal role in inflammatory signaling pathways, RIPK2 has garnered significant interest as a therapeutic target for various inflammatory diseases.[2] Several small molecule inhibitors targeting RIPK2 have been developed and are currently under investigation for their therapeutic potential in diseases such as inflammatory bowel disease (IBD), rheumatoid arthritis, and other inflammatory disorders. In view of our team's expertise in the field of inflammatory diseases, we decided to focus on this promising target.

Our project has been divided into several tasks. The first led to the establishment of structure-activity relationships (SARs) of a series of quinazolines that identified the elements required for activity. In pursuit of strategies that have the potential to lead to highly selective compounds, two emerging strategies have been selected by our team and will be presented in this second poster. The strategy of degrading kinases is emerging and has shown potential for providing greater selectivity compared to conventional inhibitors. These degraders have a tripartite structure consisting of a RIPK2 ligand selected from our series of quinazolines, a hydrophobic tag separated by a linker. The hydrophobic tag mimics the exposed parts of misfolded proteins, attracting chaperone proteins that lead our target to degradation by the proteasome. The aim of synthesizing these degraders is first to vary the linker and hydrophobic tags to establish initial RSAs and proof of concept. A second strategy aims to identify inhibitors of the XIAP-RIPK2 interaction through virtual screening. This approach is justified by the identification of XIAP as the primary ligase responsible for RIPK2 ubiquitination, which is essential for RIPK2 activation of inflammatory pathways. An electron microscopy model (PDB:8AZA)[3] was optimized using the AMBER14 method to identify the amino acids involved in the interaction. Then, a pharmacophore search using Discovery Studio software led to the identification of peptides due to the extent of the interaction. Virtual screening was performed by docking a peptide library obtained via the Protein Data Base (PDB) using AutoDock CrankPep software. These peptides have a defined three-dimensional structure, which reduces the risk of conformational changes during experimental testing. They will be the subject of further testing at our institute for their potential as new *hits*.

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P29: Carvone Derivatives: Synthesis and Screening of Anti-Inflammatory Activity

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Natural products are increasingly used for their anti-inflammatory properties and as sources of new anti-inflammatory compounds [1]. Further chemical modifications are a useful strategy to improve their bioavailability and/or potency.

Previous studies elucidated the structure-activity relationship of monoterpene compounds, derived from *p*-menthane, as potential anti-inflammatory drugs. (S)-(+)-carvone (**1**) was identified as the most potent of the compounds tested and may be efficient in halting inflammation-related diseases like osteoarthritis [2].

The α,β-unsaturated ketone group of carvone seems to be critical for activity. The replacement of the isopropenyl group at C5 by a 2-hydroxyisopropanyl group, such as in 8-hydroxycarvotanacetone (**2**), lowered the potency but provided a hydroxyl group, important to manage the lipophilic properties. Another relevant feature for activity must be the chirality, so both enantiomers of carvone must be studied [2].

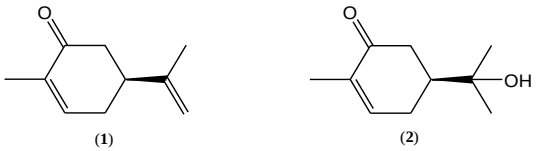

Figure 1: (S)-(+)-carvone (**1**) and 8-hydroxycarvotanacetone (**2**)

Based on these premises, recently, our group reported the synthesis of some carvone derivatives and performed a screening *in silico* and *in vitro* of their anti-inflammatory activity and pharmacokinetic properties [3]. Although the tested compounds still have low potency and specificity, they are presenting anti-inflammatory and some advantageous ADME properties, and the results encouraged us to design new structures that may overcome the detected drawbacks and yield more promising drugs. New carvone derivatives have been synthesized, namely 9-hydroxycarvone, using a 3-step synthesis, and their esters – using acyl halides under basic catalysis. This strategy allowed us to maintain the functionalities and differing at positions 9 and 8 of the molecule and either maintaining or not the double bond, respectively. After purification and structural analysis, the cytotoxicity and anti-inflammatory activity of selected derivatives were evaluated *in vitro*.

