drugs and drug candidates

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Conference Report

33rd GP_2A Annual Medicinal Chemistry Conference, XIVth Paul Ehrlich MedChem Euro-PhD Network Meeting & COST Action One Health Drugs Against Parasitic Vector Borne Diseases in Europe and Beyond (OneHealth*drugs*)

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Abstract

The 33rd Annual Conference of the Group for the Promotion of Pharmaceutical Chemistry in Academia (GP_2A), held in Nantes from 11 to 13 June 2025, marked a significant expansion of the organization's scope and collaborative efforts. Building on the success of the previous meeting in Coimbra, the 2025 edition brought together 168 participants and featured a comprehensive scientific programme comprising 102 abstracts. A key highlight of this year's conference was the collaboration with COST Action OneHealth*drugs* and the Paul Ehrlich (PE) Euro-PhD Network, fostering interdisciplinary exchange and identifying future research synergies. The event included 1 computational workshop and 8 keynote lectures by international experts, alongside a strong emphasis on early-career researchers, with 25 oral presentations and 25 flash poster communications. In addition, 77 posters were presented across three dedicated sessions. All the presentations were eligible for 18 conference awards. Staying true to the GP_2A and PE mission, the conference provided a dynamic platform for young scientists to engage with established researchers.

Keywords: medicinal chemistry; drug design; chemical biology; chemical tools; pharmaceutical chemistry; conference report

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Academic Editor: François Marceau

Received: 25 May 2026
Accepted: 28 May 2026
Published: 5 August 2026

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1. Introduction

The 33rd Annual Conference of the Group for the Promotion of Pharmaceutical Chemistry in Academia (GP_2A) [1], the XIVth Paul Ehrlich MedChem Euro-PhD Network Meeting [2] and the COST Action One Health drugs [3] conference were held jointly from 11th to 13th June 2025 at Nantes Université, in the vibrant city of Nantes. Known as the birthplace of Jules Verne, whose visionary works bridged imagination and scientific exploration, Nantes provided an inspiring setting for a meeting dedicated to innovation in medicinal chemistry and chemical biology. The city's long-standing connection to scientific curiosity and discovery echoed the conference's mission to foster creativity, interdisciplinarity, and cutting-edge research.

For the first time, the GP_2A conference was jointly organized with the COST Action OneHealth*drugs* initiative and the Paul Ehrlich (PE) MedChem Euro-PhD Network, creating a unique platform for interdisciplinary exchange across academia and international research consortia (Figure 1). This joint event brought together 168 participants from 15 different countries (France, Italy, Portugal, Spain, Germany, Belgium, the United Kingdom, Ireland, Romania, Azerbaijan, Tunisia, Algeria, Brazil, Senegal, and Ivory Coast) and diverse scientific backgrounds, reinforcing the central role of GP_2A and PE networks in connecting researchers working at the interface of medicinal chemistry, chemical biology, and drug discovery.



Figure 1. Joint MedChem Conference in Université de Nantes.

The conference featured a rich and comprehensive scientific programme comprising 102 accepted abstracts. Over three days, the meeting hosted eight keynote lectures delivered by internationally recognized experts, namely Prof. Maria Laura Bolognesi, University of Bologna—Italy; Dr. Rachael Dickman, University College London—UK; Dr. Stephanie Federico, University of Trieste—Italy; Dr. Miguel Angel González-Cardenete, Universitat Politecnica de Valencia-CSIC—Spain; Prof. Christophe Rochais, Université de Caen Normandie—France; Prof. Serge Van Calenbergh, Ghent University—Belgium; Dr. Trinidad Velasco-Torrijos, Maynooth University, Co. Kildare—Ireland; and Prof. Michele Vendruscolo, University of Cambridge—UK, covering topics ranging from kinase inhibition, antimicrobial peptides, and natural products chemistry to artificial intelligence and sustainable approaches in drug discovery, and therapeutic strategies for neurodegenerative and infectious diseases. The programme also strongly emphasized early-career researchers, with 25 oral communications and 25 flash poster presentations, alongside 77 posters presented during dedicated sessions, creating numerous opportunities for scientific discussion and networking.

The event opened with a workshop on artificial intelligence in drug discovery by Dr. Dylan SERILLON (PharmD, PhD)—WhiteLab Genomics, highlighting the growing

importance of computational approaches in molecular design. Scientific sessions were structured around key thematic areas, including antimicrobial resistance, parasitic and vector-borne diseases within the One Health framework, neurodegeneration, oncology, and emerging methodologies such as machine learning and multi-objective optimization. In addition to the scientific programme, social and networking events, including a welcome reception, a guided tour of Nantes' historic center, and the conference dinner, fostered informal exchanges and strengthened collaborations among participants.

Staying true to the missions of GP_2A and the PE networks, the conference provided a dynamic and supportive environment for young scientists to engage with established researchers. All presentations were considered for a total of 18 conference awards, further encouraging excellence and active participation. Overall, the joint conference in Nantes successfully combined high-level scientific content with a collaborative and inclusive atmosphere, reinforcing its position as a key event in the European medicinal chemistry community.

2. Pre-Conference Workshop

Artificial Intelligence in Drug Discovery: A New Era of Molecular Design

Dylan Sérillon [1]

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Artificial Intelligence (AI) is reshaping drug discovery by enhancing molecular design, optimizing ligand-target interactions, and improving predictive modeling. The integration of machine learning (ML), deep learning (DL), and computational chemistry enables faster and more accurate identification of promising drug candidates, significantly reducing development timelines. AI-driven approaches, particularly thermodynamic and knowledge-based models, are crucial for predicting binding free energy in receptor-ligand complexes. The combination of classical and quantum mechanics with machine learning algorithms refines molecular docking predictions, leading to more precise virtual screening and structure-based drug design. In peptide discovery and gene therapy vector engineering, AI accelerates protein-ligand interaction analysis, optimizing molecular properties for improved therapeutic efficacy. Deep learning models contribute to the design of novel peptides, while AI-guided optimization enhances viral and non-viral vectors for gene delivery.

This workshop explores key advancements in AI-powered drug design, including predictive modeling, AI-driven molecular docking, and generative design for small molecules and biologics. Emphasis will be placed on the synergy between computational simulations and experimental validation, bridging the gap between in silico predictions and real-world drug development.

3. Keynote Lectures

3.1. Discovery and Structure-Activity Relationships of Cyclic Antimicrobial Peptides

Sara Vasciaveo [1,2], Katharina Webhofer [1], Sarah Barry [2] and Rachael Dickman [1]

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New antimicrobials are urgently needed to address the antimicrobial resistance crisis. Historically, microorganisms have been a rich source of antimicrobial compounds, many of which are still in clinical use today. In the Dickman Lab, we are investigating the potential of cyclic peptides produced by bacteria to meet the need for new antimicrobials. To do this, we use a variety of chemical and biological approaches to discover new compounds, optimise their properties, and study their mechanisms of action.

One family of peptides we are interested in is the sactipeptides. The sactipeptides are a growing family of thioether-bridged peptides which are ribosomally synthesised and post-translationally modified. Several of the sactipeptides reported to date have potent and selective antibacterial activity, making them an attractive potential addition to the antibiotic arsenal [4]. Our second area of interest is the calcium-dependent antibiotics (CDAs). These are a family of cyclic lipopeptides which require the presence of calcium for their activity. Most of the known CDAs bind calcium with a conserved binding motif, though in recent years several CDAs which do not bear this typical motif have been reported [5].

In this talk I will cover some recent highlights from our work on these two classes of cyclic antimicrobial peptides, including the discovery and characterisation of a novel sactipeptide, and our progress towards understanding the structure-activity relationships of calcium-dependent antibiotics with non-canonical calcium-binding motifs. This workshop explores key advancements in AI-powered drug design, including predictive modeling, AI-driven molecular docking, and generative design for small molecules and biologics. Emphasis will be placed on the synergy between computational simulations and experimental validation, bridging the gap between in silico predictions and real-world drug development.

3.2. Discoveries in Natural Products Chemistry from Renewable Biomass: Addressing Synthetic and Therapeutic Challenges, Abietanes' Story

Miguel A. González-Cardenete [1]

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Nearly 200 years ago, the study of the chemistry of terpenoids started with the analysis of turpentine oil, investigating the first resin acid, abietic acid from pine oleoresin [6]. Abietic acid occurs in plants of the genus Abies and is the first member of a class of plant metabolites, the abietane-type diterpenoids. They are characterized by a tricyclic ring system and have shown a wide range of chemical diversity and biological activity [7,8]. Medicinal chemists have studied derivatives of two readily available materials such as dehydroabietic acid and dehydroabietylamine [8]. To date, there is only one commercial drug, Ecabet® [ecabet sodium], based on abietanes, which is used for the treatment of reflux esophagitis and peptic ulcer disease. The simplest phenolic abietane, ferruginol, exhibits anticancer effects and inhibition of cancer cell migration.

It is now around 15 years since our first work on abietane chemistry, particularly abietic acid derivatives [9]. During the last 10 years, we have synthesized several naturally occurring abietanes and derivatives, including ferruginol and other analogues for further biological study. The simultaneous isolation (in 2014) by Hua and co-workers, of the new abietane liquiditerpenoic acid A, a sugiol analogue, from the resin of Liquidambar formosana and from Pinus massoniana [10], by Kuo and co-workers named independently as abietopinoic acid, and the lack of synthetic studies prompted us to synthesize it and study its antitumor, GABAA modulation and antileishmanial properties along with some analogues [11] and C4-epimers [12]. Further investigation in collaboration with Prof. Fatima Rivas at Louisiana State University (USA) [13], Prof. Jose M. Prieto-Garcia at John Moores Liverpool University [14] and Prof. Jose M. Padrón at Universidad de la Laguna (Spain) has led to studies on antitumor activity of some abietane derivatives and analogues with promising results (Figure 2).

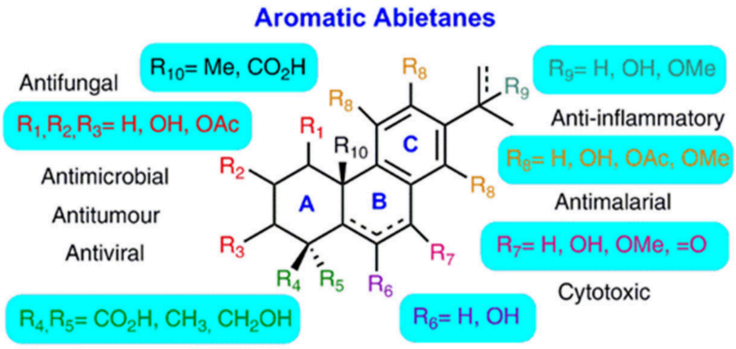


Figure 2. Abietane derivatives and analogues.

In this lecture, I will present an overview of synthetic and biological studies on abietane chemistry performed by our group in Valencia, Spain, which includes the most recent achievements as potential antitumor agents.

3.3. Leveraging Medicinal Chemistry for the United Nations Sustainable Development Goals

Maria Laura Bolognesi [1]

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Medicinal chemistry plays a pivotal role in advancing the United Nations Sustainable Development Goals (SDGs) by 2030. It can—and must—contribute to a sustainable future and improved quality of life for all [15]. This responsibility is especially evident in the context of vector-borne parasitic diseases (VBPDs), which continue to pose a significant global health challenge. The current limitations of available treatments—such as limited access, high toxicity (both human and environmental), and complex dosing regimens—highlight the urgent need for drug discovery efforts rooted in sustainability. Integrating Green Chemistry principles and the One Health approach into medicinal chemistry offers a promising pathway forward [16]. Motivated by this vision, we are committed not only to developing more effective therapeutics for VBPDs but also to ensuring they are sustainable and accessible, and do not harm the environment. One innovative and impactful strategy is to repurpose waste from the food industry as a source of novel bioactive compounds.

In this context, we have recently explored the use of cashew nutshell liquid (CNSL)—an inexpensive, inedible by-product of cashew nut processing—as a starting material for medicinal chemistry campaign. CNSL contains a variety of phenolic compounds, including cardanols, cardols, and anacardic acids, all of which share a pentadecyl alkyl side chain with varying degrees of unsaturation. By leveraging such biowaste, our approach aligns with the concept of "benign-by-design" chemistry, aiming to produce safer, more affordable, and widely accessible pharmacological tools.

In this talk, we will present our recent developments in this area and discuss how sustainable strategies in medicinal chemistry can contribute to global health [17,18].

3.4. Purine Nucleoside Analogues as Promising Agents Against Protozoan Pathogens in Humans and Livestock

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While the therapeutic utility of nucleoside analogues is well established for viral infections and cancers, their potential for combating protozoan diseases remains underexplored. Unlike mammals, most parasitic protozoa are purine auxotrophs, depending on the uptake

and processing of pre-formed purines from their hosts. To enable this, these organisms have developed specialized transporters and enzymatic machinery for salvaging and interconverting nucleosides and nucleotides, essential for DNA and RNA synthesis [19]. Inspired by these biochemical differences, our research group synthesized a library of nucleoside analogues and assessed their activity and selectivity against a representative panel of Trypanosoma and Leishmania species. Remarkably, structural modifications of tubercidin led to the discovery of several promising antiparasitic candidates, some of which demonstrated efficacy in relevant animal models for human parasitic diseases [20–22].

Additionally, our library also allowed the discovery of a therapeutic candidate for animal trypanosomiasis [23] as well as other leads for protozoan infections that afflict animal health, such as histomoniasis and cryptosporidiosis. This presentation will provide an overview of our most significant findings and new developments.

3.5. Pleiotropic Prodrugs: A Polypharmacological Approach to the Treatment of Neurodegenerative Diseases

Christophe Rochais [1] and Patrick Dallemagne [1]

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Today, acetylcholinesterase inhibitors (AChEIs) are the mainstay of treatment for Alzheimer's disease (AD). AChEIs provide only a symptomatic benefit, alleviating the cognitive dysfunction associated with AD by temporarily restoring cholinergic neurotransmission impaired by neurodegeneration. The gradual loss of efficacy of AChEIs has led to their association with drugs with potential disease-modifying properties. Multi-target-directed ligands (MTDLs) have been used in recent years with great potential utility against multiple targets involved in the complex physiopathology of AD [24] and other neurodegenerative syndromes.

Our contribution to this field has recently led to the discovery of donecopride, the first 5-HT_4R partial agonist, which also has important acetylcholinesterase (AChE) inhibitory properties. Donecopride is currently in preclinical development [25–27]. Building on this experience, we have recently developed a novel pleiotropic prodrug approach to generate promising in vivo compounds (Figure 3). Using rivastigmine as a model, novel MTDLs have been designed to act as prodrugs capable of temporarily covalently binding and inhibiting AChE (for a symptomatic effect) and secondarily releasing a drug capable of selectively reaching another AD target (for a potential disease-modifying effect).

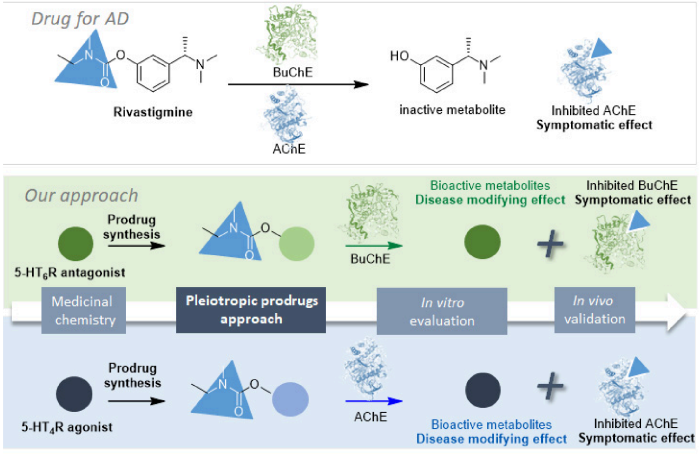


Figure 3. Pleiotropic prodrugs approach.

This concept has been applied to several secondary targets, including 5-HT receptors [28], SERT or β2ARs of interest in the context of Alzheimer's disease. The concept, the synthetic development and the in vitro and in vivo evaluation of novel candidates are presented in this communication [29,30] as well as undisclosed results on a repositioning strategy and an innovative self-immolating linker.

3.6. Casein Kinase 1: Where We Are and Where We Are Going

Stephanie Federico [1]

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Casein kinase 1 (CK1) is a family of serine/threonine kinases that also defines a subgroup within the kinome. In humans, the CK1 family consists of seven isoforms: CK1α, CK1α-like, CK1γ1, CK1γ2, CK1γ3, CK1δ, and CK1ε. These isoforms play key roles in various physiological and pathological processes, with implications for therapeutic applications ranging from sleep and metabolic disorders to cancer and neurodegenerative diseases [31,32]. Additionally, CK1 is highly conserved across eukaryotes, and due to its involvement in protozoan biology, its paralogs are emerging as potential targets for the treatment of infectious diseases caused by these parasites [33]. This presentation will provide an overview of the therapeutic potential of CK1 modulators, focusing on their structure, mechanism of action, selectivity, and current development status. Lastly, the contribution of our laboratory to the development and investigation of CK1δ inhibitors, particularly for neurodegenerative diseases, will be discussed.

3.7. Glycoconjugates as Anti-Virulence Agents to Combat Fungal Infection

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Chronic fungal infections affect over 150 million individuals. These infections can have a huge impact on immunocompromised and vulnerable populations [34]. Yeasts from the *Candida* spp. are opportunistic fungal pathogens, some of which like *C. albicans* and *C. auris* have been classified as critical priority pathogens by the World Health Organization. Adherence to host tissue is critical to their ability to colonise and infect the host. We have designed and evaluated carbohydrate-based anti-adhesion compounds as inhibitors of *C. albicans* adherence to exfoliated buccal epithelial cells (BECs). A small library of aromatic glycoconjugates were synthesised using synthetic carbohydrate chemistry and Copper-Catalyzed Azide-Alkyne Cycloaddtion (CuAAC) chemistry (Figure 4). These were evaluated as anti-adhesion ligands and it was found that a divalent galactoside showed the best anti-adhesive properties, capable of displacing over 50% of yeast cells already attached to the BECs [35].

To optimise the activity of this lead compound, several strategies have been explored: we have carried out Structure-Activity Relationship (SAR) studies, where we have investigated alternative scaffolds and glycomimetic compounds. We have also considered different multivalent presentations, where the lead compound was graphed numerous times onto a common scaffold to enhance binding affinity [36,37].

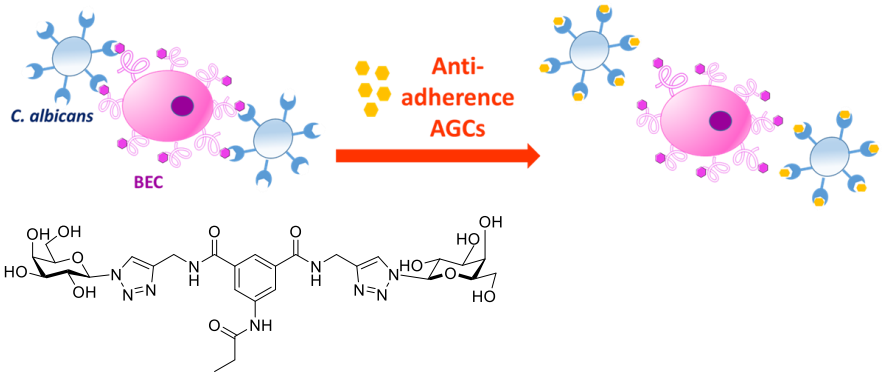


Figure 4. Graphical representation of the anti-adhesion approach (**top**) and the structure of lead compound divalent galactoside (**bottom**).

3.8. Expediting Drug Discovery for Undruggable Targets Using AI

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Protein-ligand interactions play central roles in biological processes and are of key importance in drug design. Deep learning approaches hold the promise of becoming cost-effective alternatives to high-throughput experimental methods for ligand identification. This is particularly the case for disordered proteins, where there are few experimental options for accurate binding measurements that can be scaled up to cover large chemical libraries. To predict the binding affinity between disordered proteins and small molecules, I will describe a deep learning framework based on the transformer architecture. To show the applicability of this approach, we explored the binding of small molecules to the Alzheimer's Aβ peptide, identifying compounds that delayed its aggregation. Overall, the results that we obtained illustrate the potential of deep learning methods in accurately predicting the interactions of small molecules with disordered proteins, thus uncovering molecular mechanisms and facilitating the initial steps in drug discovery for these otherwise largely undruggable targets.

4. Oral Communications

4.1. Evaluation of SQ109 and Bedaquiline Efficacy Against Mycobacterium abscessus Using Transposon Mutagenesis Under Host-Like Conditions

Benedetta Salvucci [1], Mariangela Biava [1], Sille Remm [2], Eric J. Rubin [2] and Giovanna Poce [1]

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While recent advancements have led to promising new therapies for tuberculosis, the treatment of infections caused by non-tuberculous mycobacteria (NTMs) remains a significant challenge. Among these, *Mycobacterium abscessus* (*Mab*) stands out as particularly difficult to treat due to its high drug resistance to common antibiotics. *Mab* is an opportunistic pathogen responsible for lung infections, particularly in immunocompromised individuals. The global rise in *Mab* infections reveals the urgent need to understand its chemical-genetic interactions both in axenic cultures and under host-like conditions. This study aimed to identify potential therapeutic targets to enhance the efficacy of existing antibiotics and investigational compounds. The focus was on discovering conditionally essential genes that may play a critical role under host-like conditions, compared to those

identified in standard culture media. To simulate a host-like environment, we developed an in vitro infection model using air-liquid interface (ALI) culture [38]. We evaluated two compounds—SQ109, a promising drug candidate in clinical trials for drug-resistant tuberculosis, and Bedaquiline, a novel anti-tuberculosis agent—which demonstrated low minimum inhibitory concentrations (MICs) in the ALI model. Additionally, we performed a transposon mutagenesis and sequencing screen (Tn-Seq) to identify essential genes for growth in vitro [39]. This approach aims to uncover potential targets for improving treatment strategies against *M. abscessus* and addressing the growing threat of this challenging pathogen.

4.2. Synthesis and Optimization of Novel Peptidomimetics Derivatives Inhibiting the Efflux Pumps of Pseudomonas aeruginosa

Mélanie Sebastien [1], Hilal Wehbi [1], Florent Barbault [2], Laurine Vasseur [2], Joëlle Pérard [1], Isabelle Broutin [1] and Gilles Phan [1]

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The rise of multidrug-resistant Pseudomonas aeruginosa (PA) is a critical challenge in the treatment of cystic fibrosis (CF), as this pathogen is a leading cause of morbidity and mortality in CF patients. PA's resistance is often attributed to its efficient efflux pumps, particularly the MexAB-OprM system, which expels antibiotics before they can act [40]. Addressing this mechanism is crucial to overcome treatment failures and to improve patient outcomes. In this study, funded by the French association "Vaincre la Mucoviscidose," we present an innovative approach aimed at inhibiting PA's efflux pump system. We focus on the synthesis of novel peptidomimetics designed to block the MexB transporter, a key player in the recognition and expulsion of antibiotics. Unlike traditional inhibitors, our peptidomimetics are built on a newly developed scaffold [41] that could enhance their affinity and specificity for MexB, potentially leading to more effective inhibition of efflux activity. Docking analysis and initial biological test have shown promising results. This strategy represents an encouraging new avenue in combating antibiotic resistance in CF patients. By targeting the efflux pump mechanism, we hope to restore the efficacy of existing antibiotics and offer a much-needed therapeutic solution for this vulnerable patient group.

4.3. Development of Functionalized Amidrazones as an Original Nitrogen Heterocycle for Use in DEL Chemistry

Margaux Boutin [1], Johann Leblanc [1], Jérôme Guillemont [2], Hugues Prevet [2], Jacques Lebreton [1] and Arnaud Tessier [1]

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In the context of drug discovery, the need for greater structural diversity is prominent to address the identification of new molecular scaffolds to interact with a biological target of interest. Typical high-throughput screening (HTS) which uses such large chemical libraries and requires that each compound be individually synthesized, stored, and assayed in an automated facility is being revolutionised by DNA encoded libraries (DEL), where the power of genetic encoding overcomes the limitations of HTS. This method allows mixtures of compounds to be screened, as each molecule is tagged with a DNA 'barcode' that enables

identification of the ligand that successfully binds to the target. This powerful technology represents a novel and robust approach in drug discovery for hit identification, rapid lead generation and the ability to diversify the chemical space. However, to further optimize this process, original building blocks are required. Based on the observation that 82% of FDA-approved small-molecule drugs contain a nitrogen heterocycle, but that pyridine, piperidine, and piperazine are the most common 6-membered azaheterocycles [42], due to the numerous routes described to synthetize them, it seems necessary to expand the availability of synthetic methods to access original and underrepresented azaheterocycles with the aim of using them in the DEL process.

Our team's investigations focus on 1,4,5,6-tetrahydro-1,2,4-triazines also called cyclic amidrazones as bioisosters of classical heterocycles. Our first team works reported a novel synthetic access of functionalized amidrazones, but our results were only limited to the synthesis of amidrazones derivatives featuring aliphatic or aromatic groups (Figure 5a) [43,44]. In order to use the cyclic amidrazone as an original building block in the DEL technology, we now report the synthesis of new multifunctionalized amidrazones (Figure 5b), with reactive groups that will serve as anchors to attach other building blocks for the development of new DELs.

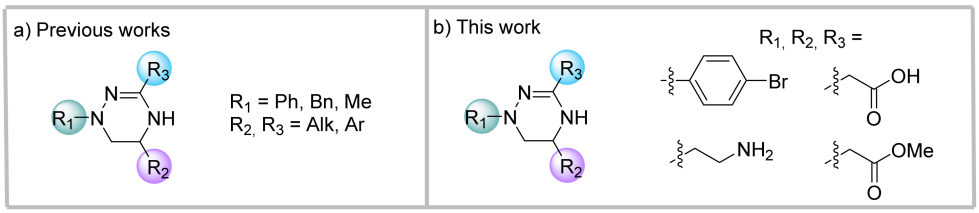


Figure 5. New advances in the synthesis of functionalized amidrazones for use as DNA encoded library building blocks.

4.4. Phenolic Cinnamic Acid Derivatives as Selective COX-2 Inhibitors: Design, Synthesis and Biological Activity Studies

João Sousa Janela [1,2], Mariana Lucas [2], Marisa Freitas [2], Elisiário Tavares da Silva [1], Eduarda Fernandes [2] and Fernanda Roleira [1]

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Cyclooxygenase (COX) is a key enzyme of the arachidonic acid cascade, a metabolic pathway leading to the synthesis of thromboxane and prostaglandins, some of which being pro-inflammatory. Inflammation is a hallmark of a wide variety of diseases, including, but not limited to, osteoarthritis, rheumatoid arthritis, obesity and cancer. Two main isoforms of COX are currently known: COX-1, which is constitutively expressed and leads to the synthesis of prostanoids with homeostatic functions, such as gastric mucosa protection and regulation of renal blood flow; and COX-2, which is induced by pro-inflammatory stimuli and catalyzes the production of prostanoids that potentiate the inflammatory process. Most of the non-steroidal anti-inflammatory drugs inhibit both COX isoforms, causing COX-1-related adverse effects such as gastric ulcers. Selective COX-2 inhibitors were developed to address those safety issues, and while they were partially successful in doing so, they have been linked to an increased cardiovascular risk. Thus, there remains a clinical need for effective and safer anti-inflammatory drugs.

We have previously shown that 3,5-di-tert-butyl-4-hydroxycinnamic acid, as well as its hexylamide and diethylamide, selectively inhibit COX-2, as evidenced by prostaglandin E2 (PGE2) quantification in a human blood assay [45]. Based on this, 23 amides derived from

the same substituted cinnamic acid have been synthesized (Figure 6) and tested for their COX-1 and COX-2 inhibition, using an in vitro fluorometric screening assay, to determine COX-2 selectivity. To assess how the amides act in a biological sample, the aforementioned PGE2 quantification assay was also performed in COX-2-inducing conditions after blood cell viability assays. Selective COX-2 inhibitors have been found, including compounds with remarkable activity in the blood model, meaning that these types of compounds could be further studied to provide new hits for anti-inflammatory therapy.

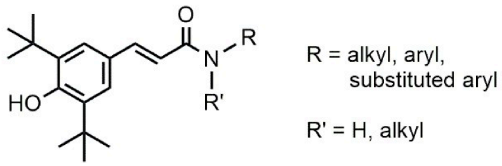


Figure 6. General structure of the synthesized amides derived from 3,5-di-*tert*-butyl-4-hydroxycinnamic acid.

Acknowledgment: Financial support and PhD grants provided by Fundação para a Ciência e a Tecnologia (FCT).

4.5. Launching into the Objective Space: Multi-Objective Optimization in REINVENT

Laura Landolfi [1], Bruno Catalanotti [2] and Jon Paul Janet [3]

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3 Molecular AI, Discovery Sciences, R&D, AstraZeneca, Gothenburg, Sweden

Designing molecules that satisfy multiple, often conflicting objectives is a central challenge in de novo drug design [46]. In this work, we present a novel multi-objective reinforcement learning framework for REINVENT [47] that exploiting Pareto optimization principles [48], enables efficient exploration of trade-offs across diverse molecular properties within a single, integrated optimization process. Our method is built upon REINVENT's scoring function with which we can combine multiple objectives through a weighted geometric mean, allowing the agent to navigate the objective space in a structured manner, covering both extreme and intermediate trade-offs.

We evaluated the framework across three case studies of increasing complexity, including optimization of FXR and GPBAR1 activities, tri-objective balancing with synthetic accessibility, and docking-based optimization against the RORγT receptor. Results show that our method consistently recovers broader, more diverse Pareto fronts than standard scalarized baselines, with improved coverage of knee points and intermediate solutions.

Overall, this strategy provides a robust, scalable, and interpretable solution for multi-objective molecule generation (Figure 7), well-suited to modern drug discovery pipelines where multiple criteria must be optimized simultaneously.

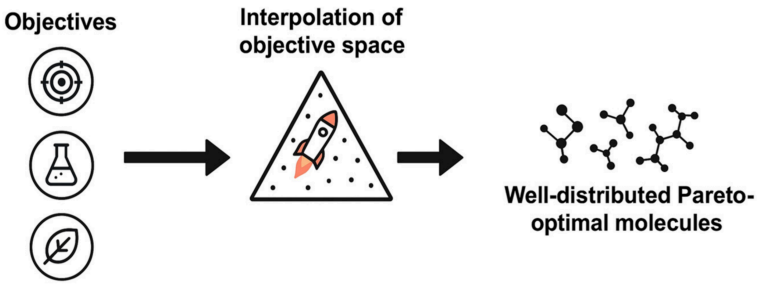


Figure 7. A visual summary of the proposed multi-objective optimization strategy in REINVENT.

4.6. NORUS: An AI-Powered Framework for Assessing Scientific Originality and Similarity

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The exponential growth of scientific literature has made it increasingly difficult to assess originality, thematic relevance, and scientific impact using traditional bibliometric indicators, such as citation counts or journal impact factors. These metrics often fail to capture the semantic novelty of a work or to distinguish incremental contributions from true innovation. To address this, we developed NORUS (Neural Originality Understanding System)—an AI-based framework for bibliometric evaluation using natural language processing (NLP) techniques. NORUS computes the Originality Uniqueness Index (OUI) (Equation (1)), a metric that combines semantic similarity (via Sentence-BERT embeddings) [49] and lexical overlap, prioritizing conceptual similarity for a more nuanced assessment of textual originality. In addition to the OUI score, NORUS integrates keyword extraction, named entity filtering, and thematic clustering [50]. It produces interactive reports with visualizations and downloadable summaries to support researchers and evaluators in analyzing document similarity and novelty. Validation on a corpus of publications related to histone deacetylase (HDAC) inhibition demonstrated NORUS's precision in detecting redundancies. Designed to be modular and cross-disciplinary, NORUS is available as a prototype web app and is currently being extended to integrate sources such as PubMed [51] and arXiv. By merging AI and bibliometric insight, NORUS offers a powerful tool to enhance originality assessment, support peer review, and foster innovation in scientific publishing.

$$OUI = \alpha \cdot (1 - similarity/100) + \beta \cdot (1 - token\ overlap/100)$$

Equation (1). OUI Index Equation: Semantic and Lexical-Based Originality Assessment.

4.7. Development and Characterization of Mucroporin-M1 Analogues: Improved Stability, Structural Analysis and Virucidal Activity

Claudia Storti [1,3], Sara Tuci [2], Annagiulia Favaro [3], Alessia Zago [2], Beatrice Mercorelli [2], Mattia Sturlese [4], Arianna Loregian [2,5], Cristina Peggion [3]

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Mucroporin is a 17-amino acid peptide derived from the scorpion venom *Lychas mucronatus* with known antimicrobial properties, particularly against Gram-positive bacteria. In 2012, Li et al. also investigated the virucidal and antiviral activity of Mucroporin. They optimized the sequence by introducing amino acid substitutions (G3R, P6K, G10K, and G11R) to improve peptide activity at lower concentrations compared to the native peptide. The substitutions increase the net positive charge of the peptide and enhance the amphipathic character of the helix. It was observed that the modified sequence, Mucroporin-M1, interacts directly with viral particles and, upon attachment of the peptide to the virus,

its strong electrostatic affinity enhances the interaction and destruction of the viral envelope [52–54].

The aim of our work was to further enhance the antimicrobial and antiviral activity of Mucroporin-M1 by appropriately modifying its sequence and studying its conformation and structure-activity relationship. We modified the sequence by incorporating the non-proteinogenic amino acid α-aminoisobutyric acid (Aib) at specific positions (Aib5I, Aib9I, and Aib13V) to strengthen the helical conformation and improve stability against proteolytic enzymes. We also synthesized several truncated analogues of Mucroporin-M1 to identify the minimal active sequence and to develop a convenient and straightforward synthetic protocol. All peptides were fully characterized and their conformation was studied by NMR and circular dichroism (Figure 8). We report a study of the stability of Mucroporin-M1 analogues against proteolytic enzymes and the propensity of the peptides to interact with biological membranes. In addition, we present data on the cytotoxicity and virucidal activity of the synthesized compounds against both enveloped and non-enveloped viruses. The correlation between biological activity and 3D structure is also discussed.

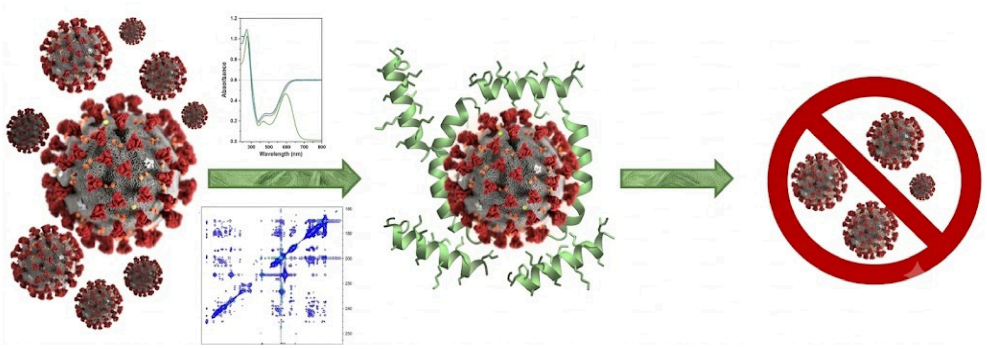


Figure 8. Methodology of peptides characterization.

4.8. Identification and Further Optimization of 4,5-Dihydropyrazole Scaffold as Potential West Nile NS3 Helicase Inhibitors

Giulia Atzeni [1], Roberta Emmolo [2], Antonio Lupia [1], Erica Sanna [1], Alessia Onali [1], Lura Demuru [1], Angela Corona [2], Rita Meleddu [1], Filippo Cottiglia [1], Simona Distinto [1], Enzo Tramontano [2] and Elias Maccioni[1]

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West Nile virus is a vector-borne RNA virus belonging to the *Flaviviridae* Family, genus Flavivirus. It represents a global health concern due to its potential to cause serious diseases such as encephalitis, meningitis, and severe muscle weakness. To date, neither vaccines nor antiviral treatments are available [55]. The 11-kb positive-sense, single-stranded RNA (ssRNA) genome is translated into a single polyprotein, which is subsequently cleaved into three structural proteins (C, prM/M, and E) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). Among them, NS3 (72kDa) represents the motor protein involved in the separation of double-stranded RNA (dsRNA) during viral replication. NS3 contains a serine-protease domain at its N terminus and an ATP-driven helicase and RNA triphosphatase at its C-terminal end. For its role in viral replication, NS3 represents a valid druggable target [56,57]. A Structure-based virtual screening has allowed us to identify four compounds characterized by 4,5 dihydropyrazole scaffold capable of inhibiting the $NS3^{hel}$ activity at low μM concentration. These results represent a valid starting point for further structural optimization.

This research was supported by EU funding within the NextGenerationEU-MUR PNRR Extended Partnership initiative on Emerging Infectious Diseases (Project no.PE00000007, INF-ACT).

4.9. Structure-Activity Relationships and ADMETox Profiling of Novel Isonipecotamide-Based O-Glycosides as Highly Potent DOACs for Thromboembolic Disorders

Caterina Deruvo [1], Rosa Purgatorio [1], Francesco Samarelli [1], Gabriella La Spada [1], Modesto de Candia [1], Marco Catto [1], Orazio Nicolotti [1], and Cosimo D. Altomare [1]

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Thromboembolic disorders remain a significant clinical challenge in adult, pediatric and high-risk (e.g., cancer) populations. Direct oral anticoagulants (DOACs), which selectively inhibit factor Xa (fXa) and thrombin (thr), have transformed the therapeutic strategies in the field. Nevertheless, limitations in safety, efficacy, and pharmacokinetics may affect their use [58]. Some years ago, we reported many diversely decorated piperidine-4-carboxamide-based DOACs, two of which achieved in-vitro excellent inhibitory potencies against fXa or thr [59,60]. Notably, a novel analog (Figure 9), incorporating a β-D-glucose moiety (and not galactose or xylose), significantly enhanced anticoagulant potency, in the picomolar concentration range for fXa. Binding kinetics and thermodynamics of the newly synthesized highly potent DOACs were studied using surface plasmon resonance (SPR). The *O*-glucoside showed a more prolonged residence time (τ) on fXa, which resulted strictly correlated with the enhanced inhibitory potency. In vitro permeability assays and ADMETox profiling highlighted good permeability in blood-brain barrier (BBB) and gastrointestinal (GI) cell models, metabolic stability, and low cytotoxicity. Interactions with P-glycoprotein (P-gp) and human serum albumin (HSA) were also investigated both in-silico and in-vitro. Ultimately, these findings provided valuable SAR insights highlighting potential applications in anticoagulation therapy, which will be herein presented and discussed.

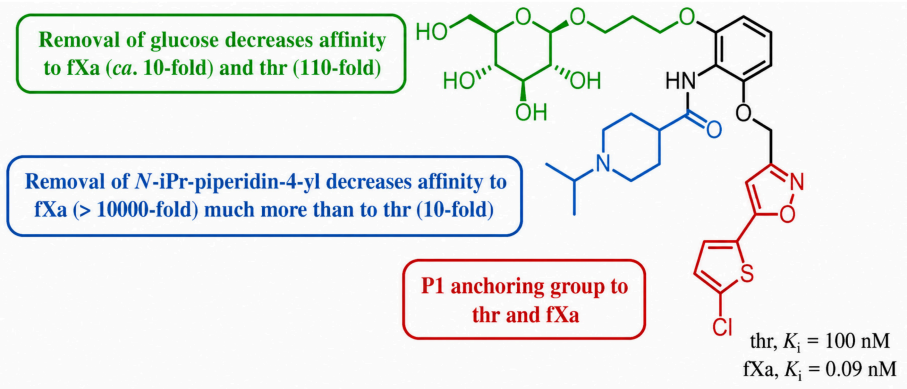


Figure 9. Key factors modulating fXa inhibition potency and selectivity over thr.

4.10. Design of Melanostatin-Based Derivatives for Application in Parkinson's Disease

Beatriz L. Pires-Lima [1], Xavier C. Correia [1], Hugo F. Costa-Almeida [1], Sara C. Silva-Reis [1], Ana Reis-Mendes [2], Vera M. Costa [2,3], Xerardo García-Mera [4], José E. Rodríguez-Borges [1], and Ivo E. Sampaio-Dias [1]

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Melanostatin (MIF-1) is an endogenous neuropeptide that acts as a selective positive allosteric modulator (PAM) of dopamine D_2 receptors (D_2R), displaying therapeutic potential for dopamine-related disorders such as Parkinson's disease (PD) [61,62]. However, its clinical application is limited by poor oral bioavailability due to enzymatic degradation and low gastrointestinal absorption [61,62]. Previous work from our group showed that replacing the d the binding of aL-proline (Pro) residue in MIF-1 with 2-furoic acid enhancegonists towards the D_2R, highlighting the viability of Pro substitution as a strategy to improve pharmacological profiles [61].

In this study, we explored the influence of the oxygen position within the furanyl ring by replacing Pro with 3-furoic acid (3-Fu) in eight newly synthesized peptidomimetics [62]. The PAM activity of these compounds was evaluated by functional assays at the D_2R. In this assay, two MIF-1 analogs significantly increased dopamine potency at 0.01 nM, confirming the potential of 3-Fu as an effective Pro bioisostere [62]. Moreover, toxicological studies in human dopaminergic SH-SY5Y neuronal cells demonstrate that these compounds display safe neurotoxicological profiles up to 200 μM [62]. These findings support the rational design of novel MIF-1-based peptidomimetics with improved PAM activity and neurotoxicological profiles for potential application in PD treatment.

Funding: This work received financial support from PT national funds (FCT/MCTES, Fundação para a Ciência e a Tecnologia and Ministério da Ciência, Tecnologia e Ensino Superior) through project 2023.14440.PEX (DOI: 10.54499/2023.14440.PEX).

Acknowledgments: FCT is also acknowledged for supporting projects 2022.01175.PTDC, UIDB/50006/2020, and UIDP/50006/2020. I.E.S.-D. thanks FCT for funding through the Individual Call to Scientific Employment Stimulus with reference 2020.02311.CEECIND/CP1596/CT0004 (DOI: 10.54499/2020.02311.CEECIND/CP1596/CT0004). V.M.C. thanks the financial support and her grant funded by national funds from FCT, in the scope of the projects UIDP/04378/2020 and UIDB/04378/2020 (UCIBIO), and the project LA/P/0140/2020 (i4HB). B.L.P.-L., X.C.C., H.F.C.-A., and S.C.S.-R. thank FCT for the Ph.D. grants 2022.14060.BD, 2024.02245.BD, UI/BD/154888/2023, and SFRH/BD/147463/2019, respectively. X.G.-M. thanks Xunta de Galicia for financial funding with reference GPC2020/GI1597.