Funding: *This work was financed by the European Regional Development Fund (ERDF), through the COMPETE 2020 - Operational Programme for Competitiveness and Internationalization and Portuguese national funds via FCT – Fundação para a Ciência e a Tecnologia, under projects UIDB/04539/2020, UIDP/04539/2020 and LA/P/0058/2020.*

Acknowledgements: *The authors thank to UCQFarma for FTIR/ATR facility and UC-NMR for NMR facility.*

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P30: Discovery of Potent Isoquinolinequinone *N*-oxides to Overcome Cancer Multidrug Resistance

Ryan D. Kruschel[a], Mélanie A. G. Barbosa[b,c,d], Maria João Almeida[b,c], Cristina P. R. Xavier[b,c], M. Helena Vasconcelos [b,c,d], Florence O. McCarthy[a],*

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Multidrug resistance (MDR) of human tumours has resulted in an immediate need to develop appropriate new drugs. Our research has previously identified isoquinolinequinones (IQQ) effective against cancer cell lines and uniquely against the NCI-ADR/RES MDR cell line.[1] This work outlines the development of twenty potent IQQ *N*-oxide derivatives in two isomeric families, both exhibiting nano-molar GI_{50} values against human tumour cell lines.[2] Preliminary NCI-60 tumour screening sees the C(6) isomers achieve a mean GI_{50} >2 times lower than the corresponding C(7) isomers. MDR evaluation of nine selected compounds reveals that each presents lower GI_{50} concentrations in two MDR tumour cell lines. Four of the series display nanomolar GI_{50} values against MDR cells, having selectivity ratios up to 2.7 versus the sensitive (parental) cells. The most potent compound **25** inhibits the activity of drug efflux pumps in MDR cells, causes significant ROS accumulation and potently inhibits cell proliferation, causing alterations in the cell cycle profile. Our findings are confirmed by 3D spheroid models, providing new candidates against MDR cancer.

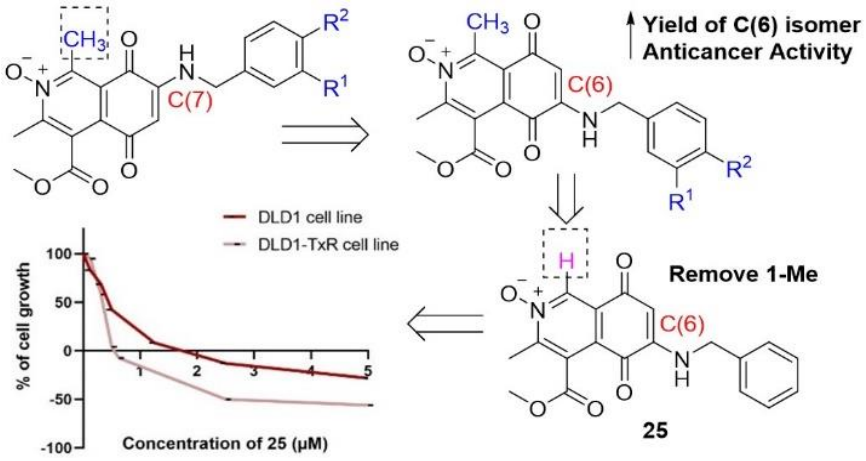

Figure 1. IQQ *N*-oxides as a framework for potent inhibition of MDR cancer cell lines

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P34: Design, synthesis, and evaluation of benzhydrylpiperazine-based novel molecular hybrids as potent COX-2/5-LOX inhibitors with anti-proliferative activity

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The strategy of the development of safer anti-inflammatory drugs resulted in effective and promising leads for the treatment of multifaceted inflammatory diseases. In the current research, we have performed the virtual screening of piperazine-containing compounds from the ChEMBL database and optimized the hit to design and synthesize molecular hybrids of benzhydrylpiperazine and 1,3,4-oxadiazole. The envisioned compounds have been successfully synthesized, characterized, and assessed biologically. The biological activities revealed an appealing inhibitory potential of synthesized derivatives against target enzymes. Surprisingly, the novel compounds also displayed antiproliferative activity in A549-Lung cancer cell lines and COLO-205-colon cancer cell lines. Amongst the investigated compounds, **9d** containing 4-Cl substitution at the terminal phenyl ring appeared to be the most promising lead with inhibition of COX-2 (IC_{50} = 0.25 ± 0.03 µM), and 5-LOX (IC_{50} = 7.87 ± 0.33 µM). The enzyme kinetics investigation of **9d** against COX-2 indicated competitive inhibition (Kd = 0.22 µM). Compounds **9d** and **9g** were evaluated in paw edema models of inflammation, which indicated a significant anti-inflammatory response. These potential compounds demonstrated reduction of PGE_2, IL-6, and TNF-α, and an increase in IL-10 concentrations. Furthermore, the promising compounds displayed gastrointestinal (GI), liver, and kidney safety along with antioxidant properties. Moreover, treatment with compounds **9d** and **9g** limits platelet aggregation and suggests no indication of cardiotoxicity when examined on rats with myocardial infarction. The most promising compound **9d** also displayed anti-cancer potential in the Drosophila flies model. The results were also correlated with *in silico* docking and molecular dynamics simulation studies.

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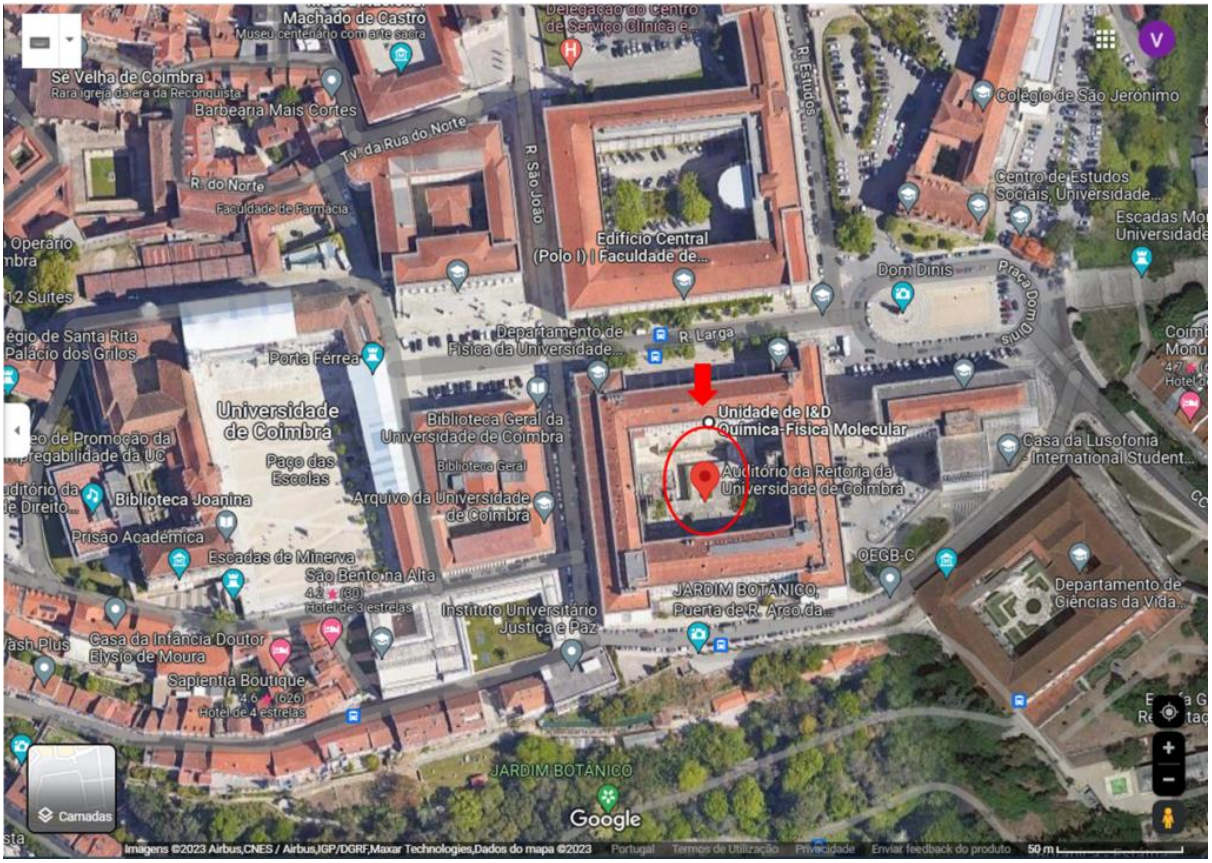
GP2A Meeting Information