4.11. Discovery of Potent Acyl-CoA Synthetase Long Chain Family Member 4 (ACSL4) Inhibitors with Anti-Ferroptotic Properties

Emeline Charnelle [1], Alexandre Gobert [1], Romain Marteau [2], Maela Pautric [1,3], Nicolas Renault [4], Aurélie Jonneaux [1,3], Darius Mazhari Dorooee [2], Amelie Laversin [1], Jean-Christophe Devedjian [1,3], Patricia Melnyk [1], Saïd Yous [1], David Devos [1,3], Raphaël Frédérick [2], Severine Ravez [1] and Jamal El Bakali [1]

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Ferroptosis, an iron-dependent regulated cell death characterized by the buildup of toxic lipid peroxides, has recently emerged as a drug target for pathologies such as cancer

and neurodegenerative diseases [63]. Most ferroptosis inhibitors act through a radical trapping antioxidant (RTA) mechanism, and molecules that specifically target enzymes conferring ferroptosis sensitivity remain largely lacking. Acyl-coenzyme A synthetase long-chain family member 4 (ACSL4), a key enzyme in the execution of ferroptotic cell death, has emerged as a promising target, creating a demand for potent, selective, and well-validated inhibitors [64]. Current ACSL4 inhibitors suffer from low potency and poor selectivity. Here, we report a fragment screening that identified a benzofuran hit (IC_{50} = 33 μM), which was further optimized to yield **LIBX-A403**. Molecular modeling studies combined with site-directed mutagenesis point to a potential binding mode for **LIBX-A403** in the fatty acid pocket. To the best of our knowledge, **LIBX-A403**, with an IC_{50} of 49 nM against ACSL4 and no inhibitory activity against ACSL3, is the most potent ACSL4 inhibitor identified to date. It also displays robust anti-ferroptotic properties in two different cell lines, with a demonstrated target engagement.

This work was supported by the Région Hauts-de-France (Start-AIRR FerInh4Park).

4.12. Targeting CtBP1 in Acute Myeloid Leukemia: Optimization of HIPP Derivatives and PROTAC Development

Chaimae El Hadri [1,2], Isaure Dewitte [2], Filip Matthijssens [3], Martijn Risseeuw [1], Pieter Van Vlierberghe [3], Steven Goossens [1], Serge Van Calenbergh [2]

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Acute myeloid leukemia (AML) is a hematopoietic malignancy characterized by the rapid and aggressive proliferation of immature progenitor cells, typically in the bone marrow. Due to its aggressive nature, AML is commonly associated with a poor prognosis. The pathophysiology of acute leukemia involves complex genetic and molecular alterations that drive the uncontrolled growth and survival of malignant cells.

ZEB2, together with its obligate cofactor CtBP1, has been identified as a critical dependency in the onset and progression of AML [65,66]. Building on these findings, our efforts focused on optimizing 2-hydroxyimino-3-phenylpropanoic acid (HIPP), a known inhibitor of the D-2-hydroxy acid dehydrogenase (D2-HDH) activity of CtBP1 [67].

We designed and synthesized a focused library of HIPP derivatives, which were characterized for D2-HDH inhibitory activity, nano differential scanning fluorimetry (nanoDSF), isothermal titration calorimetry (ITC), and X ray crystallography. This yielded two series of potent binders, one of which was prioritized for proteolysis-targeting chimera (PROTAC) development (Figure 10). The potential PROTACs were subsequently designed, synthesized, and comprehensively assessed for enzyme inhibition, E3 ligase engagement, and target degradation.

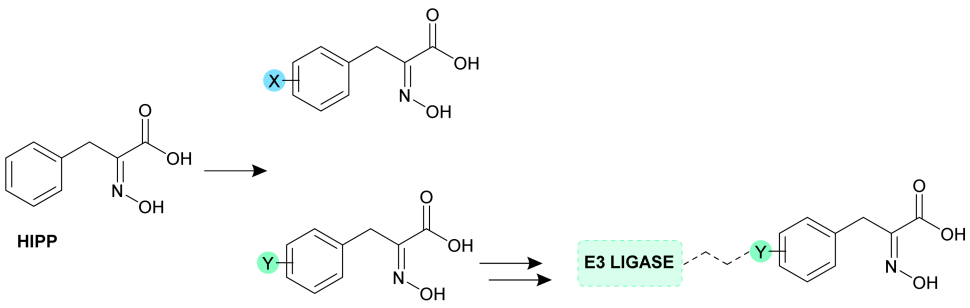


Figure 10. Conversion of the known HIPP into two series of strong CtBP1 binders, one of which was selected for the construction of a PROTAC.

4.13. Development of Orellanine Conjugates for the Treatment of Cancer

Mark J. Lyons [1] and John J Walsh [1]

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Antibody drug conjugates (ADCs) are a growing class of targeted therapies in the treatment of cancer [68]. By harnessing the targeting capabilities of antibodies, ADCs facilitate the delivery of highly potent cytotoxic "warheads" directly to the tumor tissue, resulting in significantly reduced side effects [69]. This strategy can enable novel treatment approaches with cytotoxins which were previously limited by selectivity issues.

The fungal nephrotoxin orellanine (Figure 11) is found in several mushrooms from the *Cortinarius* genus and exhibits strong cytotoxicity in proximal tubular cells [70]. While it is currently undergoing clinical trials for the treatment of advanced kidney cancer, orellanine's significant nephrotoxicity has restricted treatment to patients on hemodialysis [71]. Our research is focused on the synthesis of orellanine conjugates, to improve the compound's selectivity for tumor cells and potentially reduce the need for dialysis during treatment. By synthesizing the compound with differential protection of the phenolic hydroxyls (Figure 12) we have generated a tunable scaffold, enabling the regiospecific conjugation to one or more homing devices. This will allow for convenient iteration of conjugate design and the optimization of orellanine's tumor targeting.

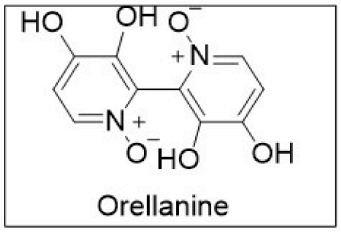


Figure 11. Structure of orellanine.

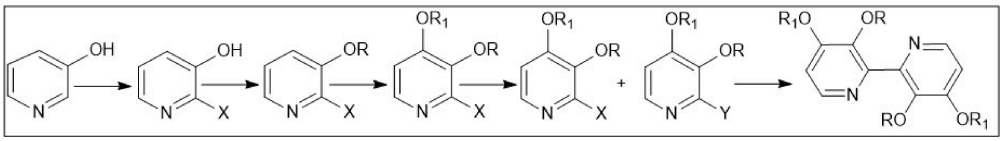


Figure 12. General scheme for the synthesis of differentially protected orelline X = I; R = CH_3 or CH_2OCH_3; Y = $SnBu_3$.

4.14. Unlocking New Allosteric Chemotypes for AKT1 Modulation in Cancer

M. Casciari [1], E. Primavera [1], A. Astolfi [1], M. Pacetti [1], F. Milano [2], V. Cecchetti [1], M.P. Martelli [2], M. Morlando [3], M.L. Barreca [1], and S. Massari [1].

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[2] Hematology and Clinical Immunology, Department of Medicine and Surgery, University of Perugia, Italy

[3] Department of Biology and Biotechnology "C. Darwin", Sapienza University of Rome, Italy

The serine/threonine kinase AKT is a key component of the PI3K/AKT/mTOR signalling pathway, whose hyperactivation is strongly implicated in the progression of several human cancers and the development of chemotherapy resistance [72]. Recently, our research group identified AKT1 inhibitors with potent activity against acute myeloid leukemia (AML), in particular the compound **T126** (5,6,7,8-tetrahydrobenzo [4,5]thieno[2,3-

d]pyrimidin-4(3*H*)-one), which exhibited an IC_{50} of 1.99 ± 0.11 μM. Further studies confirmed that **T126** acts as an ATP-competitive AKT1 inhibitor, effectively suppressing cell growth and inducing apoptosis in AML cells at low micromolar concentrations [73].

In this study, we focused on identifying novel AKT1 allosteric inhibitors. To achieve this, we developed a 3D pharmacophore model based on the AKT1 allosteric inhibitors currently in clinical trials. By combining the key pharmacophore features with the core structure of **T126** (Figure 13), we designed and synthesized a small set of potential AKT1 allosteric inhibitors. Some of these compounds effectively inhibited AKT1 via an allosteric mechanism, exhibiting potent activity in the low micromolar range. In addition, they exhibited a promising anticancer profile across multiple solid tumor cell lines and in AML cell models harboring the NPM1 mutation, laying the groundwork for subsequent hit-to-lead optimization campaigns.

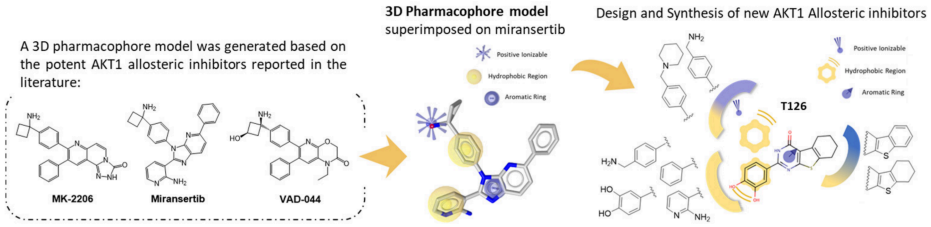


Figure 13. Schematic representation of the work herein reported.

4.15. Design, Synthesis and Screening of Novel Prenylated Chalcones as Potential Anti-Cancer Agents

Mouna Hind Laiche [1], Niamh Scully [2], Brona Murphy [2], and James W. Barlow [1]

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The anti-cancer potential of simple chalcones has been an intense area of research for some years, which has allowed structure-activity relationships to be well defined. Although many such examples display cytotoxic properties, important predictors of activity are the presence and position of hydroxyl and methoxy groups. More complex chalcones are those incorporating branched alkyl substituents, borne either on carbon or oxygen atoms. An important example is the liquorice metabolite, licochalcone A (LA), which, alongside related prenylated chalcones are increasingly seen as valuable lead compounds, due to their interesting anti-cancer activities [74,75]. To prepare novel chalcones derived from LA, we reacted *O*-prenylated aldehydes with different acetophenone derivatives, substituted at 3′ and 4′ positions of the phenyl ring. We also varied the phenyl ring by replacement with heteroaromatics. Reaction of the novel *O*-prenylated chalcones via 3,3-sigmatropic rearrangement [76] resulted in the novel LA analogues (Figure 14).

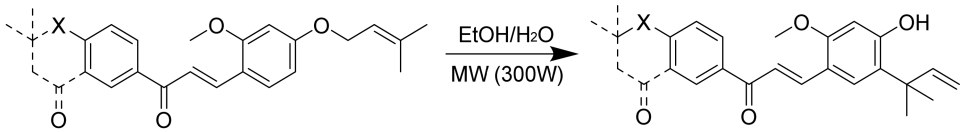


Figure 14. [3,3]-Sigmatropic rearrangement towards novel LA analogues.

This work presents the synthetic methods developed to prepare the aldehyde and ketone precursors of a family of LA and prenylated chalcone analogues, and to describe the reaction conditions necessary for the condensation of these precursors. Requisite prenylated

aldehydes were condensed with either monocyclic acetophenone derivatives or various heterocycles (including chromans and chromanones), with a key subsequent reaction being Claisen rearrangement of the substituted alkenyls. Furthermore, the presentation will include the results of cell viability assays of the prenylated chalcones and LA analogues on the U87 glioblastoma cell line. Some of these chalcones have shown interesting activity, and were further tested on primary brain cancer cells from both newly diagnosed and recurrent patients. Cell imaging using CD7 was employed alongside flow cytometry to determine their ability to stop invasion and induce cell death. Finally, Western blot analysis was applied to profile potential binding proteins, to further our understanding of the mechanism of action of these chalcones.

4.16. Discovery of Highly Potent BET Inhibitors Based on a Tractable Tricyclic Scaffold

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The bromodomain and extra-terminal domain (BET) protein family is a class of epigenetic reader proteins that recognise *N*-acetylated lysine residues in histone tails, playing a crucial role in gene expression and cell transcription [77]. Selective inhibition of bromodomain-containing proteins (BRDs) disrupts transcription in key oncogenes such as cellular myelocytomatosis (c-Myc) [78]. Over the past decade there has been considerable interest in developing small molecule BET inhibitors for the treatment of haemotological malignancies and solid tumours [79]. Herein, we report the development of a triazinoindole scaffold (**1**) capable of inhibition of bromodomain-containing protein 4 (BRD4), with either dimethylisoxazole or dimethyltriazole substituents acting as chemomimetics of the *N*-acetylated lysine residues (Figure 15) [80]. Derivatisation of the parent scaffold afforded the lead compound (**2**), which displays low nanomolar affinity towards BD1 of BRD4 with a favourable physicochemical and in vitro stability profile.

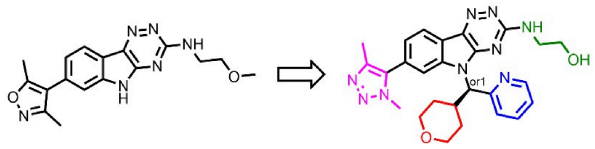


Figure 15. Structures and biological data of parent scaffold **1** and lead compound **2**.

4.17. Another Way of Predicting PROTAC Permeability In Silico

Laura Márquez-Cantudo [1], Claire Coderch [1], Liuba Mazzanti [2], Tâp Ha-Duong [2] and Beatriz de Pascual-Teresa [1]

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PROteolysis TArgeting Chimeras (PROTACs®) are beyond rule of 5 molecules capable of inducing the ubiquitination and subsequent degradation of a protein of interest (POI) by recruiting the ubiquitin-proteasome system (UPS) of a cell. They are composed of a POI ligand and an E3 ligase binder connected by a linker. Despite their therapeutic potential,

their poor solubility and permeability remain significant challenges [81]. Traditional in silico approaches for predicting PROTAC permeability rely on studying the behavior of the PROTACs in different solvents (e.g., water, chloroform, toluene) [82]. However, although useful, these methods fail to accurately mimic membrane environments.

To address this limitation, we applied an Umbrella Sampling (US) approach to model PROTAC permeability across a membrane model (Figure 16), leveraging its prior success with small molecules and cyclic peptides [83,84]. Our study focuses on **CP2**—the only reported CK2-directed PROTAC [85] along with two newly designed CK2 degraders synthesized in our research group. Additionally, we included **ARV-825** and **YANG7**, two PROTACs known to be cell-permeable and active in the same breast cancer cell line as **CP2** (MDA-MB-231) [86,87].

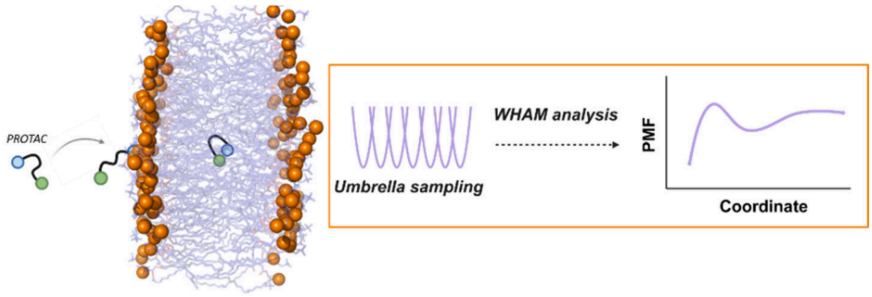


Figure 16. Umbrella Sampling (US) approach to model PROTAC permeability across a membrane model.

The results reveal key insights into PROTAC permeability, demonstrating the potential of US simulations as a predictive tool. These findings pave the way for more effective in silico screening strategies in PROTAC and bRo5 drug discovery campaigns.

Acknowledgments: Financial support from PID2021-123786OB-I00 (MICIU/FEDER, UE) is kindly acknowledged. L. M.-C. thanks Universidad San Pablo-CEU and Banco Santander for a Young Researcher contract.

5. Paul Ehrlich Awards

5.1. Design and Synthesis of SARS-CoV-2 Helicase Inhibitors

Erica Sanna [1], Angela Corona [1], Antonio Lupia [1], Alessia Onali [1], Roberta Emmolo [1], Rita Meleddu [1], Giulia Atzeni [1], Laura Demuru [1], Filippo Cottiglia [1], Fernanda Borges [2], Carlos Fernandes [2], Enzo Tramontano [1], Simona Distinto [1] and Elias Maccioni [1]

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Helicase of human coronaviruses (hCoVs) is responsible for the RNA unwinding in a 5′ to 3′ direction, a process driven by the ATP hydrolysis. Given its crucial role in viral replication and its highly conserved sequence among hCoVs, this enzyme represents a promising and attractive target for the development of new antiviral drugs [88].

In this study, with the goal to identify potential Pan-hCoVs helicase inhibitors, we have rationally designed and synthesized a library of 120 compounds. These compounds were characterized using structural (single-crystal X-ray diffraction) and spectroscopic (NMR, MS) techniques, and subsequently, evaluated for their biological activity. Our results revealed that most of compounds were able to inhibit both SARS-CoV-2 helicase-associated enzyme activities, namely NTPase and unwinding activity, showing IC_{50} values in the low micromolar range. Among them, several compounds also demonstrated potent antiviral

effects, significantly inhibiting SARS-CoV-2 replication at low EC_{50} values, without causing notable cytotoxicity (CC_{50}).

Furthermore, among the 130 tested compounds, the most promising candidates were selected to evaluate their potential broad-spectrum anti-hCoVs activity, using MERS-CoV and hCoV-229E as viral models. Results showed EC_{50} values in the low micromolar range with a good selectivity index, highlighting their potential to be developed as Pan-hCoVs inhibitors. Further investigations were carried out on the most promising compounds, including ATP competition assays, Yonetani-Theorell plot with a reference compound, Surface Plasmon Resonance, association studies with Remdesivir and Nirmatrelvir, Molecular Docking Experiments, in silico prediction of drug-like properties, evaluation of the cytotoxicity profile in Human Hepatocellular Carcinoma Cells (HepG2), and physicochemical and biomimetic property assessments through HPLC-based measurements.

These findings underscore the potential of targeting hCoV helicase as a strategy for developing effective treatments against SARS-CoV-2 and other hCoVs, opening the door to the development of novel therapeutic agents that could address both current and future emerging coronavirus-related diseases.

This research was supported by EU funding within the NextGenerationEU-MUR PNRR Extended Partnership initiative on Emerging Infectious Diseases (Project no. PE00000007, INF-ACT).

5.2. New Prospects on the Benzo[b]thiophene-3-ol Scaffold: Design, Synthesis, and Biological Evaluation of Novel Monoamine Oxidase Inhibitors & Photocatalytic Functionalization of Dehydroalanine-Derived Peptides

Francesca Arrighi [1], Michele Coluccia [1], Paolo Guglielmi [1], Nikolaos Kaplaneris [2], Merve Akdeniz [2], Méritxell Fillols [2], Timothy Noël [2] and Daniela Secci [1]

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Monoamine oxidases (MAOs) are enzymes responsible for the oxidative degradation of neurotransmitters and play a key role in regulating levels of dopamine, serotonin, and other biogenic amines in the central nervous system [89]. The inhibition of MAOs has therapeutic relevance in treating neurodegenerative disorders such as Parkinson's and Alzheimer's disease [90]. This research project focused on the design, synthesis, and preliminary biological evaluation of novel MAO inhibitors based on benzo[*b*]thiophene-3-ol derivatives. Guided by previous studies highlighting this scaffold's potential, a range of new carboxamide analogues were developed and characterized. The synthesized compounds were evaluated for their ability to inhibit MAO-A and MAO-B isoforms, with several showing promising selectivity and inhibitory activity.

In parallel, novel analogues based on the methyl 2-(benzylthio)benzoate core were synthesized and tested for MAO inhibition. These compounds further expanded the chemical diversity and provided new insights into the structure–activity relationships within this class of potential neuroprotective agents.

The final part of the project explored the photocatalytic functionalization of dehydroalanine (Dha)-containing peptides. Using arylthianthrenium salts under mild photocatalytic conditions, a hydroarylation strategy was developed for late-stage peptide modification in both batch and flow setups. This approach allowed the efficient synthesis of unnatural amino acids and enabled the incorporation of diverse aromatic groups,

offering significant advantages for peptide diversification and potential pharmaceutical applications [91].

5.3. MAATrica: A Measure for Assessing Consistency and Methods in Medicinal and Nutraceutical Chemistry Papers

Giulia Panzarella [1,2], Alessandro Gallo [1], Sandra Coecke [3], Maddalena Querci [3], Francesco Ortuso [1], Martin Hofmann-Apitius [4], Pierangelo Veltri [5], Jürgen Bajorath [2] and Stefano Alcaro [1,6,7]

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6 Net4Science srl, c/o Università "Magna Græcia" of Catanzaro, Campus Universitario "S. Venuta", Viale Europa, 88100 Catanzaro, Italy
7 Associazione CRISEA, Centro di Ricerca e Servizi Avanzati per l'Innovazione Rurale, Località Condoleo, Belcastro (CZ), 88055, Italy

The growing number of scientific papers and document sources highlight the need for methods capable of evaluating the quality of publications. Researchers who are looking for relevant papers for their studies need ways to assess the scientific value of these documents. One approach involves using semantic search engines that can automatically extract important knowledge from the growing body of text [92–94]. In this study, we introduce a new metric called "MAATrica," which serves as the foundation for an innovative method designed to evaluate research papers [95]. MAATrica offers a new way to analyse and categorize text, focusing on the consistency of research documents in the life sciences, particularly in the fields of medicinal and nutraceutical chemistry. This method utilizes semantic descriptions to cover in silico experiments, as well as in vitro and in vivo essays. Created to aid in evaluation processes like peer review, MAATrica uses toolkits and semantic applications to build the proposed measure, identify scientific entities, and gather information. We have applied MAATrica to roughly 90,000 papers and present our findings here.

5.4. Targeting Proteins Involved in Neurodegenerative Diseases and Cancer: From Traditional Structure-Based Approaches to Artificial Intelligence Models

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Computer-aided drug design (CADD) and machine learning (ML) techniques are transforming drug discovery by enabling the efficient identification of small molecules with therapeutic potential. Neurological disorders, which affect approximately 43% of the global population and are the leading cause of ill health and disability worldwide, and cancer, with over 2 million new cases and 611,720 deaths projected in the United States in 2024,

underscore the urgent need for effective therapeutic interventions [96,97]. My PhD research addresses this challenge by applying CADD and ML methodologies to discover ligands targeting proteins implicated in neurological and oncological conditions, specifically Sigma Receptors (SRs) and Tyrosinase (TYR). The research on TYR, a therapeutic target associated with melanoma and Parkinson's disease [98], focused on identifying new inhibitors for two distinct enzymes: *Agaricus bisporus* (AbTYR) and human tyrosinases (hTYR). CADD techniques, including molecular docking, MM-GBSA calculations, and molecular dynamics (MD) simulations, were employed to rationalize experimental data. These approaches offered valuable insights into ligand-receptor interactions and revealed key structural determinants of binding, advancing our understanding of tyrosinase modulation. In the investigation of SRs, increasingly recognized as versatile targets in oncology and neurology [99], the study integrated MD simulations with a grid-based approach to develop a pharmacophore model for Sigma-1 Receptor (S1R) ligands, leading to the identification of promising candidates. Additionally, ML techniques were employed to predict SRs selective compounds, achieving high accuracy in classifying SR ligands and enhancing precision in the drug discovery process. The findings presented in this research demonstrate the significant contributions of CADD and ML to modern drug discovery, offering innovative methodologies and insights for the design and optimization of compounds targeting TYR and SRs.

This work was supported by PhD research fellowships funded under the Programma Operativo Nazionale Ricerca e Innovazione 2014–2020, risorse FSE REACT-EU Azione IV.4 "Dottorati e contratti di ricerca su tematiche dell'innovazione" e Azione IV.5 "Dottorati su tematiche Green".

5.5. Unraveling the Mechanism of Action of the Innovative Antileishmanial Agent H80 Through Fluorescence Imaging and Multi-Omics Profiling

Lorenzo Tagliazucchi [1], Giulia Malpezzi [2], Sara di Persio [2], Nuno Santarem [3], Joana Tavares [3], Theodora Katsila [4], Alberto Venturelli [2], Anabela Cordeiro-da-Silva [3], Glauco Ponterini [2] and Maria Paola Costi [2]

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Leishmania infantum is a parasite that causes zoonotic leishmaniasis in humans, dogs and wild animals, mainly in the Mediterranean Basin, the Middle East, and Central Asia [100]. Recently it becsame more important for Europe due to climate changes and populations movements [100]. The disease manifests as cutaneous (CL) or visceral leishmaniasis (VL), with VL being potentially fatal due to complications like hemorrhage or secondary infections, especially in HIV co-infected patients. Few currently available treatments, including amphotericin B, miltefosine, and antimonials, are limited by toxicity, and increasing drug resistance phenomena [101]. Despite visceral leishmaniasis incidence followed a decreasing trend over the last 20 years in Europe, animal and human cutaneous leishmaniasis remain highly underreported, and would benefit One Health approach to complete eradication [102].

Drug resistance in Leishmania infantum arises through reduced drug uptake, increased efflux pumps, target mutations, and metabolic adaptations. To overcome these challenges, a novel benzothiophene-flavonol derivative, **H80**, has been identified [103],

which demonstrates a more potent anti-leishmanial activity in vitro in comparison to miltefosine, anti-*Trypanosoma cruzi* activity and lower toxicity [104]. As a major advantage **H80** can escape drug resistance. While in vivo pharmacokinetic studies are ongoing and delivery system under studies, **H80** mechanism of action has been investigated. Using fluorescence spectroscopy, MS-based proteomics, and metabolomics, were adopted to investigate **H80** subcellular biochemical effects when administered to THP-1 cells. A fractionated MS-based proteomics analysis revealed that, unlike miltefosine, which primarily targets cellular membrane composition, **H80** acts mainly in the cytosol, affecting energy metabolism and causing TCA cycle imbalance. Fluorescence internalization assays in THP-1 cells infected with *L. infantum* promastigotes at different concentrations confirmed its uptake via endocytosis and a progressive cytosolic accumulation. Ongoing untargeted MS metabolomics on **H80**- and MIL-treated promastigotes will further clarify **H80**'s mechanism of action and potential off-target effects. This will contribute to a better understanding of **H80**'s engagement with biological pathways, better supporting lead optimization.

The Authors acknowledge the COST Action CA21111 for financial support.

5.6. Exploring Triazole and Thiazole Systems for Antiviral Applications

Roberta Bivacqua [1], Isabella Romeo [2], Roberta Emmolo [3], Marilia Barreca [1], Maria Valeria Raimondi [1], Virginia Spanò [1], Stefano Alcaro [2], Angela Corona [3], Paola Barraja [1], Lieve Naesens [4], Enzo Tramontano [3], Graciela Andrei [4] and Alessandra Montalbano [1]

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Despite the progress made in the discovery of new antiviral agents, many viral infections still lack a specific treatment. In this scenario, there is considerable interest in the identification of chemical entities acting with new mechanisms of action. Among nitrogen-based heterocycles, triazoles and thiazoles have been extensively investigated for their antiviral properties, thus representing a valuable source of new therapeutic agents [105,106].

A small library of [1,2,3]triazolo[4,5-*h*][1,6]naphthyridines and [1,3]thiazolo[5,4-*h*][1,6]naphthyridines has been synthetized through a multistep procedure to assess their antiviral activity as potential anti-CoVs agents. Biochemical assays on SARS-CoV-2 Nsp13 helicase revealed interesting thiazole derivatives with inhibitory activity at micromolar level. Based on these results, a scaffold hopping strategy has been applied starting from [1,3]thiazolo[5,4-*h*][1,6]naphthyridines to obtain more potent compounds, thus leading to a series of variously decorated *N*-(2-phenyl-1,3-thiazol-5-yl)benzamides.

With the aim of searching for novel antiviral therapeutics with a broad spectrum of action, the newly synthesized compounds have also been evaluated in cell-based assays for their efficacy in inhibiting the replication of a panel of different viruses. The 8-(2-methoxyphenyl)-2-phenyl[1,3]thiazolo[5,4-*h*][1,6]naphthyridine emerged for its strong antiviral activity against human coronavirus HCoV-229E with an EC_{50} value of 0.85 μM, while two *N*-(2-phenyl-1,3-thiazol-5-yl)benzamides proved to potently inhibit the replication of different influenza virus A/H1N1 strains with EC_{50} values ranging from 0.04 μM to 1.80 μM. Pseudovirus entry assay in MDCK cells confirmed their ability to strongly inhibit the H1N1 HA-mediated entry process. Further insights into this class of compounds will be discussed.

5.7. Development and Characterization of Novel 2-Aroylbenzofuran Derivatives as Potent and Selective Human Monoamine Oxidase B Inhibitors: New Tools to Tackle Neurodegenerative Diseases

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Human monoamine oxidases (hMAOs) are flavin-containing enzymes deputed to the oxidative deamination of exogenous and endogenous amines, including fundamental molecules such as dopamine, serotonin and norepinephrine. Since their discovery in 1928, two isoforms, A and B, have been observed in the human organism, and their physiological role has been extensively investigated [107]. Their involvement in the fine regulation of monoamine neurotransmitters concentration has emerged as a pivotal process in the central nervous system. A dysregulation in hMAOs levels or activity can hence contribute to the development of pathological conditions, including neurodegenerative diseases like Parkinson's and Alzheimer's diseases. Furthermore, hMAOs seem to be involved in the pathogeneses of these conditions also through specific molecular pathways that have not been completely understood yet [108]. In the last decades, researchers have developed hundreds of hMAOs inhibitors based on numerous and different chemical structures. Our research group developed, in 2019, a series of micromolar inhibitors of hMAO-B based on the benzo[b]thiophen-3-ol scaffold [89]. To further increase the activity of these compounds, we have operated an isosteric replacement of the sulphur atom with an oxygen and other structural modifications that have led to the development of eight libraries of novel compounds, all based on the 2-aroylbenzofuran scaffold. Their activities have been evaluated in vitro. The elimination of the hydroxyl group in position 3 led to an enhancement of the activity and the selectivity, and so did the introduction of the methoxy or the nitro group in position 5 or 6 of the benzofuran ring. The modification of the carbonyl linker has been investigated too, with the development of libraries IVA and IVB, formed by N-phenylbenzofuran-2-carboxamides and N′-phenylbenzofuran-2-carbohydrazides, respectively. Overall, except for the 2-aroylbenzofuran-3-oles series (IA) and N′-phenylbenzofuran-2-carbohydrazides (IVB), all compounds have shown impressive activity and selectivity against hMAO-B, with IC50 values as low as 2.01 nM. The increase of potency was particularly significant with 5 and 6-nitrosubstituted compounds. The results obtained have shown that the developed compounds can potently and selectively inhibit hMAO-B, and some compounds have reported IC_{50} values in the used experimental conditions in the low nanomolar range. These promising results, which must be enriched by molecular modelling studies and cell assays for each library, indicate that the 2-aroylbenzofuran structure is a privileged scaffold for the development of hMAOs inhibitors.

5.8. Identification of Small Heterocycles to Tackle Emerging Infectious Threats

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The rise of antimicrobial resistance (AMR) is a critical global health problem, making once-treatable infections increasingly difficult to manage. As resistant strains proliferate, the potential for widespread outbreaks and in severe cases pandemics, such as COVID-19, grows highlighting the vulnerability of our healthcare systems and the need to boost the pharmacological armamentarium. In bacteria, resistance often stems from genetic mutations or the transfer of resistance genes, which lead to mechanisms that compromise

antibiotic efficacy. In viruses, particularly RNA viruses such as HIV, influenza, and SARS-CoV-2, resistance tends to arise from random point mutations or genetic reassortment events, resulting in the emergence of drug-resistant variants [109]. Within this framework, my PhD research has taken two main directions: on one side, the COVID-19 pandemic exposed the shortcomings of available antiviral treatments and highlighted the necessity of developing broad-spectrum antivirals to address both current and future viral outbreaks, as well as resistant strains. To support this effort, a drug repurposing strategy was employed, performing a phenotypic screening on the in-house small molecules library. This led to the identification of the 2-phenylquinoline (2-PhQ) scaffold—previously reported for its activity as a *Staphylococcus aureus* NorA efflux pump inhibitor (EPI) [110]—as a promising candidate for the development of anti-SARS-CoV-2 agents [111]. The subsequent synthesis and evaluation of novel 2-PhQ derivatives revealed the SARS-CoV-2 helicase NSP13 as their primary molecular target. On the other side, since years the research group where I carried out my PhD has been involved in the fight against AMR. Consequently, efforts were focused on investigating a series of pyrazolobenzothiazine-based compounds as *S. aureus* NorA EPIs that resulted able of synergizing with ciprofloxacin against various *S. aureus* strains. Moreover, due to structural and functional similarities between NorA and efflux systems in non-tuberculous mycobacteria (NTM), a set of structurally modified compounds was tested in combination with clarithromycin against NTM strains leading to the identification of new and potent *Mycobacterium avium* EPIs [112]. The search for antimicrobials with novel mechanisms of action, combined with the development of EPIs represents a promising avenue in the fight against AMR.

6. Flash Poster Communications

6.1. Bivalent and Monovalent Degraders: Two Possible Strategies for the Discovery of Original Anti-Ovarian Cancer Molecules

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Ovarian cancer is one of the most common and deadliest gynecologic cancers, with a high mortality rate. Diagnosis often occurs at advanced stages, making treatment less effective. A key characteristic of the tumor's progression is its ability to evade apoptosis, largely due to the overexpression of anti-apoptotic proteins from the Bcl-2 family, such as Bcl-2, Bcl-x_L, and Mcl-1. Targeting these proteins for inhibition is a promising strategy to overcome resistance, and their combined inhibition can restore apoptosis [113].

To restore apoptosis, enhance tissue selectivity, and minimize toxicity, we opted to develop compounds that simultaneously degrade these proteins by hijacking the UPS (Ubiquitin Proteasome System) pathway. The UPS is a key mechanism for protein degradation in vivo, accounting for nearly 80% of cellular protein breakdown. This quality control system uses E3 ligases to recognize and tag damaged or misfolded proteins for degradation by the proteasome, often referred to as the "cell's trash-disposal machinery." Bivalent degraders are heterobifunctional molecules composed of two distinct ligand-binding domains connected by a linker [114]. Monovalent degraders, also known as molecular glues, facilitate protein degradation by stabilizing an interaction between an E3 ubiquitin ligase and a target protein [115]. They do not have two distinct binding domains; instead, they induce a conformational change in the ligase or the target, promoting ubiquitination and subsequent proteasomal degradation.

Our work therefore consists of designing and synthesising new bivalent and monovalent degraders directed against two proteins of interest (POIs): Mcl-1 and Bcl-x_L. The molecular scaffolds used to begin this work have been studied in previous work by the research team and have shown interesting inhibition activities [116]. (Figure 17) The syn-

thesis of around 20 degraders will be presented in this study, including in silico, in vitro and *in cellulo* results for some of them.

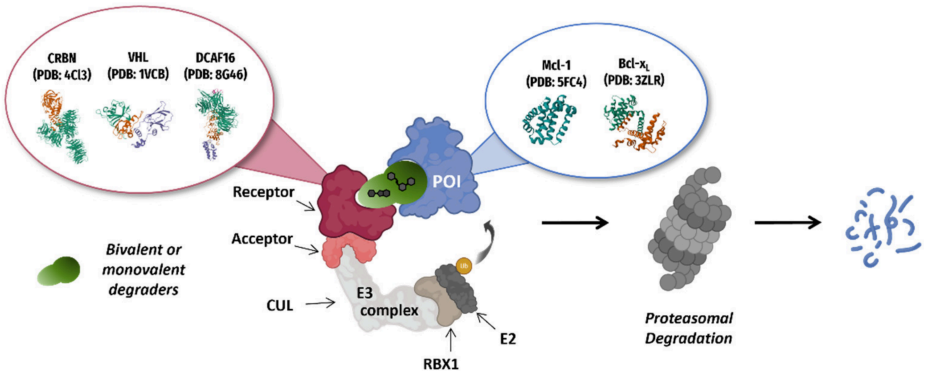


Figure 17. Schematic representation of a bivalent or monovalent degrader ternary complex with POIs and E3 Ligases.

6.2. 2,3-Dihydrophthalazine-1,4-Dione Derivatives as Nanomolar Inhibitors and Chemical Tools for Investigating Mono-ART PARP10

Chiara Sarnari [1], Juho Alaviuhkola [2], Maria Giulia Nizi [1], Chiara Vagaggini [3], Mirko M. Maksimainen [2], Chiara Bosetti [2], Saurabh S. Dhakar [2], Serena Massari [1], Giuseppe Manfroni [1], Elena Dreassi [3], Patricia Korn [4], Lari Lehtiö [2] and Oriana Tabarrini [1]

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ADP-ribosylation, a reversible post-translational modification of proteins, is catalysed by a large family of enzymes known as PARPs. While the therapeutic use of poly-ADP-ribosyltransferases (poly-ARTs) inhibitors is well established, mono-ADP-ribosyltransferases (mono-ARTs) still remain less explored. However, these enzymes have recently been implicated in several pathophysiological processes (e.g., cancer progression, neuronal development and immune response). This has highlighted the need to develop potent and selective inhibitors, both as valuable pharmacological tools and possibly as future drugs, as their therapeutic potential in the treatment of not only cancer, but also inflammation and neurological disorders has become apparent. In this scenario, we have mainly focused on the mono-ART PARP10, which has been associated with different activities, including a role as an anti-cancer drug target [117,118]. In particular, through the exploration of novel different nicotinamide mimetic scaffolds, compounds with good selectivity and high potency against PARP10 have been identified [119,120]. Starting from **OUL35** and its 4-(benzyloxy)benzamidic derivative, we introduced a more drastic modification by incorporating the amide moiety into a more rigid bicyclic ring. This led to the development of a new nicotinamide mimetic scaffold, 2,3-dihydrophthalazine-1,4-dione, that, when properly functionalised, gave compounds with IC_{50} values in the nanomolar range (130–150 nM) not only against PARP10 but also PARP15 thus emerging as potent PARP10/PARP15 dual-inhibitors [120].

Here, with the aim of improving the selectivity toward PARP10, we carried out a second round of H2L optimization, by modifying the substituents of the aromatic ring of the central core as well as their length.

Compounds with single-digit nanomolar potencies were obtained, with up to 150-fold selectivity over all other PARP enzymes, including PARP15. The most interesting compound achieved an IC_{50} value of 2 nM, making it the most potent and selective compound reported to date for PARP10. This study provides new insights into the design of selective mono-ARTs inhibitors that may be useful for the further investigation of the pathophysiological roles of PARP10.

6.3. Rationally Designed Microfluidic Production of Sphingosomes and Liposomes Encapsulating a Novel MAO-B Inhibitor

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Monoamine oxidase B (MAO-B) is a key enzymatic target in neurodegenerative disorders such as Parkinson's disease [107]. Current MAO-B inhibitors, including selegiline and safinamide, face limitations in selectivity, bioavailability, and inter-individual variability [121]. To address these challenges, this study investigates the microfluidic-assisted production of sphingosomes and liposomes encapsulating BT12, a novel synthetic MAO-B inhibitor, leveraging a Design of Experiments approach to optimize critical process parameters such as lipid composition, drug-to-lipid ratio, and flow conditions [122]. This enabled the successful engineering of the first application of sphingosomes for a synthetic MAO-B inhibitor delivery, alongside a phosphatidylcholine-based liposomal formulation, both meeting selected critical quality attributes in terms of size, polydispersity, and encapsulation efficiency (Figure 18). This work highlights the tunability of microfluidic platforms for scalable production of sphingosomal and liposomal formulations, offering a promising strategy to improve the delivery and therapeutic efficacy of MAO-B inhibitors in neurodegenerative disease management.

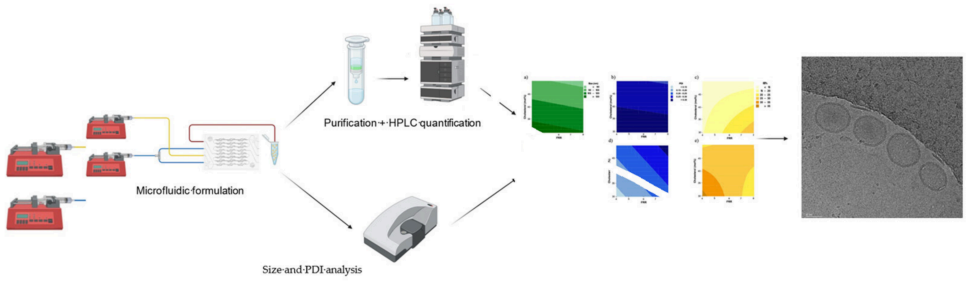


Figure 18. Schematic representation of the project workflow.

6.4. C-Nucleoside-Modified Antisense Oligonucleotides for lncRNA-Targeted Melanoma Therapy

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Melanoma, the most aggressive form of skin cancer, remains a major clinical challenge due to its high metastatic potential and limited treatment options [123]. Long non-coding

RNAs (lncRNAs) have emerged as key regulators of cancer progression, with MALAT1 (Metastasis Associated Lung Adenocarcinoma Transcript 1) acting as a competing endogenous RNA by sequestering miR-34a. This interaction modulates the expression of oncogenes such as c-Myc and Met, which are crucial for melanoma progression. The identification of a specific sequence of MALAT1 that binds miR-34a provides a rational starting point for the design of antisense oligonucleotides (ASOs) aimed at disrupting this oncogenic axis [124].

To achieve effective and selective MALAT1 knockdown, we are exploring the incorporation of C-nucleoside analogues into ASO sequences. Specifically, we have synthesized 4-aza-7,9-dideazapurine C-nucleoside analogues structurally related to the active metabolite of the FDA-approved broad-spectrum antiviral drug remdesivir [125]. The synthesized nucleoside analogues will be converted into their respective phosphoramidite derivatives to enable solid-phase oligonucleotide synthesis. The modified ASOs will be systematically evaluated for hybridization efficiency, thermodynamic stability, and specificity toward the MALAT1 target sequence.

Furthermore, given the established antiviral potential of C-nucleoside analogues, the synthesized compounds will be assessed for their potential activity against RNA viruses as well, expanding their therapeutic versatility.

6.5. Strategic Design of Ferrocenyl-Imidazopyrimidinones as Novel Antifungal Agents

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Invasive fungal infections (IFIs) are rising overall and particularly among immunocompromised populations. They are caused by some species like *Cryptococcus neoformans*, *Candida auris*, *Aspergillus fumigatus* and *Candida albicans* [126]. The emerging global health threat of IFIs is exacerbated by the rapid emergence of antifungal resistance. It is therefore important to accelerate the development of a new generation of antifungal agents with broad-spectrum activity, including against resistant strains.