Venue

GP2A 2024 conference will be held in Coimbra from the 28th to the 30th of August 2024.
The meeting will take place at the Auditório da Reitoria da Universidade de Coimbra, R. Larga 3000, 3000-370 Coimbra (GPS 40.207571,-8.423987)



Flying in

You can reach Portugal by one of the two main airports, located in Lisbon or Porto.
Coimbra Airport Shuttle provides a door-to-door shared or private transfer between the city of Coimbra and the airports from Lisbon and Porto.

FROM LISBON AIRPORT (2h30 away from Coimbra)

1. LISBON AIRPORT https://www.aeroportolisboa.pt/pt/lis/home
2. There are a subway and taxi connections to the train station “LISBOA ORIENTE”
3. You can book your train to “COIMBRA-B” either on site or previously from:
https://www.cp.pt/passageiros/pt
OR

You can book an AIRPORT SHUTTLE from the website below: https://www.airportshuttle.pt/

FROM PORTO AIRPORT (1h15 min away from Coimbra)

1. PORTO AIRPORT https://www.aeroportoporto.pt/pt/opo/home
2. There are a subway and taxi connections to the train station "PORTO CAMPANHÃ"
3. You can book your train to "COIMBRA-B" either on site or previously from: https://www.cp.pt/passageiros/pt

OR

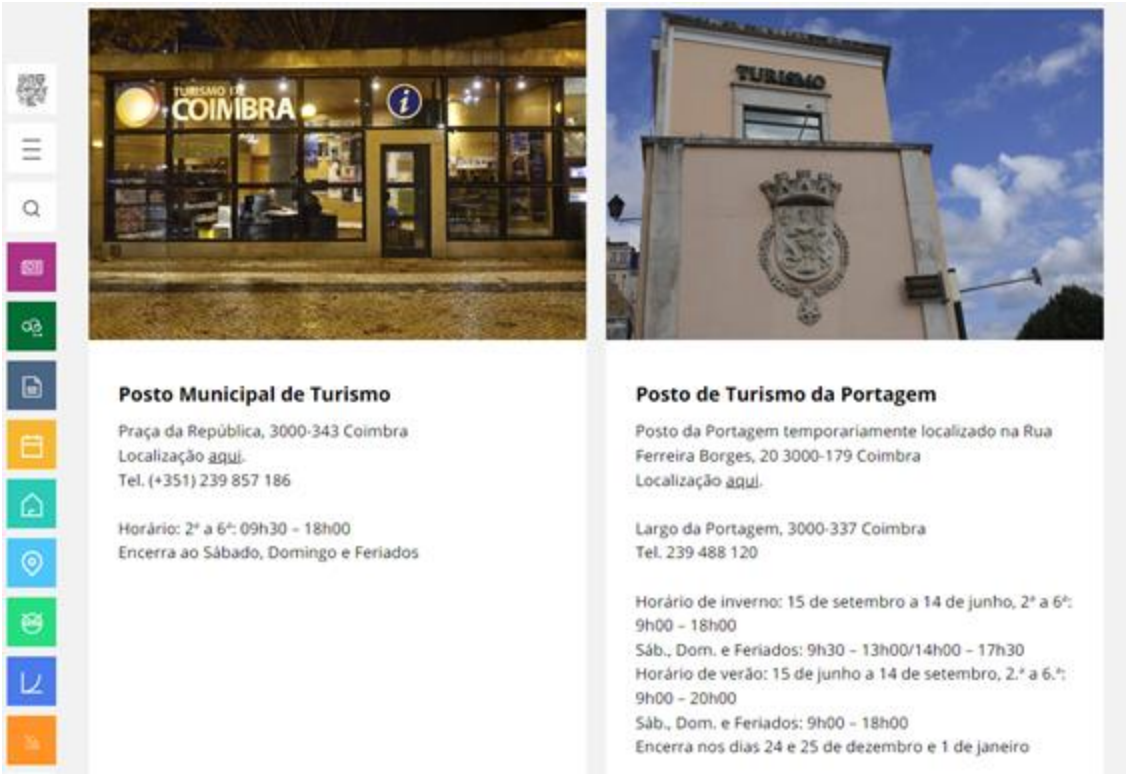
You can book an AIRPORT SHUTTLE from the website below: https://www.airportshuttle.pt/