Our azole antifungals with an imidazo[1,2-*c*]pyrimidin-5-one scaffold [127] are modified by the addition of a ferrocenyl moiety in expected to improve their therapeutic profile (Figure 19). In the literature, these derivatives may have the capacity to overcome resistant strains by generating reactive oxygen species *via* redox activation [128].

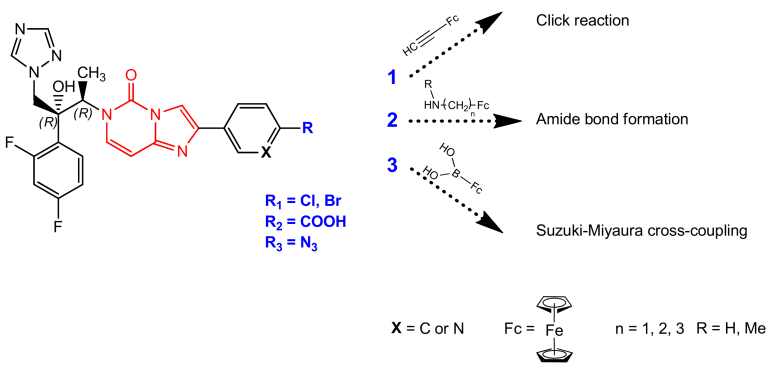


Figure 19. General structures of triazoles and their hypothetic ferrocenyl derivatives.

The in vitro antifungal activities of the compounds were evaluated against *Aspergillus fumigatus* and *Candida* spp. strains including azole-resistant clinical isolates and compared with those of fluconazole and itraconazole

6.6. Expanding the AKT1 Drug Discovery Landscape: From Allosteric Inhibitors to Protein Folding Interferers

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AKT1 is a key regulator of cell growth and survival, implicated in diseases such as Acute Myeloid Leukemia (AML) and Proteus Syndrome, a rare pediatric disorder caused by the E17K mutation. [72] While the first competitive AKT1 inhibitor was FDA-approved in 2023 for breast cancer, no allosteric inhibitors have yet reached the clinic. To address this gap, we pursued two complementary strategies (Figure 20):

(i) a traditional approach to expand the chemical space of AKT1 allosteric inhibitors, and
(ii) an innovative method to discover selective small molecule degraders targeting the E17K mutant via the "Pharmacological Protein Inactivation by Folding Intermediate Targeting" (PPI-FIT) technology [129].



Figure 20. A schematic overview of our drug discovery efforts targeting AKT1 protein.

For the first strategy, we used literature data [130] and computational studies to design new 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives. In vitro tests showed effective AKT1 inhibition, with some compounds active at low micromolar levels in solid tumors and NPM1-mutant AML cells. In the second approach, involving a collaborative effort between academia and the company Sibylla Biotech S.p.A. (www.sibyllabiotech.com), we applied the PPI-FIT platform to AKT1 E17K. This method targets folding intermediates rather than native protein structures, leading to degradation through the cell's quality control system. This allowed the identification of about 200 potential hits, currently under biological validation.

6.7. Design, Synthesis and Biological Evaluation of New MT5-MMP Inhibitors with Potential 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 [131]. 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 [132]. MT5-MMP is a metalloproteinase which acts as η-secretase and releases a neurotoxic Aη-α and Aη-β 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 either an amide or sulfonamide linker (Figure 21). We present here a series of compounds that were tested in enzymatic inhibition assay on MT5-MMP and MT1-MMP to assess their potency and selectivity. SAR studies were conducted on both aromatic moieties which modulation led to highly potent inhibitors.

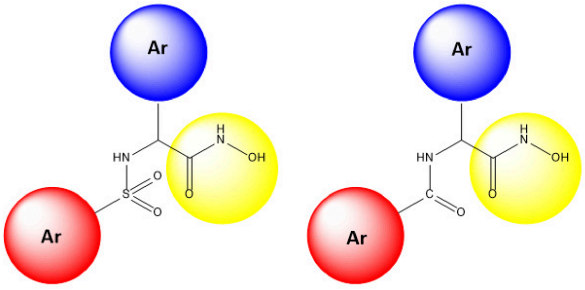


Figure 21. General structure of the designed inhibitors.

6.8. Computational Insights into the Structural Basis for Reduced Hepatotoxicity of Novel Non-Opioid Analgesics

Claire Coderch [1], Hernan A Bazán [2], Nicolas G Bazan [3,4], Bhattacharjee Surjyadipta [5], Julio Alvarez-Builla [6] and Beatriz de Pascual-Teresa [1]

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Management of acute and chronic pain is one of the most prevalent and costly public health issues worldwide [133]. Despite the risk of liver damage, Acetaminophen (ApAP) is one of the most frequently used over-the-counter (OTC) analgesic and antipyretic

drug [134]. ApAP toxicity is primarily caused by the reactive intermediate *N*-acetyl-*p*-benzoquinoneimine (NAPQI) [135] produced by interaction with CYP2E1. Due to the narrow therapeutic index of ApAP and the clinical demand for safer novel non-opioid analgesics, we undertook a research effort to find ApAP analogues with reduced hepatotoxicity [136].

To shed light on the molecular basis for the improved safety profiles of these new chemical entities (NCE), the structure and Normal Modes of CYP2E1 were studied to provide as many different conformations of the protein as possible to perform the docking calculations. Although not all of the ligands were found to bind in the automated docking calculations due to the limitations of the method, we obtained the binding mode of the compounds that were at each side of the toxicity spectrum (**6** and **6o**, Figure 22).

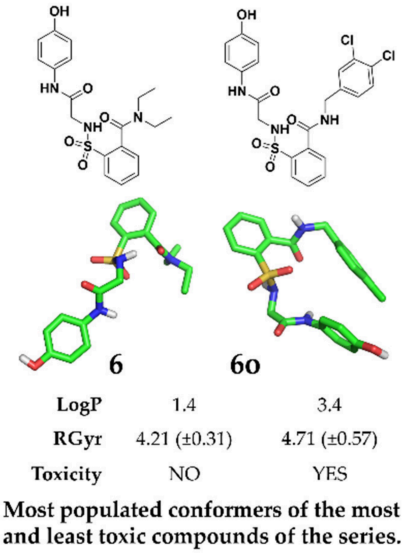


Figure 22. Most populated conformers of the most and least toxic compounds of the series.

The interactions established with the ligand binding site of CYP2E1 that could lead to the formation of the NAPQI were studied by means of 20 ns Molecular Dynamics (MD) simulations. In addition, 100 ns MD simulations in free water solvent were carried out for all compounds previously reported considering their protonation state at physiological pH and the conformation of the microstates was thoroughly analyzed and compared to the predicted bioactive conformations. Our findings provide a rational explanation for their differing toxicity profiles and contribute to a deeper understanding of their metabolic pathways.

Acknowledgments: This work was supported by PID2021-123786OB-I00 (MICIU/FEDER, UE).

6.9. Development of ACSL4 Inhibitors as Anti-Ferroptotic Agents

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Identified in 2012, ferroptosis is a regulated iron-dependent cell death characterized by excessive peroxidation of polyunsaturated fatty acids (PUFAs) present in membranes [137].

In 2017, a study showed that Acyl-CoA Synthetase family member 4 (ACSL4) is a key enzyme of the ferroptotic mechanism since it dictates ferroptosis by activating PUFAs [138]. Thus, inhibiting ACSL4 proves to be a promising strategy to block ferroptosis. Therefore, our laboratory is working on the development of new selective and potent ACSL4 inhibitors with anti-ferroptotic properties.

1200 FDA-approved drugs were screened against recombinant human ACSL4 using thermal shift assay (TSA) as primary screen technique. This gave 11 primary hits which were validated by microscale thermophoresis (MST), NMR and biochemical assay. Several hits were highlighted and in particular Rosiglitazone (ROSI) [139], a known ACSL4 inhibitor, with an inhibitory activity of 1 μM. This molecule is initially known to be a PPARγ agonist. Priliminary structure activity relationship (SAR) allowed to keep ACSL4 activity while abolishing the effect on PPARγ [140].

Based on these results, we describe herein, the hit optimization approach that culminated in the discovery of a potent and selective ACSL4 inhibitor. This molecule protects LUHMES cells from ferroptosis through an ACSL4-depedent mechanism.

Acknowledgments: This work was supported by l'agence nationale de la recherche (ANR-23-CE18-0051).

6.10. Natural Products Modulating Ferroptosis as an Alternative for Crop Protection

Auriane Leblond [1], Jean-Jacques Helesbeux [1], Guillaume Viault [1] and Denis Séraphin [1]

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Ferroptosis is a form of iron-dependent cell death characterized by lipid peroxidation which can be limited by iron chelators and lipophilic antioxidants [63]. Although it has been widely studied in animal systems, particularly for its applications in human health (cancer, neurodegenerative diseases), its role in plant health remains poorly explored [63,141]. Recent evidence has shown its involvement during biotic and abiotic stress in plants, in particular in plant-pathogen interactions, such as between *Oryza sativa* and the fungus *Magnaporthe oryzae* [141,142]. Modulation of ferroptosis for fungal control remains to be characterized but could represent an alternative solution for crop protection [141].

The aim of this study is to identify new natural products that modulate ferroptosis and explore their potential as an alternative for crop protection (Figure 23). A screening of 147 plant extracts from the in-house library was conducted using a lipid emulsion-based antioxidant assay, called the Conjugated Autoxidizable Triene assay (CAT) [143]. Among them, 68 extracts had a CAT value superior of the green tea extract used as a reference (1.29 TE in mmol Trolox/g). A second assay based on iron chelating property will be used to further investigate the selected extracts.

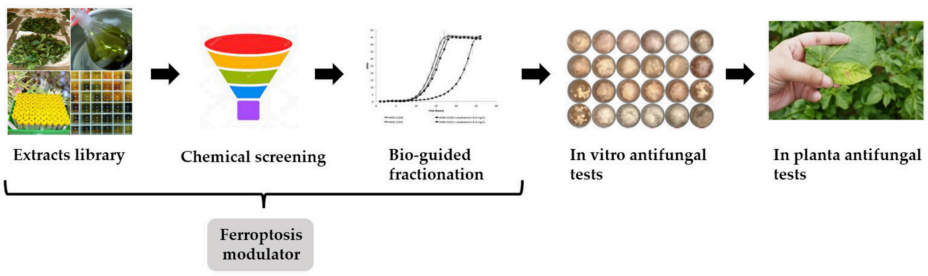


Figure 23. Screening strategy for discovering natural ferroptosis modulators and evaluating their antifungal activity.

The next steps of this study will focus on the bio-guided fractionation of extracts, the identification and the evaluation of the natural products on pathogenic fungi to assess their antifungal potential alone or in combination with plant defense molecules.

6.11. Development of Optimized Suzuki-Miyaura Strategies for Aryl and Pyridyl Benzo[b]thiophene Derivatives: Toward Improved Yields and Pharmaceutical Relevance

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Sulfur-containing heterocyclic compounds are interesting objects of research because they are found in various natural products and several drugs containing sulfur heterocycles have been approved by the FDA and are used for various medical diseases [144,145]. The main priorities in the synthesis of pharmaceutical substances are to perform highly selective reactions towards the target molecule, to prevent the formation of by-products and unwanted isomers, and to carry out the reactions under optimal conditions to obtain high product yields [146]. In this regard, one of the ideal methods is the Suzuki Miyaura cross-coupling reaction [147]. In this study, using the Suzuki-Miyaura cross-coupling process, new aryl and pyridyl derivatives of benzo[b]thiophene were produced in 59–79% yield. ^{1}H and ^{13}C NMR spectroscopy were used to confirm the structures of the produced compounds. To boost the reaction's yield, crucial variables like the solvent, base, temperature, duration, and catalyst were examined and improved (Figure 24).

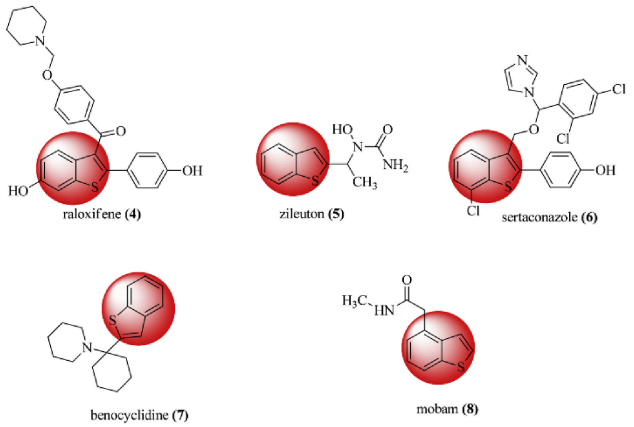


Figure 24. The multifunctional nucleus known as the benzo[b]thiophene moiety.

Using a two-fold microdilution assay, the antibacterial activity of the synthesized compounds (G1-G5) was assessed against clinical isolates of *S. epidermidis*, *S. aureus*, E.coli, and K. pneumoniae. Thiophene derivatives, especially G1, were found to have strong antibacterial action against Gram-positive bacteria (*S. aureus*, *S. epidermidis*). In the cases of S. aureus (64 μg/mL) and *S. epidermidis* (32 μg/mL), compound G1's MIC value was lower than ampicillin's. By discovering the synthetic and possible biological activity of benzo[b]thiophene derivatives, this work advances the research of ideal circumstances and biological activity.

The research funding by Azerbaijan Science Foundation, project number AEF-MCG-2022-1(42)-12/11/4-M-11.

6.12. Design, Synthesis, and Biological Evaluation of Neuroprotective Peptide Constructs

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Glypromate (glycyl-L-prolyl-L-glutamic acid, GPE) is an endogenous neuropeptide with the potential to treat neurodegenerative diseases [148]. Despite exhibiting neuroprotective activity in several in vivo experiments and clinical trials, its pharmaceutical use is limited by poor bioavailability and biochemical stability. In this sense, novel GPE analogs were synthesized via conjugation with amantadine, memantine, and (*R*)-1-aminoindane. Additional conjugates were prepared by replacing the L-proline residue with L-pipecolic acid.

Using a sustainable one-pot chemoselective methodology [149], 36 conjugates were synthesized and screened for cytotoxicity in differentiated SH-SY5Y neuroblastoma cells via the MTT reduction assay. Pipecolyl-based conjugates showed generally higher cytotoxicity than prolyl-based counterparts. The neuroprotective activity was then evaluated in dopaminergic differentiated SH-SY5Y cells exposed to the 6-hydroxydopamine (6-OHDA) neurotoxicant. Among prolyl-based GPE conjugates, five of them significantly reduced the 6-OHDA-induced toxicity, with one displaying a 2.3-fold improvement over GPE.

In conclusion, the conjugation strategy of GPE herein described led to the discovery of bioactive conjugates with interesting biological responses and superior biological performance in comparison with the parent neuropeptide.

Funding: This work received financial support from PT national funds (FCT/MCTES, Fundação para a Ciência e a Tecnologia and Ministério da Ciência, Tecnologia e Ensino Superior) through project 2023.14440.PEX (DOI: 10.54499/2023.14440.PEX). **Acknowledgments:** FCT is also acknowledged for supporting projects 2022.01175.PTDC, UIDB/50006/2020, and UIDP/50006/2020. I.E.S.-D. thanks FCT for funding through the Individual Call to Scientific Employment Stimulus with reference 2020.02311.CEECIND/CP1596/CT0004 (DOI: 10.54499/2020.02311.CEECIND/CP1596/CT0004). V.M.C. thanks the financial support and her grant funded by national funds from FCT, in the scope of the projects UIDP/04378/2020 and UIDB/04378/2020 (UCIBIO), and the project LA/P/0140/2020 (i4HB). H.F.C.-A., S.C.S.-R., X.C.C., and. B.L.P.-L. thank FCT for the Ph.D. grants UI/BD/154888/2023, SFRH/BD/147463/2019, 2024.02245.BD, and 2022.14060.BD, respectively. X.G.-M. thanks Xunta de Galicia for financial funding with reference GPC2020/GI1597.

6.13. Synthesis of Modified T-1106-5′-α-Thio-Triphosphates as Exoribonuclease (ExoN) Stable Inhibitors of SARS-CoV-2 RdRp

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The COVID-19 pandemic, spanning from 2020 to 2022, has clearly shown the urgent need for effective antiviral therapies. Nucleoside analogues have historically been used to combat viral infections by targeting the viral RNA-dependent RNA polymerase (RdRp). Previous studies have demonstrated that the triphosphate form of the nucleoside analogue T-1106 is rapidly incorporated into the SARS-CoV-2 genome by its RdRp, inducing C-to-U and G-to-A transition mutations, and causing an antiviral effect through lethal mutagenesis [150].This study aims to synthesize and evaluate modified T-1106-5′-triphosphates for their potential antiviral properties. These modifications are expected to alter the mechanism of polymerase inhibition and improve in vivo efficacy compared to unmodified T-1106. We successfully developed a robust synthesis route for these modified triphosphates. Through SARS-CoV-2 primer extension assays, we assessed their properties as RdRp substrates. Notably, the 2′-*C*-methyl-T-1106-5′-triphosphate demonstrated efficient incorporation by RdRp, substituting GTP and causing immediate chain termination. However, it remained susceptible to excision by the ExoN proofreading complex (Figure 1). To enhance stability against ExoN, an α-thio modification was introduced. This resulted in a compound that maintained efficient incorporation by RdRp and exhibited resistance to ExoN-mediated excision. Based on these results, we synthesized several prodrugs of the 2′-*C*-methyl-T-1106-5′-α-thio-triphosphate. Preliminary results indicate that prodrugs with an α-thio-modification may exhibit enhanced antiviral potency (Figure 25).

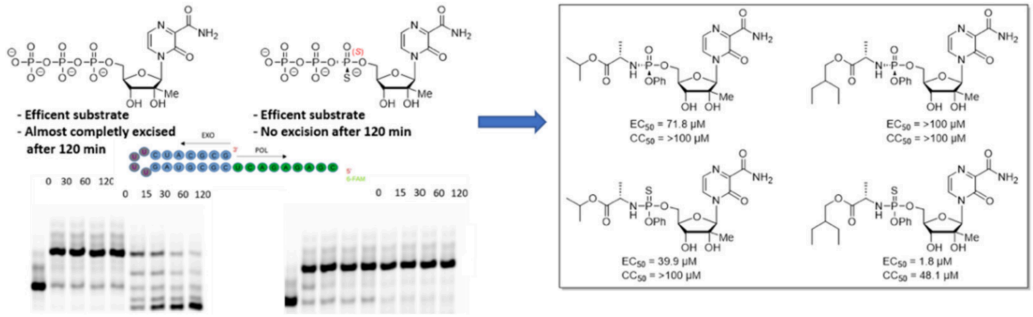


Figure 25. Primer extension assays and preliminary antiviral data.

This research was supported by the Corona Accelerated R&D (CARE) in Europe and the SFB CRC1648.

6.14. Development of Anthranilic Acid Based Dihydroorotate Dehydrogenase Inhibitors for the Use as Antiviral Agents

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Dihydroorotate dehydrogenase (DHODH) is a mitochondrial enzyme involved in de novo pyrimidine synthesis, leading to the formation of uridine monophosphate (UMP). Afterwards, UMP is converted to other pyrimidine nucleotides needed for the biosynthesis of RNA and DNA. Large amounts of natural nucleotides are necessary during a viral infection. Blocking DHODH with small synthetic molecules should result in a depletion of pyrimidines in the nucleotide pool [151]. An advantage of inhibiting essential cellular

enzymes is the lower risk of resistance development. In combination therapy, DHODH inhibitors have the potential to enhance the effectiveness of viral RNA-polymerase targeting nucleoside analogs by reducing the competition with cellular pyrimidine nucleotides for their incorporation into the viral RNA [152].

We have developed different series of DHODH inhibitors based on anthranilic acids (Figure 26) that showed broad-spectrum antiviral activities against several RNA viruses, including bunyaviruses, flaviviruses and filoviruses [153]. Herein, we describe structural optimizations using identified lead structures of the different series, especially with regard to the enzymatic stability and aqueous solubility. The objective of this study is to improve the drug-like properties of the selected compounds without the loss of antiviral efficacy.

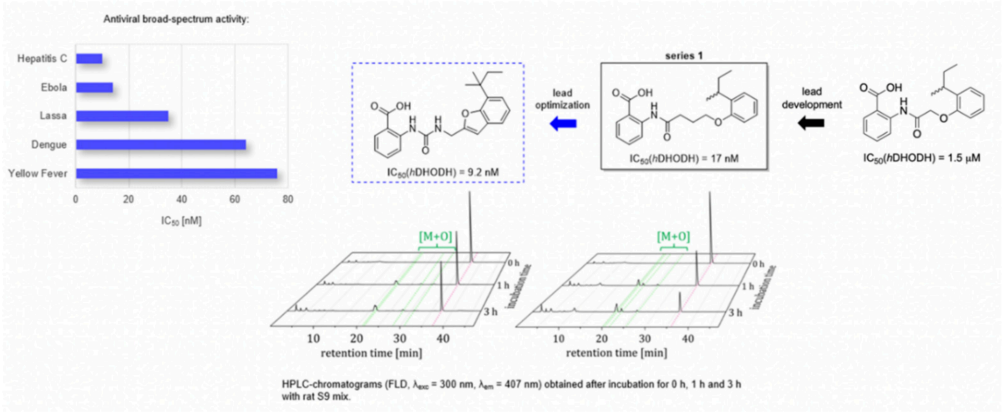


Figure 26. Preliminary results in the development of the first DHODH inhibitor series.

The authors gratefully acknowledge the financial support of SFB CRC 1648.

6.15. Phenanthrolinone Derivatives as Possible NAT Inhibitors in the Treatment of Tuberculosis

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Mycobacterium tuberculosis is the bacterium responsible of the tuberculosis. It is very resistant and can adapt fast to its environment making it one of the most murderous bacterium [154]. Thus, it is appropriate to find a countermeasure to face this resistance by targeting proteins which are involved in these processes [155]. It has been demonstrated through the literature and bio-assays realized by our collaborator in Pasteur Institute that the protein TBNAT (TuBerculosis arylamine *N*-AcetylTransferase) is associated to the deactivation of Isoniazid (INH), one of the four drug sfrom the actual treatment, by acetylation of the terminal amine. Various antibacterial drugs are based on quinolones and more precisely on fluoroquinolones (Ciprofloxacin, Moxifloxacin) which were a basis for our choice of structure [156]. Thus, several novel 1,10-phenanthrolinone derivatives were synthesized, tested and have shown some interesting activity on the bacterium [157]. Those phenotypic assays were completed by molecular modeling with docking of our molecules of interest in TBNAT (Figure 27) to better understand the mechanism of the protein and compare it with INH [158]. Results from this study will allow us to refine our structure to get better activity and physical properties.

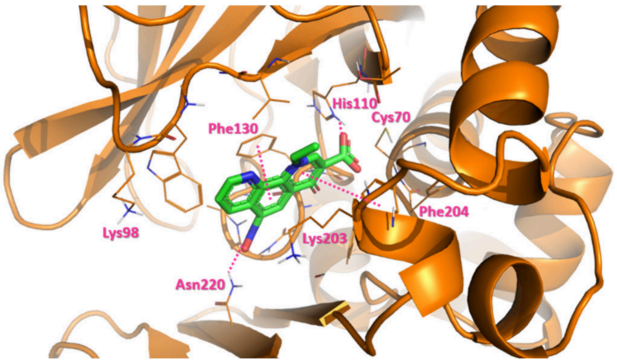


Figure 27. Overlay of the docking of INH (blue) and M06 (green) in TBNAT active site (orange).

6.16. Identifying Potential Allosteric Inhibitors of ZIKV NS3^{pro} Through a Combined Computational and Biochemical Approach

Laura Demuru [1], Antonio Lupia [1], Salvatore Nieddu [1], Roberta Emmolo [1], Annalaura Paulis [1], Francesca Esposito [1], Simona Distinto [1], Sharon D. Bryant [2], Alessia Onali [1], Erica Sanna [1], Giulia Atzeni [1], Filippo Cottiglia [1], Nicole Grandi [1], Angela Corona [1], Enzo Tramontano [1], Elias Maccioni [1] and Rita Meleddu [1]

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Zika Virus (ZIKV) belongs to the Flavivirus genus. The infection is transmitted by *Aedes* species mosquitoes and continues to pose an ongoing threat to public health. The ZIKV genome contains NS2B-NS3 protease (NS2B-NS3^{pro}), essential for viral replication that cleaves the viral polyprotein to yield structural and non-structural proteins [159]. The NS3^{pro} is a chymotrypsin-like enzyme characterised by the catalytic triad—S135, H51, D75—at the N^{-ter} region. The structural homology between the active centre of NS3^{pro} and various host serine proteases with important biological activities and the inefficacy of covalent peptide derivatives inhibitors made developing selective competitive inhibitors challenging. Thus, the identification of allosteric inhibitors is nowadays the preferred option [160]. Currently, neither medicines nor vaccines are commercially available.

In our study, an integrated approach, combining various in silico techniques with biochemical assays, was employed to identify novel potential hit compounds. The drug design strategy included Molecular Dynamic simulations (MDs) of the ZIKV NS2B-NS3^{pro} in complex with NSC86314 (PDB ID: 7M1V), followed by the generation of a dynamic pharmacophore, which was subsequently used as query to perform a Structure-Based (SB) pharmacophore Virtual Screening.

The FDA-approved drugs and SPECS databases were screened to identify new hit scaffolds. Sixteen hits were selected for biological evaluation, among which three exhibited IC_{50} value below 30 μM against ZIKV NS3^{pro}. Given the high homology between ZIKV NS3^{pro} and other Flavivirus proteases, these compounds were also evaluated against West Nile Virus (WNV) NS3^{pro}. In this secondary screening, four of the sixteen compounds exhibited IC_{50} values between 11 and 33 μM. Based on these findings, we chose to focus on the scaffolds of the active compounds and synthesized new libraries to establish structure activity relationships and for further evaluation.

6.17. Integrated CADD and Data Mining for the Identification of Novel Viral Helicase Inhibitors

Alessia Onali [1], Roberta Emmolo [1], Antonio Lupia [1], Erica Sanna [1], Giulia Atzeni [1], Laura Demuru [1], Angela Corona [1], Rita Meleddu [1], Filippo Cottiglia [1], Elias Maccioni [1], Enzo Tramontano [1] and Simona Distinto [1]

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Viral helicases are essential enzymes in viral replication that are involved in the unwinding of nucleic acids, making them attractive targets for antiviral drug design [161]. Helicases, which are grouped into different superfamilies (SFs), possess specific sequences of amino acids known as motifs [162]. These motifs are conserved within each SF and exhibit similarities across different SFs [163]. Targeting these conserved motifs could lead to compounds that interact with a broad range of viral helicases, paving the way for the development of effective antiviral therapies. In this study, we used the Helicase-targeting Small Molecule Antiviral Compound Collection (Heli-SMACC) from CHEMBL, which covers 20,432 bioactivity entries targeting viral, human, and bacterial helicases. This collection included helicases from Coronaviridae (e.g., SARS-CoV-2, MERS-CoV, HCoV-229E) and Flaviviridae (e.g., Dengue, Zika, Yellow Fever, West Nile, Hepatitis C virus) [164]. A KNIME workflow was applied to manage the data and identify compounds active against viral helicases, characterised by IC_{50} values <10 μM. These compounds were then clustered based on their chemical diversity and subjected to a detailed analysis for best compound selection. Subsequently, synthetic procedures were set up, leading to the synthesis of selected compounds for biological testing and repurposing across diverse helicases. Considering the biological results, we will use them for similarities screening to derive focused libraries and obtain more insights about the structure activity relationships (SAR). These insights will be exploited for subsequent compounds' optimization.

"This research was supported by EU funding within the Next GenerationEU-MUR PNRR Extended Partnership initiative on Emerging Infectious Diseases (Project no.PE00000007, INF-ACT)".

6.18. Development of Quinoline-Based Carboxamides Against Non-Tuberculous Mycobacteria

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Since last years, non-tuberculous mycobacteria (NTM) represent a growing-health concern and are closely monitoring by public health authorities. In North America and Europe, NTM incidence exceeds that of tuberculosis, with 1.0 to 1.8 case per 100,000 people [165]. NTM are ubiquitous in the environment and some of them cause opportunistic infections in humans. These bacteria are known for their pulmonary pathogenicity and can be particularly harmful to individuals with compromised immune system or pre-existing lung diseases such as bronchiectasis, cystic fibrosis or chronic obstructive pulmonary disease. NTM species are identified according to their growth: the slow-growing strains such as *Mycobacterium avium* complex (MAC), *M. xenopi* and *M. kansasii*, and the rapid-growing strains such as *M. abscessus* and its MABC complex, which exhibits both smooth and rough morphotypes, and *M. fortuitum* [166,167]. Treatment options are based on a combination of three antibiotics including a macrolide, depending on the strain. The treatment covers 18 to 24 months, with many associated side effects, and the cure rate remains moderate (52% to 60% for MAC infections). An additional problem is macrolide resistance, a worrying phenomenon for MAC. Our project aims to develop a new family of antibiotics with antimycobacterial activity which will target slow-growing species, rapid-growing species or both. Some developed or commercial antibiotics containing a quinoline ring have shown potent activity against NTM, such as bedaquiline (BQ) or mefloquine (MQ). Our strategy consists of the synthesis of innovative quinoline-based carboxamides (Figure 28), which contain a differently substituted amide group in position 4 of the quinoline. Amide function

and its derivatives were found in a number of compounds with proven antimycobacterial properties, including the well-known antituberculosis drug isoniazid (INH). The design, the synthesis and biological evaluation of this new quinolone-based carboxamides series will be presented.

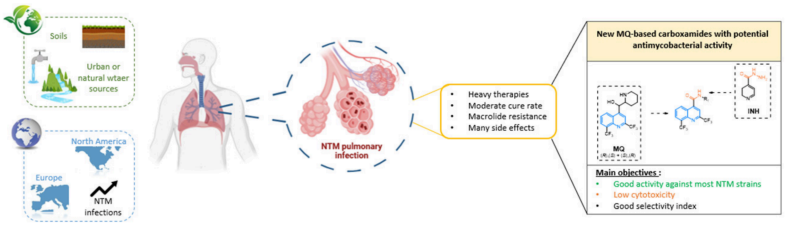


Figure 28. Non-tuberculous mycobacteria infection and design of quinoline-based carboxamides.

6.19. Expertise in the Design, Synthesis and Biological Evaluation of PROTAC Compounds for Cancer Treatment

Marie Cornu [1], Thomas Lemaitre [1], Florian Schwalen [1,2], Jocelyn Pezeril [3,4], Nuria Profitos [5], Laurent Poulain [3,4], Gaël Roué [5], Mike Maillasson [6], Marc Since [1], Jana Sopkova-De Oliveira Santos [1], Charline Kieffer [1] and Anne Sophie Voisin-Chiret [1]

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The escape of ovarian cancer and lymphoma cells from apoptosis is partly due to the overexpression of two anti-apoptotic proteins: Mcl-1 and Bcl-x_L [114]. Inhibiting these proteins can cause cardiac and platelet toxicity, and blocking one leads to the overexpression of the other. Their simultaneous degradation could restore cellular balance and promote apoptosis [168]. This project aims to synthesize dual-activity molecules capable of degrading both Mcl-1 and Bcl-x_L. To achieve this, we use the PROTAC approach, developed in 2001 by Prof. Crews [169]. The synthesized PROTAC compounds include oligopyridines (ligands developed by CERMN [117], targeting Mcl-1 and/or Bcl-x_L) and a ligand that recruits an E3 ligase, connected by a linker (Figure 29).

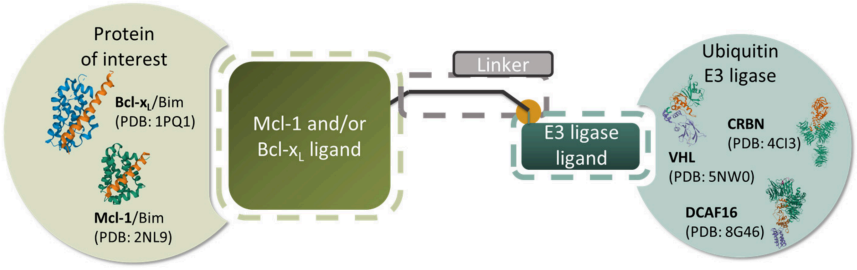


Figure 29. Schematic representation of the structure of our PROTAC compounds.

Over the past five years, Prof. Anne-Sophie Voisin-Chiret's team has developed a chemical library of around a hundred PROTAC compounds designed to degrade these

two proteins. To optimize this degradation, a range of expertise has been mobilized within the laboratory and through various collaborations. In silico models were used to characterize the ternary complex formation and assess the oral bioavailability of the compounds. Additionally, their chameleon-like properties, which facilitate membrane passage, were evaluated to refine pharmacokinetic parameters. Pharmacodynamic parameters were studied in vitro using analytical methods such as HTRF, MST, and SPR to examine the formation of the ternary complex between the PROTAC compounds, target proteins, and E3 ubiquitin ligase. Finally, in collaboration with two research teams, these compounds were tested on cancer cell lines—IGROV1-R10 (chemoresistant ovarian cancer) and Pfeiffer (lymphomas) (Dr. Poulain, Anticipe team; Dr. Roué)—to assess their efficacy in protein degradation. Simultaneously, some compounds are being studied *in ovo* using the CAM model to evaluate their anti-cancer activity.

6.20. Macrocyclization as a Strategy for Optimizing PROTACs Targeting Aurora Kinase A

Anouk Van Hauwermeiren [1], Simon Krols [1], Hanne Van De Putte [1], Muhammad Rishifi [2], Fien Martens [2], Kaat Durinck [2] and Serge Van Calenbergh [1]

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Previous efforts at the Laboratory for Medicinal Chemistry successfully led to the design and synthesis of PROTACs targeting Aurora Kinase A (AURKA). While these PROTACs demonstrated potent in vitro degradation in neuroblastoma cell lines, their in vivo efficacy was limited, primarily due to poor metabolic stability, preventing further development as viable drug candidates [170]. Emerging data indicate that macrocyclization can enhance a compound's potency and drug-like properties. This approach improves selectivity, even among closely related targets, reduces the entropic cost of binding, and might enhance metabolic stability by rigidifying the more flexible regions of the molecule, potentially preventing enzymatic degradation [171–173].

A co-crystal structure of MK-5108, a selective AURKA inhibitor, bound to AURKA suggested that macrocyclization between the ortho/meta position of the phenyl ring and the thiazole moiety could be feasible (Figure 30). Based on this insight, macrocyclic AURKA inhibitors were synthesized using a Buchwald-Hartwig amination for the cyclization step. These retained similar affinity for AURKA compared to their parent compound, MK-5108. The macrocyclic analogues were subsequently incorporated into PROTACs, which exhibited comparable potency in neuroblastoma cell line growth inhibition assays as their non-macrocyclic counterparts, indicating that macrocyclization is well tolerated in the PROTAC context.

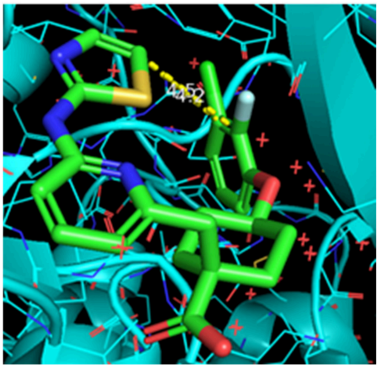


Figure 30. Co-crystal structure of MK-5108, a selective AURKA inhibitor.

These findings highlight macrocyclization as a promising yet underexplored strategy for optimizing PROTACs. As we continue to evaluate the metabolic stability of these compounds, this approach could open new avenues in the rational design of next-generation targeted degraders.

6.21. Small Nitrogen Heterocycles as Correctors for F508del-CFTR Mutation in Cystic Fibrosis

Fabiana Lo Mascolo [1], Marilia Barreca [1], Alessandra Lipani [1], Stefano Giuffrida [1], Virginia Spanò [1], Maria Valeria Raimondi [1], Alessandra Montalbano [1], Mario Renda [2], Anna Borrelli [2], Arianna Venturini [2], Daniela Guidone [2], Michele Genovese [2], Luis J. V. Galietta [2] and Paola Barraja [1]

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Cystic Fibrosis (CF), a genetic disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, affects approximately 89.000 individuals worldwide. Absent or decreased function of the CFTR protein is associated with multiorgan dysfunction and the main comorbidity involves the respiratory system with bronchiectasis and airflow obstruction. This defect can be corrected by the use of modulators that improve the production of CFTR protein and increase its expression on the cell surface [174–176]. Despite the significant progress in the pharmacological treatment of CF with the development of Kaftrio, there is still a need for new modulators to optimize the rescue of F508del and other CFTR mutations with trafficking defects. During our research, we have identified a very promising class of small tricyclic compounds (PP), some of which were found to be effective candidates for rescuing F508del-CFTR in primary airway epithelial cells from CF patients [177]. After the identification of an initial candidate with modest corrector activity, the tricyclic scaffold was further optimized leading to the lead compound PP028 which showed high efficacy and ability to produce strong synergistic effect when combined with class 1 correctors (i.e., VX-809). Importantly, the combination of these two correctors led to a three-fold increase in CFTR-dependent current compared to vehicle-treated cells. From the first discovery we started a multiparametric optimization process based on iterative cycles of chemical synthesis, to obtain wide structural diversification of the lead scaffold to gain insight into the structure-activity relationship (SAR). The manipulation of the PP scaffold provided a library of new analogues generating a family of correctors from which several potent candidates were identified. To assess potency and maximal efficacy, the new synthetized compounds were screened at the Telethon Institute of Genetics and Medicine (TIGEM) using the HS-YFP test on CFBE41o- cells expressing the CFTR protein with the F508del mutation. The most promising compounds were subsequently validated through: (1) testing on primary airway epithelial cells (bronchial and/or nasal) derived from CF patients; (2) in biochemical assays and microscopy analyses. To assess the mechanism of action, PP compounds were studied in combination with type 1, 2 and 3 correctors. Synergistic effect was found with class 1 (VX-809) and class 2 correctors, but not with class 3 suggesting that our compounds act as class 3 correctors. A multiparametric optimization, also taking into account the ADMETox properties is still ongoing with an extensive exploration of the chemical space around PP scaffold. Our aim is to generate new chemical entities with the best balance between potency/efficacy and drug-likeness in order to develop candidates for preclinical and clinical development.

6.22. Lipid-Polymer Hybrid Nanoparticles Containing Salvia Officinalis L. Extracts for Neurodegenerative Disorders

Maria Marra [1], Jessica Ceramella [1], Cláudia Sofia Machado [2], Daniel Chavarria [2], Domenico Iacopetta [1], Antonio Gattuso [3], Monica Rosa Loizzo [1], Vincenzo Sicari [3], Rosa Tundis [1], Stefano Alcaro [4,5,6], Fernanda Borges [2], Carlos Fernandes [2] and Maria Stefania Sinicropi [1]

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3 Department of Agriculture, University "Mediterranea" of Reggio Calabria, Via dell'Università, 89125, Reggio Calabria, Italy
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5 Net4Science SRL, Academic Spinoff, Università "Magna Græcia" di Catanzaro, Viale Europa, 100 Catanzaro, Italy
6 Associazione CRISEA-Centro di Ricerca e Servizi Avanzati per l'Innovazione Rurale, Belcastro, 88055 Catanzaro, Italy

Nature is an inexhaustible source of bioactive compounds with remarkable medicinal properties and technological applications, which can help to prevent the onset and progression of various diseases, including cancer, neurodegenerative disorders, and cardiovascular conditions. Among them, sage species have been used in traditional medicine and culinary practices since ancient times. In this study, the chemical quali-quantitative characterization of four extracts obtained from the leaves of Calabrian *Salvia officinalis* L. was performed [178]. Moreover, the extracts were analysed for their biological activities, demonstrating significant antioxidant, anti-inflammatory, and anticancer properties, and the ability to target specific enzymes involved in neurological and neurodegenerative diseases (MAO-A and -B, AChE, and BChE). Recognizing the limitations of natural compounds due to poor bioavailability, low permeability and restricted blood-brain barrier penetration, lipid-polymer hybrid nanoparticles containing the studied *Salvia officinalis* L. extracts were also developed [179,180]. This nanotechnological approach will allow to obtain new formulations containing the sage extracts potentially effective in treating a range of diseases, including neurodegenerative disorders.

6.23. Stability Assessment of Quercetin in Ethanolic and Hydroalcoholic Solutions Using a Chemometric Approach

Martina Chieffallo [1], Romà Tauler [2], Stefan Platikanov [2], Giuseppina Ioele [1] and Michele De Luca [1]

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Quercetin (QCT), a flavonoid known for its remarkable antioxidant properties, has been extensively investigated for its potential health benefits. However, its chemical stability in solution remains a critical factor influencing both its bioactivity and shelf life. In this study, a comprehensive stability assessment of quercetin was carried out in ethanolic (Figure 31) and hydroalcoholic solutions under various experimental conditions.

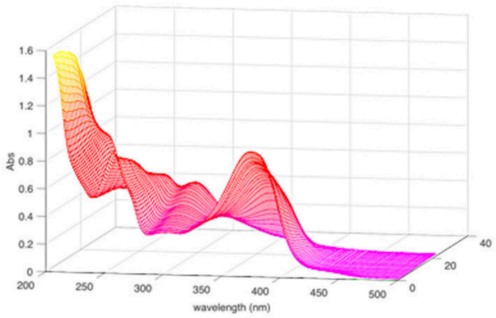


Figure 31. Multivariate resolution of spectral data recorded during QCT photodegradation experiments, a 3D plot of the recorded matrix in ethanolic solution.

The degradation process was evaluated both in the dark and under forced photodegradation, exposing the solutions to light at different pH levels. A combined spectrophotometric and chromatographic approach was employed, integrated by multivariate analysis. Specifically, a chemometric strategy was applied to process multiset data obtained from LC-DAD and spectrophotometric analyses during acid-base titration and kinetic degradation experiments. Column- and row-wise augmented data blocks were jointly processed using the multivariate curve resolution–alternating least squares (MCR-ALS) algorithm, enabling the simultaneous interpretation of heterogeneous datasets from different analytical techniques.

The pH-dependent degradation pathways were elucidated, and several degradation products were identified, providing a deeper understanding of quercetin's stability and behavior under different physicochemical conditions [181–183].

6.24. New Quinoline-Based Amides as Promising Human Topoisomerase I Inhibitors

Eva Scarcelli [1], Jessica Ceramella [1], Domenico Iacopetta [1], Camillo Rosano [2], Francesca Aiello [1] and Maria S. Sinicropi [1]

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One effective strategy for treating cancer consists in interfering with a large number of DNA-managing enzymes, including topoisomerases (Topos). They are enzymes involved in essential cellular processes such as DNA replication, transcription and recombination [184]. Recently, research has focused on the inhibition of these enzymes due to their overexpression in different cancers, including breast cancer, which represents one of the most prevalent tumours, with 2.3 million new cases diagnosed each year, according to the World Health Organisation [185,186]. Given these considerations, *via* a pharmacophore rational approach, a library of quinoline-based amides was designed and synthesized by a solvent free, *N*,*N*′-carbonyldiimidazole (CDI) mediated amidation [187] (Figure 32). The obtained compounds were tested as human Topo I (hTopo I) inhibitors, using an in vitro relaxation assay, and *N*-(4-fluorobenzyl)quinoline-3-carboxamide was found to be the most promising. Moreover, some derivatives showed a good anticancer activity against two breast cancer cell lines, MCF-7 and MDA-MB-231, as well. These evidences suggest the importance of the quinolin-3-carboxyamides as a promising scaffold for future researches in the anticancer field.