Accommodation options

Hotel	Details (28-30th aug, 2024)	Contact
Tivoli Hotel Coimbra****	28 minute walk from conference venue	Rua João Machado, nº 43000-226 Coimbra **GPS** 40.2142145,-8.4420342 (+351) 239 858 300 *Call to national landline network (+351) 239 858 345 coimbra@tivoli-hotels.com https://www.tivolihotels.com/pt/tivoli-coimbra
Vila Galé Coimbra****	33 minute walk from conference venue	Rua Abel Dias Urbano, 20 3000-001 Coimbra GPS N40º 12' 51'' – W8º 26'08'' (+351) 239 240 000 portugal.reservas@vilagale.com
Hotel Dona Inês****	32 minute walk from conference venue	R. Abel Dias Urbano 12, 3000-001 Coimbra +351 239 855 800
Hotel Coimbra Aeminium****	23 minute walk from conference venue	Av. Armando Gonsalves, 20, 3000-059 Coimbra +351 23 9480 800 reservas.coimbra@melia.com
Sapientia Boutique Hotel****	6 minute walk from conference venue	Rua José Falcão Nº4 3000-062, Coimbra hello@sapientiahotel.com (+351) 239 151 803
Quinta das Lágrimas*****	30 minute walk from conference venue	Rua António Augusto Gonçalves Coimbra, Santa Clara, 3041-901 +351 239 802 380 reservas@quintadaslagrimas.pt
Casa S. Bento Lofts & suites	8 minute walk from conference venue	Rua Tomar nº7, 3000-041 Coimbra (+351) 239 006 919 (+351) 914 411 128 (+351) 916 220 636 geral@casadesaobento.com
Hotel Mondego	18 minutes away from conference venue	Largo das Ameias 3-4, 3000-024 Coimbra +351 239 496 239 info@hotelmondego.com
ibis Coimbra Centro**	14 minutes away from conference venue	Avenida Emidio Navarro n°70, Edificio Topazio, Nº RNET: 281 3000-150 COIMBRA **GPS**:40.20486, -8.426453 +351 239852130 H1672@accor.com
IBN Arrik Hotel****	8 minute walk from conference venue	Rua Alexandre Herculano,18-24 3000-019 Coimbra +(351) 915071961 geral@ibn-arrik.pt

What to visit?