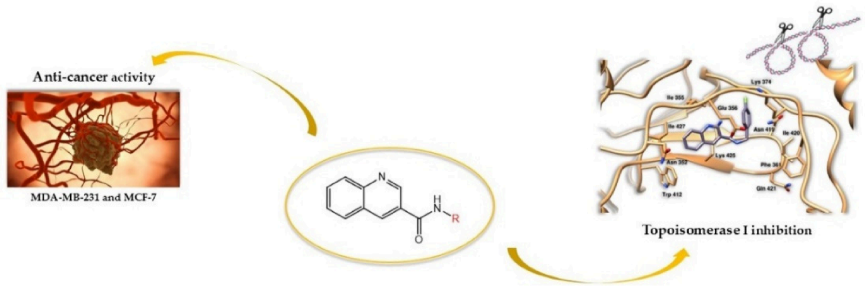


Figure 32. Anticancer effects of quinolin-3-carboxyamides on breast cancer cell lines (MDA-MB-231 and MCF-7) and their inhibitory activity against hTopo I.

6.25. Precision Targeting of the Vimentin-G-Quadruplex Repeats Complex: From Ligand Identification to Optimization

Nicolò Dal Ponte [1], Marta Cozzaglio [1], Martina Rotondo [2], Barbara Biondi [2], Riccardo Rigo [1] and Claudia Sissi [1]

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G-quadruplexes (G4s) are non-canonical nucleic acid secondary structures that can arise at guanine-rich tracts, mainly enriched at telomers and gene promoters. When two or more G4 modules are located nearby, an intramolecular crosstalk can occur leading to the formation of higher-order structures called G4 repeats (G4rps). Few proteins are reported as G4rps binding partners. Recently, we proved that the cytoskeletal protein vimentin interacts selectively with these arrangements over single G4s and other DNA structures [188]. Vimentin is a type III intermediate filament protein, mainly present in the cytoplasm where it is arranged into filaments. In some cancer cells, it can also be found in the nucleus as soluble tetramers. Vimentin filaments are involved in cell architecture, but the protein also plays additional functional roles, i.e., in driving the Epithelial-to-Mesenchymal Transition (EMT), a physio-pathological process that promotes cell invasion thus supporting metastasis in several types of tumors. In these malignant cells, vimentin is generally overexpressed, indicating it as a promising target for preventing cell cancer invasion [189]. Although no structural data of the vimentin-G4rps complex are available yet, this system represents a novel and attractive pharmaceutical target. Herein, we decided to apply a "divide and conquer approach" based on the individual targeting of the protein and G4rp domains involved in this interaction by employing different classes of potential competitors. By Hydrogen Deuterium Exchange Mass Spectrometry and Surface Plasmon Resonance, we identified a portion of the protein N-terminal domain that is actively responsible for G4 repeat binding. A subsequent alanine-scanning approach enabled us to identify the key residues involved in this interaction. Based on this evidence, we have produced different mutated vimentin forms, to obtain a protein with reduced or elicited affinity for G4 repeats. Regarding the DNA counterpart, by screening a library of novel G4 binders we identified a promising G4 ligand that will serve as a scaffold to design new derivatives selective for G4rps vs. G4s. Lastly, we screened several chemical compounds for their ability to bind vimentin at different sites. We are going to cluster them according to their ability to alter the polymerization pattern of the protein, potentially stabilizing one of its structural forms (i.e., filaments vs. tetramers), or to their efficiency in impairing the vimentin-G4rps interaction. At the end of this process, a proper combination of the different strategies is expected to provide new entities worth to be developed to prevent EMT.

7. Poster Presentations

7.1. Xylose-Based Biosurfactants as Emulsifying Agents

Loulou Fatma [1] and Bidjou-Haiour Chahra [1]

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Sugar Fatty Acid Esters (SFAEs) are of great interest in the field of biocompatible components [190]. Because of their amphiphilic nature, non-toxicity and bio-degradability these non-ionic bio-surfactants are used in the pharmaceutical industries [191]. They can be synthesized using biological catalysts under mild reaction conditions by enzymatic synthesis which is considered as a green pathway that ensures a high regio- and chemo-selectivity [192]. In this paper one-pot synthesis of a homologous series of 1-*O*-acylxylose esters derived from fatty acids was performed via enzymatic esterification using *Candida antarctica* lipase B as a biocatalyst. Surface-active properties such as surface tension, critical micellar concentration, area per molecule and packing parameter were determined and the effect of fatty acid chain length on the surface activity was evaluated. Results (Figure 33) indicate that the surface tension values (γ_{CMC}) increase with increasing of the fatty acid chain length from 30 to 47.17 mN/m and a relationship was established between the chain length of the obtained xylose monoesters and their surface-active properties.

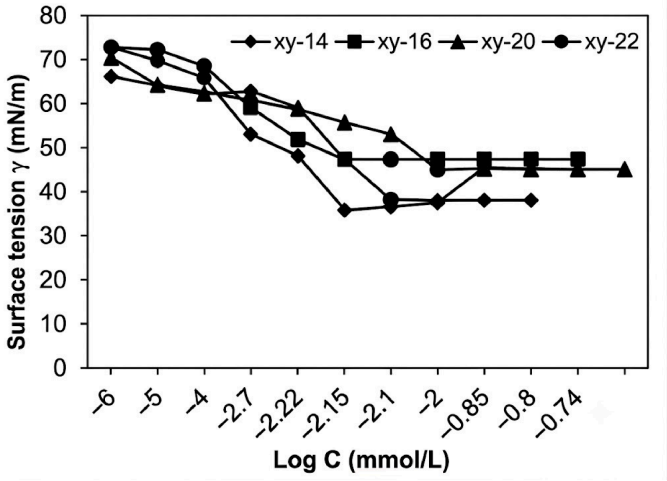


Figure 33. Surface tension measurements for xylose esters in water. (xy14-1-O-tetradecanoyl-α,β-D-xylopyranose. xy16-1-O hexadecanoyl- α,β-D-xylopyranose. xy20-1-O-eicosanoyl- α,β-D-xylopyranose. xy22-1-O-docosanoyl- α,β -D-xylopyranose).

Emulsifying ability is also studied at 25 °C. Synthesized compounds exhibit a good emulsifying power and obtained values are between 83 and 100%. We observed that an increase in the length of the lipophilic chain increases the stability of the monoester emulsion. All results showed that the carbon chain was the most important factor influencing the surface properties [193].

7.2. Rational Design of SIRT2 Inhibitors: Integrating 3D-QSAR, Molecular Docking and Machine Learning Techniques

Aleksandra Ilic [1], Nemanja Djokovic [1], Teodora Djikic [1] and Katarina Nikolic [1]

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SIRT2 influences processes such as apoptosis, DNA repair, and the cell cycle, making it an attractive target for therapeutic intervention in cancer treatment. Although

potent inhibitors have been developed, the main challenge remains the design of highly selective SIRT2 inhibitors, especially due to the structural similarity of the NAD^+ binding site across other members of the sirtuin family. Currently, derivatives of 5-((3-amidobenzyl)oxy)nicotinamides stand out as some of the most selective and effective SIRT2 inhibitors, paving the way for further research toward the development of new therapeutically relevant molecules [194].

In this study, we developed a 3D-Quantitative Structure-Activity Relationship (3D-QSAR) model based on a dataset of 86 nicotinamide-based SIRT2 inhibitors complemented by GRIND-derived pharmacophore models [195]. External validation confirmed the reliability of the 3D-QSAR model in predicting SIRT2 inhibition within the defined range of application [196]. The model interpretation enabled the design of novel SIRT2 inhibitors. Furthermore, based on molecular docking results for the SIRT1–3 isoforms, we developed two classification machine learning models to predict the selectivity of inhibitors for the SIRT1/2 and SIRT2/3 isoforms, which was confirmed by external validation. The integration of 3D-QSAR, selectivity modeling and ADMET predictions facilitated the identification of promising selective SIRT2 inhibitors (Figure 34). These in silico identified inhibitors will be synthesized and tested in vitro to confirm their efficacy and selectivity and pave the way for novel SIRT2-targeted therapies for cancer and neurodegenerative diseases.

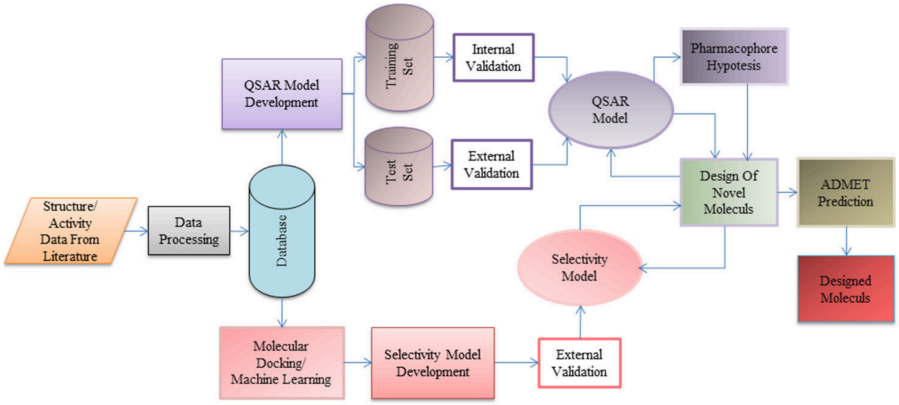


Figure 34. A workflow diagram illustrating the step-by-step procedure of the methodology.

This work was funded by the Ministry of Science, Technological Development and Innovation of the Republic of Serbia and the European Community COST Actions CA22125, CA22103 and CA21135.

7.3. Synthesis and Evaluation of In Vitro Anti-Toxoplasma Gondii Activity of N-(9-Acridinyl) Amino Acid Derivatives

Đorđe Zlatković [1], Vladimir Dobričić [2], Jelena Srbljanović [1], Olivera Lijeskić [1], Neda Bauman [1], Vladimir Ćirković [1] and Tijana Štajner [1]

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Acridine, an aromatic heterocyclic compound, serves as a basis for the synthesis of potent bioactive derivatives, displaying broad spectrum of biological activity, such as antibacterial, antitumor, and antiparasitic [197]. With the ability to undergo various types of electrophilic substitutions, derivatization of the acridine scaffold could lead to compounds

acting towards various and potentially multiple biotargets. *Toxoplasma gondii*, a ubiquitous protozoan parasite with a worldwide distribution, poses a major health threat, particularly in immunocompromised patients and fetuses. Treatment options for toxoplasmosis, other than being limited, also prove to be inadequate, due to their side myelotoxicity and ineffective since they act only on circulating parasites. The aim of this study was to evaluate selected *N*-(9-acrydinil) amino acid derivatives as potential anti-*T. gondii* agents. Synthesis of new derivatives was performed using a two-step method, with the initial mixing of 9-chloroacridine with methanol and sodium alkoxide solution and subsequent adding of appropriate amino acid [197]. Cytotoxicity of the tested compounds was evaluated on Vero cell line, using MTT assay, while their anti-*T. gondii* activity was investigated using *T. gondii* RH strain tachyzoites. Molecular docking analysis was conducted to obtain data on potential binding abilities of the synthesized derivatives regarding the known anti-*T. gondii* drug targets. CC_{50} values of the derivatives ranged from 41.72 to 154.10 μM. Anti-*T. gondii* activity, displayed as a reduction in the number of viable tachyzoites compared to untreated control, ranged from 0 to 33.3%. One of the derivatives displayed activity comparable to standard treatment option, while retaining acceptable cytotoxicity. Molecular docking results showed that PRP4K kinase, enoyl acyl carrier protein reductase, cystathionine gamma-lyase and prolyl-tRNA synthetase could be potential targets of some of the derivatives tested in this study. However, further structural modifications of *N*-(9-acrydinil) amino acid derivatives are needed, to obtain drug candidates competitive to standard treatment options for toxoplasmosis.

This research was funded by the Science Fund of the Republic of Serbia, 7328, Reinvention of the diagnostic algorithm and treatment options for reactivated toxoplasmosis—ToxoReTREAT.

7.4. Identification of Pharmacophores with Inhibitory Activities on the Immune Response In Vitro

Aya Stéphanie Kra [1,2], Hoa-Le Mai [3], Thi-Van-Ha Nguyen [3], Cédric Logé [1], Christelle Ambeu [1,2], Sophie Brouard [3] and Jean-Michel Robert [1]

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3 Nantes Université, Centre de recherche en Transplantation et immunologie, INSERM, UMR 1064, F-44000, France

Regulatory B cells (Bregs) that produce interleukin-10 (IL-10) play a key role in the modulation of the immune response, particularly in the tumor microenvironment, where they may exert immunosuppressive effects or, conversely, participate in the regulation of chronic inflammation that promotes tumor progression [198]. The tetraspanin (TSPAN) CD9, a transmembrane glycoprotein involved in various immunological processes, is emerging as a potential marker for Bregs [199,200] and could represent a promising therapeutic target. Specifically blocking this protein could thus inhibit tumor progression at multiple levels. To date, few studies have focused on targeting this protein. Among the most advanced investigations, some have involved the production of recombinant large extracellular loops (LELs) to act as decoys, while others have explored the potential of antibodies directed against these same LELs, although without achieving clinical applicability [201]. Studies have also been conducted on the potential of small molecules interacting with these LELs to disrupt TSPAN function. These studies demonstrated the possibility of interaction with TSPANs using structural tools than macromolecules and led to the identification of reference compounds.

We therefore developed a series of 30 organic molecules with both lipophilic properties to facilitate anchoring in the membrane and a scaffold capable of interacting with LEL and/or SEL chains (large extracellular loop and/or small extracellular loop, respectively). Human B lymphocyte, isolated by magnetic sorting from leukocyte-platelet-rich blood fractions of healthy donors (Établissement Français du Sang), were cultured for 2 to 3 days in the presence of different combinations of stimulants. Cells were then stained with antibodies and analyzed by flow cytometry. The immunomodulatory effect of these molecules was tested using various in vitro cell culture models. (1) IL-10 production by regulatory B cells, (2) generation of granzyme B expressing Bregs (Breg $GZMB^+$), (3) B cell proliferation via CD40 and TLR9 stimulation. Among the tested molecules, six were identified as having significant immunomodulatory effects. These compounds almost completely inhibited IL-10 production by Bregs, but had no effect on the generation of $GZMB^+$ Bregs, while slightly increasing CD9 expression on these Bregs. Importantly, lymphocyte viability was not affected at the tested concentration (10 μM).

7.5. N-Aryl Imino-1,2,3-Dithiazoles as Inducers of P. Aeruginosa Biofilm Dispersion

Daphnée De Crozals [1], Corentin Layec [1], Chloé Rémondin [1], Nathan Broudic [1], Mathieu Gonzalez [2], Ali Tahrioui [2], Sylvie Chevalier [2], Corinne Fruit [1] and Thierry Besson

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Pseudomonas aeruginosa (*PA*) is an opportunistic pathogen that causes acute and chronic infections in immunodeficient patients. *PA* has the ability to form biofilms, making it extremely difficult to eradicate. Since chronic infections associated with biofilms require extensive treatment, increasing the risk of resistance development, promising anti-infectious strategies are emerging with the aim of developing chemical agents able to promote biofilm dispersion and return bacteria to a planktonic state, restoring their vulnerability to antimicrobials [202]. *N*-Aryl Imino-1,2,3-dithiazoles are developed in our lab. as intermediates in the synthesis of more complex bioactive molecules [203]. They are resulting from the condensation of aromatic amines on 4,5-dichloro-1,2,3-dithiazolium chloride, commonly known as Appel's Salt. In the present study, a chemical library of fifty of these *N*-aryl imino-1,2,3-dithiazoles was tested as potential inducers of *P. aeruginosa* biofilm dispersion (Figure 35).

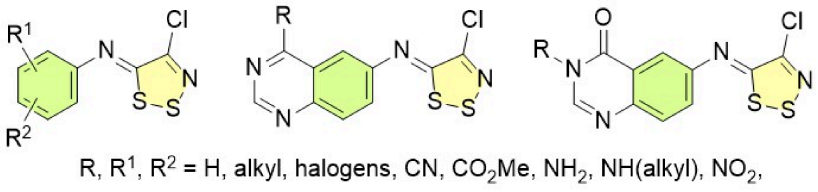


Figure 35. *N*-Aryl imino-1,2,3-dithiazole tested in these studies.

Among the tested molecules, three quinazoline derivatives were able to destabilize by around 50% a mature biofilm formed by *P. aeruginosa* 14 (PA 14). It was also demonstrated that these compounds are not bactericidal, and do not increase neither virulence or cytotoxicity towards eukaryotic cells. Moreover, the most promising derivative induced rigidity of PA14 membrane upon exposure, suggesting that the activity of the ECF sigma factor SigX, which is involved in membrane fluidity homeostasis, may be affected [204]. This poster describes the synthetic routes and details preliminary results of the biological evaluation. It

suggests that imino-1,2,3-dithiazole-derived compounds can be considered as promising dispersing agents of *P. aeruginosa* biofilms.

All authors thank Univ Rouen Normandie, Univ Caen Normandie and Region Normandie for multiform support.

7.6. Development of Linker-Modified DOTA-Peptides as Theranostic Probes Targeting GPC-3 in Hepatocellular Carcinoma

Céleste Souche [1,2], Luc Brunel [2], Yann Dromard [3], Emmanuel Deshayes [1,3], Nicolas Masurier [2] and Cyril Fersing [1,2]

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Hepatoblastoma is a malignant tumor that primarily affects infants and young children, making it the most common malignant liver tumor in this population [205]. This cancer is difficult to distinguish from other malignant liver tumors, as current detection techniques lack specificity and reliability. Furthermore, available treatments are both limited and associated with high toxicity and significant aggressiveness. Therefore, advancements in both detection and treatment are urgently needed. Targeting glypican-3 (GPC3), a membrane receptor overexpressed in hepatoblastoma, has gained increasing interest for the development of diagnostic agents and targeted therapies [206]. In this context, the investigation of radiolabeled peptides targeting GPC3 for applications in nuclear medicine, particularly in targeted radionuclide therapy (TRT), has become a major area of research. Among the currently studied radiopharmaceuticals, the anti-GPC3 radiopeptide [^{68}Ga]Ga-NOTA-TJ12P2 has emerged as a promising candidate for positron emission tomography (PET) imaging of hepatoblastoma [207]. To further explore its potential for both diagnostic and therapeutic applications, we synthesized TJ12P2 analogs, using solid-phase synthesis functionalized with a DOTA chelator. This modification enables radiolabeling with a broader range of radioisotopes compared to NOTA, thereby expanding its versatility in nuclear medicine. Additionally, several derivatives incorporating a linker (either alkyl or linear polyether) between the chelator and the peptide were also designed, radiolabeled with ^{68}Ga, and evaluated for their physicochemical properties (Figure 36). A total of six DOTA-peptides were synthesized and characterized. ^{68}Ga radiolabeling conditions were optimized to achieve a radiochemical purity > 97% with excellent radiochemical yield (>86%). Physicochemical characterization of the six ^{68}Ga-labeled peptides revealed that the linker influenced the logP values and plasma protein binding. Based on these results, 3 candidates were selected for preliminary in vivo evaluations (imaging and biodistribution), and ^{177}Lu radiolabeling studies.

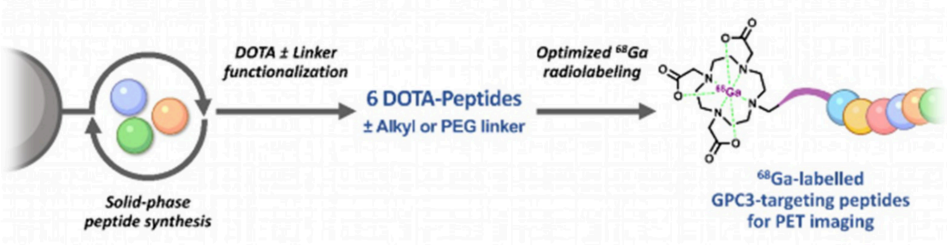


Figure 36. General strategy for synthesis and ^{68}Ga radiolabeling of GPC3-targeting DOTA-peptides.

7.7. Development of a Novel Class of Azaheterocyclic Ligands to Promote Diversity in Bioinorganic Chemistry

Lucas De Biasi [1], Jacques Lebreton [1], Didier Dubreuil [1], Virginie Blot [1] and Arnaud Tessier [1]

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Coordination complexes are playing an increasing role in medicinal chemistry, particularly in the development of anticancer and diagnostic agents. Their modularity and ability to interact with biologic target of interest make them promising therapeutic tools.

However, their development is hindered by the limited diversity of ligands, which are often restricted to well-established scaffolds such as terpyridine (tpy) and bipyridine (bpy). Any structural modification aiming at optimization of their pharmacological properties requires major chemical synthesis works to modify the ligand's core from the outset and to provide organometallic derivatives, allowing better functionalization and enhanced physico-chemico-pharmacological properties.