While in Coimbra, take the opportunity to get to know the University of Coimbra, Alta & Sofia, UNESCO WORLD HERITAGE SITE
https://visit.uc.pt/pt
https://www.uc.pt/en/patrimonio
Below are the contacts for the local Tourism Offices in Coimbra



If you have some spare time, you can also check the tourism website for the "Região Centro"- "Coimbra", for places to visit:
https://turismodocentro.pt/regiao/coimbra/

Where to eat?

For a taste of our local gastronomy we can recommend the following restaurants:

Sabores da Romeira
AV. João das Regras 30, 3040-256 COIMBRA
https://www.saboresdaromeira.pt/

Cordel Maneirista
R. Carlos Alberto Pinto de Abreu 4, Santa Clara
3040-245 Coimbra, Portugal
https://cordelmaneirista.eatbu.com/?lang=pt#services

O Açude
Av. da Guarda Inglesa 63 Santa Clara,
Coimbra 3040-193 Portugal

https://oacude.pt/

Fangas Maior
R. de Fernandes Thomas, nº 29
3000-168 – Coimbra
https://fangas.pt/home/

Restaurante Papa
R. Alexandre Herculano, N 37
3000-019 Coimbra
https://papa.eatbu.com/?lang=pt

O Loggia
Museu Nacional de Machado de Castro,
Largo Dr. José Rodrigues
3000-236 Coimbra
https://www.loggia.pt/

For a taste of the traditional **Roasted Piglet** (Leitão à Bairrada):

Restaurante Albatroz
Coimbra – Torre de Vilela
R IC 2, Fornos
3020-923 TORRE DE VILELA
http://www.restaurantealbatroz.pt/

Rui dos Leitões
Rua da Barraca, 9 Fornos – Torre de Vilela
Coimbra 3025-125
https://www.tripadvisor.pt/Restaurant_Review-g189143-d4213841-Reviews-Restaurante_Rui_dos_Leitoes-Coimbra_Coimbra_District_Central_Portugal.html

Participants

Keynotes

#	Name	Institution	Title
K1	Prof. Michael Decker	Julius-Maximilian-University Würzburg, Germany	Chemical Neuroscience in Alzheimer's Disease: Hybrid Molecules and Photopharmacology
K2	Prof. Maria Paola Costi	University of Modena and Reggio Emilia, Italy	The One Health concept in antiparasitic drug discovery, what matters?
K3	Prof. Line Bourel	University of Strasbourg, France	Fighting against multiresistant fungal infections – a state of the art update and the beginning of a chemical biology study of synthetic antifungal substances
K4	Assist. Prof. Tiago Rodrigues	University of Lisbon, Portugal	Machine learning to accelerate the chemical sciences
K5	Assoc. Prof. Antimo Gioiello	University of Perugia, Italy	Accelerating medicinal chemistry by flow-enhanced synthesis
K6	Prof. Stefania Butini	University of Siena, Italy	Novel inhibitors of the endocannabinoids' catabolic enzymes as potential therapeutics for epilepsy and neuroinflammatory conditions
K7	Dr. Michael Altun	Karolinska Institute, Sweden	Working with degradation and protein instability in drug discovery
K8	Diego Muñoz-Torrero	University of Barcelona, Spain	Serendipity and drug-unlikeness in the discovery of a new antimalarial agent

Oral Communications

#	Name	Institution	Title
OC1	Thomas Guiselin	Université de Caen Normadie, France	A MTDL's approach against Alzheimer's disease: deconstruction of a tricycle
OC2	Katia Sirna	University of Helsinki, Finland	Advances in the development of synthetic allosteric modulators of protein kinase C
OC3	Inês Costa	University of Algarve, Portugal	Synthesis and evaluation of thio-linked pyrimidine-based compounds against *Leishmania donovani*: *In silico* and *in vitro* assessments
OC4	Hadia Almahli	University College London, UK	Development of new antivirals using a high throughput fragment merging strategy
OC5	Eva Schaller	University of Würzburg, Germany	Photopharmacology on Factor Xa
OC6	Rodrigo Ribeiro	University of Coimbra, Portugal	Development of novel sirtuin-1 activators: promising therapeutic tools against neurodegenerative diseases
OC7	Thomas Lemaitre	Université de Caen Normadie, France	From inhibitors to degraders: Application to the design of innovative compounds for the treatment of chemoresistant ovarian cancer
OC8	Lucía González	University of Santiago de Compostela, Spain	A versatile conjugation platform for the development of PROTACs and molecular probes for their characterization
OC9	Ana Laura Dias	University of Lisbon, Portugal	Benchmarking traditional and deep learning models for protein target activity prediction
OC10	Daniela Pereira	University of Porto, Portugal	Development of new nature-inspired synthetic flavonoids for marine biofouling prevention

#	Name	Institution	Title
O11	Constance Dalton	The University of Nottingham, UK	Design and synthesis of novel allosteric modulators for the prostaglandin EP2 G protein-coupled receptor
OC12	Morgane Rivoal	Université de Lille, France	4-Anilinoquinazoline derivatives as new potent and selective NOD1-RIPK2 inhibitors for the treatment of inflammatory diseases

Poster Presentations

#	Name	Institution	Title
P01	Anna Kryshchyshyn-Dylevych	Danylo Halytsky Lviv National Medical University, Ukraine	Use of machine learning methods and pharmacophore screening to search for compounds with dual antiparasitic and anticancer activity among different thiazolidinone and pyrazoline derivatives
P02	Johana Charles	University Claude Bernard Lyon 1, France	Synthesis of Indeno[1,2-b]indoles: Challenges and Insights from Literature to Experiment
P03	Florian Schwalen	Université de Caen Normadie, France	Fragment-based drug design: an effective approach for aiming at challenging targets to discover new anti-inflammatory agents
P04	Gabrielle Bangay	Lusófona University	Semisynthetic Anti-cancer Halimane Derivatives from *Plectranthus ornatus* Codd
P05	Lhana Tisseur	Nantes Université, France	Modifying positions 2 or 8 of the imidazo[1,2-*a*]pyrazine lead compound CTN1122 affects its antileishmanial activity, L-CK1.2 kinase inhibition, and safety profile
P06	Márcia S. Martins	University of Porto Portugal	*In Vitro* Evaluation of Potential Substance P Antagonists Designed for Dermatological Applications
P07	Maria-João R. P. Queiroz	University of Minho Portugal	Synthesis and anti-tumor evaluation of thieno[2,3-b]pyrazine derivatives
P08	Mariia Nesterkina	Helmholtz Institute for Pharmaceutical Research Saarland, Germany	Targeting tuberculosis: exploring dual-action terpenoid derivatives as Promising agents
P9	Mirjana Antonijevic	Université de Caen Normadie, France	Translational Approach to Combat RNA Viral Infections in Horses: A Pathway Towards Equine and Human Health Protection
P10	Ricardo J. F. Ferreira	Universuty of Lisbon, Portugal	Covalent modification of wild-type p53 with a tryptophanol-derived oxazoloisoindolinone
P11	Ronaldo N. De Oliveira	Federal Rural University of Pernambuco, Brazil	Synthesis of Glycosyl-Triazole-Phthalimides as Antiviral Agents
P12	Ana Silva	University of Coimbra, Portugal	Effect of LUSO's thermal water on LPS-induced macrophage inflammation
P13	Asier Selas	University of Santiago de Compostela, Spain	Discovery and SAR exploration of novel a_{2a} antagonists as anticancer agents
P14	Carla Fernandes	University of Porto, Portugal	Marine-derived cyclodepsipeptides: synthesis though an emerging alternative to conventional peptide cyclization
P15	Cláudia Pinto	University of Porto, Portugal	Introducing chirality into nature-inspired flavones as promising eco-friendly antitumor agents

#	Name	Institution	Title
P16	Emília Sousa	University of Porto, Portugal	Conjugation of siderophore mimetics with antibiotics/antimicrobial adjuvants as a new approach to overcome antibacterial resistance
P17	Jayendra Z. Patel	University of Helsinki, Finland	Drug Repurposing to Discover Novel Antibacterial Agents: Our Experience
P18	José Marco-Contelles	University of Madrid, Spain	QN6 as a new ligand for the therapy of diseases of aging and stroke
P19	Mathieu Scaviner	Nantes Université, France	New azole antifungals with a fused imidazopyrimidone scaffold
P20	Sandra Ortigueira-Noya	University of Santiago de Compostela, Spain	Conformational Restriction of Designer Drugs Provides Potent and Selective CB_2 Agonists with Neuroprotective Effect
P21	Tomás R. G. Monteiro	Universidade de Lisboa, Portugal	Development of novel small molecules to reactivate R273H mutant p53
P22	Antoine Magniez	Université de Caen Normandie, France	Design, synthesis and biological evaluation of new MT5-MMP inhibitor as potential therapeutic interest in Alzheimer's disease
P23	François-Hugues Porée	Rennes University, France	Targeting IRE1 for an adjuvant therapy in gliobastoma
P24	Catarina Montargil	University of Coimbra, Portugal	Approaches to the Synthesis of Isatin-based Molecules as Inhibitors of BACE-1 and Cholinesterases
P25	Maria Moura	University of Coimbra, Portugal	The Bucherer-Bergs Multicomponent Reaction for Accesing Chiral spiro-oxindole-hydantoins: Screening against *Leishmania donovani*
P26	Rita Oliveira	University of Coimbra, Portugal	Leveraging the identification of novel ubiquitin specific protease 7 (USP7) inhibitors through a structure-based virtual screening protocol
P27	Sara Moura	University of Coimbra, Portugal	Design, synthesis and biological evaluation of novel madecassic acid derivatives with anticancer potential
P28	Natascha LELEU-CHAVAIN	University of Lille, France	Development of emerging strategies to target the Ser/Thr kinase RIPK2
P29	Lara Mingatos	University of Coimbra, Portugal	Carvone Derivatives: Synthesis and Screening of Anti-Inflammatory Activity
P30	Florence McCarthy	University College Cork, Ireland	Discovery of Potent Isoquinolinequinone *N*-oxides to Overcome Cancer Multidrug Resistance
P31	Matthias Gehringer	University Tübingen, Germany	Mapping the protein kinases' cysteinome by a kinase-focused covalent fragment library
P32	Vânia M. Moreira	University of Coimbra, Portugal	Design and synthesis of 12-thiazole abietanes as selective inhibitors of human metabolic serine hydrolase hABHD16A
P33	Jędrzej Kukułowicz	Jagiellonian University Medical College, Poland	Structural studies of the neutral amino acid transporter B0AT2 revealed tiagabine as a potent inhibitor
P34	Poorvi Saraf	Indian Institute of Technology, India, India	Design, synthesis, and evaluation of benzhydrylpiperazine-based novel molecular hybrids as potent COX-2/5-LOX inhibitors with anti-proliferative activity

Alphabetic List of Delegates

Name	Firstname	Affiliation/Company	Country
Almahli	Hadia	University College London	UK
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Antoniuk	Olha	University of Coimbra	PT
Antunes	Pedro	SpecAnalítica	PT
Bangay	Gabrielle	Lusófona University	PT
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Bourel	Line	University of Strasbourg	FR
Burke	Anthony	University of Coimbra	PT
Butini	Stefania	University of Siena	IT
Cardoso	Vitor	Qlabo	PT
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Logé	Cédric	Nantes Université	FR
Lomberget	Thierry	Université Lyon 1	FR
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Marchand	Pascal	Nantes Université	FR
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Patinha	Tiago	Solitica	PT
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Name	Firstname	Affiliation/Company	Country
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Ribeiro	Rodrigo	University of Coimbra	PT
Rijo	Patrícia	Lusófona University	PT
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