Exploring new ligands and more adaptable synthetic strategies is therefore crucial to expand the biomedical applications of such coordination complexes. Our approach is based on the substitution of one pyridine moiety and also on the functionalization of heteroaromatic compounds. The validation of this novel class of ligand have been achieved through complexation with a variety of metals (Figure 37A). According to previous works [208,209], further functionalization of these new ligands could proceed via a post-functionalization strategy, thus promoting vectorization, bioconjugation or the installation of a probe (Figure 37B).

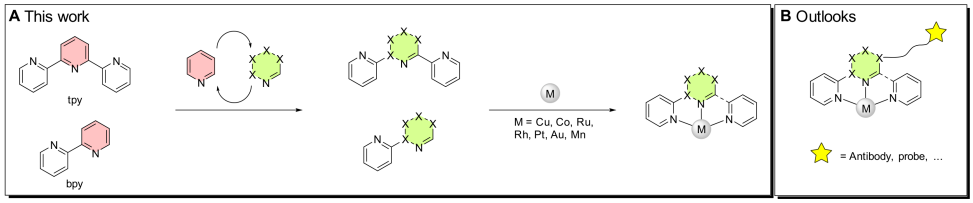


Figure 37. (**A**) Substitution of pyridine ring in terpyridine and bipyridine by an original azaheterocycle; (**B**) Possible post-functionalization of our new scaffold.

7.8. Novel 1,2,3,4-Tetrahydrobenzo[h][1,6]naphthyridine-Based Hybrids as Dual Inhibitors of β-Amyloid and Tau Aggregation with Anticholinesterase Activity

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The structural requirements imposed by the 20 Å-deep catalytic gorge of acetylcholinesterase (AChE) when designing multisite inhibitors that bind at both the catalytic and peripheral aromatic sites of the enzyme have a templating effect that leads to compounds that also fit well in other proteins with pathogenic roles. In this context, we have consistently found that linked hybrids bearing aromatic moieties at both ends of their structures can inhibit protein aggregation [210]. This is the case of the multisite AChE inhibitor DP-128, a 1,2,3,4-tetrahydrobenzo[*h*][1,6]naphthyridine–6-chlorotacrine hybrid that inhibits the aggregation of 13 different amyloidogenic proteins [211]. Here, we present a lead optimization campaign around DP-128 (Figure 38), mainly aimed at improving DMPK properties while retaining the potencies on AChE and Aβ42 and tau aggregation.

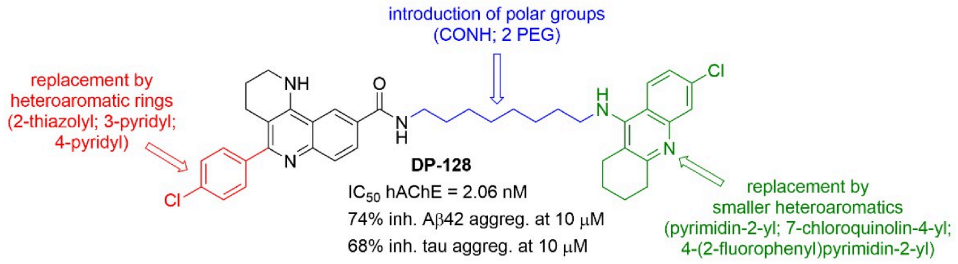


Figure 38. Design strategy of the novel DP-128 analogues.

Funded by grant PID2023-147004OB-I00 from MICIU/AEI/10.13039/501100011033 and FEDER, EU.

7.9. Synthesis and Bioactivity of New Enantiopure Ag(I)- and Au(I)-NHC Complexes

Domenico Iacopetta [1], Jessica Ceramella [1], Assunta D'Amato [2], Annaluisa Mariconda [3], Maria Marra [1], Camillo Rosano [4], Pasquale Longo [2] and Maria Stefania Sinicropi [1]

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Transition metal complexes represent an important field of research for drug development. Particularly, the complexes stabilized by *N*-heterocyclic carbene (NHC) ligands attracted the interest of many researchers because of their various applications [212]. NHC complexes were demonstrated to modulate important biological targets involved in different cellular pathways, whose deregulation is involved in the onset of different diseases [213]. Several studies reported the synthesis of complexes possessing an NHC ligand bearing at least a stereogenic center that were assayed as racemates. Herein, some silver(I)- and gold(I)-NHC complexes, bearing one (**L1**) or two (**L2**) stereogenic centers at the NHC ligand, were synthetized as pure enantiomers (Figure 39) and studied for their anticancer, anti-inflammatory and antioxidant properties. The ability in regulating the activity of the human topoisomerase I and murine inducible nitric oxide synthase (iNOS) was investigated by in silico and in vitro assays. The obtained results highlight a different behavior of the enantiopure NHC-complexes toward the selected targets, disclosing interesting features that depended on the considered enantiomer and pointing out the attention on the importance of chirality in the design and development of therapeutic drugs.

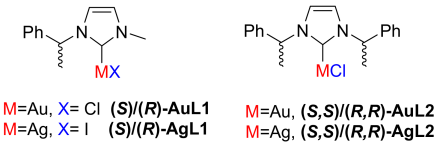


Figure 39. Enantiopure NHC-silver complexes **(*S*)-AgL1/(*R*)-AgL1** and **(*S*,*S*)-AgL2/(*R*,*R*)-AgL2** and enantiopure NHC-gold complexes **(*S*)-AuL1/(*R*)-AuL1** and **(*S*,*S*)-AuL2/(*R*,*R*)-AuL2**.

This work was supported by PRIN PNRR P20222BLAZ, Enhanced pharmacological activity of noble metal carbene-N-heterocyclic complexes by oligopeptide counterion (CUP MASTER: C53D23004490001; CUP: H53D23007840001).

7.10. Exploring the Antileishmanial and Anti-Trypanosoma Cruzi Activities of Thiazole-Hybrids Derivatives

Igor J.S. Nascimento [1], Paulo F.S.S. Júnior [1], João X.A. Júnior [1], Edeildo F.S. Júnior [1], Francisco J.B.M. Júnior [2], Teresinha G. Silva [3], Klinger A.F. Rodrigues [4], Isabelle Ourliac-Garnier [5], Pascal Marchand [5] and Thiago M. Aquino [1]

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Neglected tropical diseases (NTDs), including Chagas disease and leishmaniasis, remain major public health challenges, particularly in low- and middle-income countries. In this study, we designed, synthesized, and evaluated a series of thiazolidinone-based hybrid derivatives bearing thiophene, phenyl, or pyridine moieties, aiming to improve trypanocidal and leishmanicidal activity [214,215]. The compounds were screened in a sequential in vitro workflow involving promastigote/trypomastigote inhibition, IC_{50} determination, and cytotoxicity assays. A series of phenyl- and pyridine-containing derivatives exhibited outstanding activity against both *T. cruzi* and *L. amazonensis*, surpassing reference drugs in potency and selectivity (Figure 40). Against *T. cruzi*, compounds **29c**, **33b**, and **36b** displayed IC_{50} values of 2.58, 3.86, and 1.37 µM, respectively, with SI values exceeding 27. For *L. amazonensis*, compounds **36b** (IC_{50} = 1.37 µM, SI = 58.11), **40b** (IC_{50} = 1.85 µM, SI = 34.49), and **32d** (IC_{50} = 2.09 µM, SI = 45.53) demonstrated excellent potency and superior safety profiles when compared to amphotericin B and meglumine antimoniate. SAR analyses revealed that isosteric replacement of the thiophene core by phenyl or pyridine, along with the presence of allyl or benzyl moieties, significantly enhanced biological activity. In conclusion, this work identified several promising thiazolidinone-based lead compounds with dual antiparasitic activity, reinforcing the potential of these derivatives for the treatment of Chagas disease and leishmaniasis.

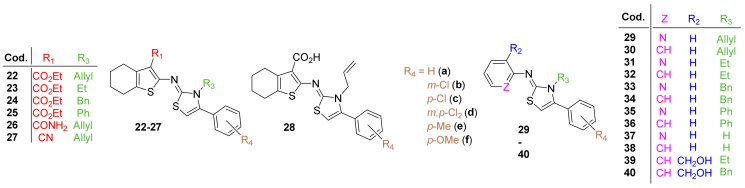


Figure 40. Structures of synthesized thiazolidinone-based hybrid derivatives.

The authors thank CAPES, CNPq and COFECUB.

7.11. Divergent by Design: Rapid Access Towards Chemically Diverse C-Nucleoside Analogues as Potent Anti-Trypanosomatid Agents

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C-nucleosides are an enticing class of nucleoside analogues that carry a C-C glycosidic bond. In comparison with the conventional nucleoside analogues, the metabolic stability of C-nucleoside derivates are unrivaled as glycosidic cleavage by purine salvage hydrolases and phosphorylases is precluded. The absence of nitrogen in the glycosidic bond allows for a vast chemical space of purine-like scaffolds with a high variability of nitrogen/carbon ratios and positioning, creating new pharmacophores. The potent in vivo activity of 9-deazainosine and formycin B against *Trypanosoma* and *Leishmania* highlights the potential of C-nucleoside analogues as anti-trypanosomatid agents [216]. Despite their potential, the synthesis of C-nucleosides remains challenging. In our efforts to synthesize a sizeable chemically diverse C-nucleoside library, we have designed an optimized divergent route that allows for late-stage diversification at the very last synthesis step (Figure 41). This strategy was proven robust as different purine scaffolds were well tolerated and diversification was carried out using various nucleophiles. These endeavours have led to the discovery of several potent and selective hits in an in vitro phenotypic screening. One compound has advanced to an in vivo stage and provided a 92% reduction in *T. cruzi* parasitemia without any signs of morbidity or mortality.

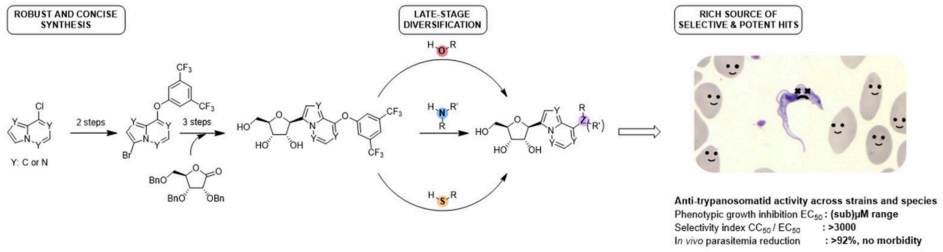


Figure 41. Synthesis scheme and phenotypic screening overview.

7.12. Isoquinolinequinone N-Oxides with Diverging Mechanisms of Action Against Multidrug Resistant Cancer Cells

Mélanie A.G. Barbosa [1,2], Ryan D. Kruschel [3], Maria João Almeida [1,2], Rúben F. Pereira [1], Cristina P.R. Xavier [1,2], Florence O. McCarthy [3] and M. Helena Vasconcelos [1,2]

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Overcoming multidrug resistance (MDR) has become a primary challenge in cancer research. The development of collateral sensitizers, i.e., compounds capable of exploiting the enhanced defense mechanisms of MDR cells as weaknesses, has been proposed as a strategy to overcome MDR. Our previous work reported novel Isoquinolinequinone

(IQQ) *N*-oxide compounds capable of inducing collateral sensitivity in MDR P-glycoprotein overexpressing non-small cell lung cancer (NSCLC) and colorectal cancer cell lines [217]. Herein, we investigate the mechanisms underlying the antitumor and collateral sensitivity activity of two compounds RK2 and RK3 (Figure 42). Our results show that both compounds successfully reduced the viability of MDR cells, grown as 2D cell cultures or as spheroids, while not decreasing the growth of a human non-tumorigenic cell line, and inhibited drug efflux in MDR NCI-H460/R cells. Compound RK2 caused increased ROS production, disruption of the GSH balance, and altered expression of proteins associated with protection against oxidative stress, particularly in the NCI-H460/R cells. While the collateral sensitivity effect of compound RK3 in NCI-H460/R could not be justified by a disruption of the redox balance, further investigation is warranted to assess the impact of an increased expression in IDH1 following treatment with this compound. Taken together, our data highlights RK2 and RK3 as promising candidates to advance to the next stages of drug development [218].

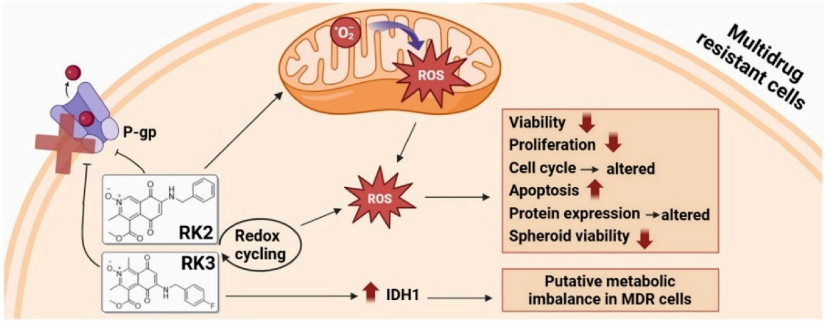


Figure 42. Influence of RK2 and RK3 on multidrug resistant cancer cells.

7.13. Discovery of Sphingosine Kinase Inhibition by Modified Quinoline-5,8-Diones

Ryan D. Kruschel [1], Kyle Malone [2], Alison N. Walsh [1], Christian Waeber [2,3] and Florence O. McCarthy [1]

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Sphingosine kinase (SphK) overexpression is observed in many cancers, including breast, renal and leukaemia, which leads to increased cellular proliferation, survival and growth. SphK inhibition has been an attractive target for anticancer drug development for the past decade, with SphK inhibitors such as PF-543 and opaganib exhibiting clinical antitumour effects [219]. By exploiting both CB5468139 and PF-543 as structural leads, we report on the first quinoline-5,8-dione-based SphK inhibitor using a fragment-based approach (Figure 43). The quinoline-5,8-dione framework was developed to incorporate two defined regions, namely a polar quinoline core, which links to an aryl lipophilic chain. All synthetic molecules were assayed against SphK 1 and 2, molecular docking studies were performed and a subset of compounds was screened for anticancer activity. As the binding site of SphK accommodates the lipophilic tail of sphingosine, we initially set out to explore the substitution of the C(7) aryl moiety to attain eight novel C(7) ether-linked quinoline-5,8-diones, which were screened for SphK1 and SphK2 activity with good potency identified. To improve SphK binding, structural fragments were adapted from PF-543 to participate in hydrogen bonding within the binding site of SphK1. A model study was performed to yield novel compounds through activated C(2) formyl intermediates. Two pyrrolidine-based

quinoline-5,8-diones were assayed for SphK activity, with **21** revealing an improvement of SphK1 binding efficacy relative to the parent compound and **20** (and its precursor **4**). Molecular modelling on the pyrrolidine quinoline-5,8-dione construct revealed favourable docking, low binding energies and opportunities for further improvement. Although the screening of anticancer activity was inconclusive, low micromolar dual SphK1/2 inhibition with the quinoline-5,8-dione framework has been identified for the first time, and a plausible new binding mode has been identified [220].

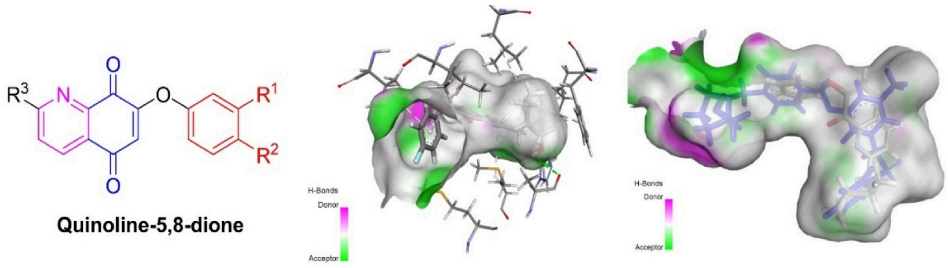


Figure 43. The quinoline-5,8-dione framework and the discovery of novel SphK inhibitors.

7.14. Computational Study on Bioactive Compounds from Agricultural By-Products of Olea Europaea L. and Punica Granatum

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The increasing interest in food supplements and medical devices based on botanicals has driven research towards sustainable sources of bioactive compounds. One promising approach involves the valorization of agricultural by-products as sources of botanical extracts, enhancing the sustainability of production processes. The phytocomplexes derived from these by-products exhibit potential in preventing prevalent diseases, including chronic degenerative and metabolic disorders [221]. The presented project aims to explore the potential of agricultural by-products, specifically pomegranate peel and olive pomace, to produce high-value extracts. By studying their impact on key biological pathways—such as Nrf2/ARE, NFkB, and PKM2—this research aims to provide a deeper understanding of their bioactive properties and their role in promoting human health.

The chemical characterization of pomegranate peel and olive pomace extracts revealed a diverse array of phenolic compounds, including flavonoids, secoiridoids, and ellagitannins known for their antioxidant, anti-inflammatory, and metabolism-modulating properties. Within the framework of the study (Figure 44), molecular modeling simulations were conducted to investigate the potential molecular recognition between the main phenols of each phytocomplex and key protein targets involved in oxidative stress and inflammatory pathways: Keap1, IKKβ, and PKM2. Docking simulations highlighted that several compounds exhibit favorable theoretical binding affinities to these targets, suggesting possible synergistic effects. Based on the molecular modeling results, a subset of molecules was proposed for further testing as pure standards, in addition to the crude extracts. Notably, two of them showed strong binding affinities across all investigated targets, particularly with Keap1 and PKM2. These compounds will be prioritized for

future in vitro or in vivo studies to assess their bioactivity and potential functional food ingredients or nutraceutical agents.

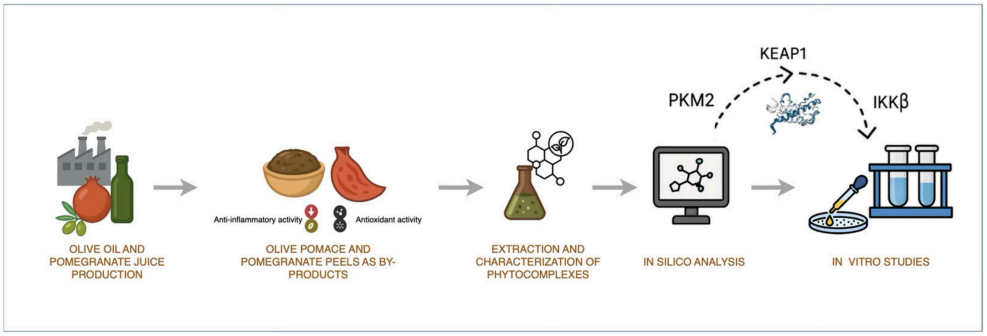


Figure 44. Schematic illustration of the project workflow.

7.15. Improvement of the Antileishmanial Activity of 2-Aminothiophene Derivatives Through Sulfur-Selenium Isosteric Replacement

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Leishmaniasis is a tropical disease caused by protozoa of the genus Leishmania, affecting approximately 12 million people worldwide [222]. The therapeutic options are outdated, limited, and obsolete, with drugs that have high toxicity and low therapeutic efficacy. For this reason, the development of new drugs is urgent. In this context, previous studies from our laboratory have shown that 2-aminothiophene derivatives (2-AT) are potential drug candidates for leishmaniasis [223]. In this work, based on the structure of 2-AT prototypes and the principle of bioisosterism, we decided to synthesize new 2-aminoselenophenes (2-AS) as novel drug candidates against leishmaniasis. Nine 2-AS compounds were synthesized in good yields through a modified Gewald reaction. All compounds were structurally characterized and evaluated in vitro for their anti-promastigote activities against Leishmania amazonensis and L. major, as well as for cytotoxicity against macrophages. Six 2-AS compounds were able to inhibit the development of both Leishmania species, with IC_{50} values lower than 10 μM. Among them, three compounds—6CNSE2 (4-NO_2-indole), 6CNSe04 (7-CH_3-indole), and 6CNSE11 (5-OCH_3-indole)—stood out, presenting IC_{50} values of 2.14 and 1.71, 2.92 and 5.79, and 2.15 and 2.50, respectively, against L. amazonensis and L. major. Against RAW 264.7 macrophages, these compounds exhibited CC_{50} values of 189.37, 185.89, and 178.46, yielding Selectivity Index (SI) values between 32 and 110, indicating a high safety index. A comparison of the antileishmanial activity and safety profile of these derivatives with the 2-AT prototypes showed that the bioisosteric S–Se modification was favorable for antileishmanial activity and also improved the safety profile. This demonstrates once again the applicability of bioisosterism in the hit-to-lead optimization. The next steps will involve evaluation against amastigote forms, in vivo, and target deconvolution studies, aiming to expand the assessment of biological potential and facilitate the identification/validation of potential targets.

Acknowledgments: FAPESQ-PB/PRONEX, grant number #030/2023; CNPq grant number #316996/2023-8.

7.16. Synthesis and Antiparasitic Evaluation of Tetracyclic Lactones Derivatives of Thieno[2,3-b]quinoline-2-carboxylic Acid

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Thieno[2,3-*b*]quinolines have attracted significant attention in medicinal chemistry due to their diverse biological activities [224]. Herein, we report the synthesis of tetracyclic lactones derivatives of thieno[2,3-*b*]quinoline disubstituted in the pyranone ring. The process involves a Rh(III)-catalyzed formal [4+2] cycloaddition between thieno[2,3-*b*]quinoline-2-carboxylic acid and symmetrical or unsymmetrical internal alkynes, triggered by C-H activation. The carboxylic group acts as a dynamic directing group as it participates in the subsequent reaction (Figure 45). The conditions used were selected based on our previous application of the same method to the thieno[2,3-*b*]pyridine system where the nitrogen and the sulfur occupy the same relative positions [225].

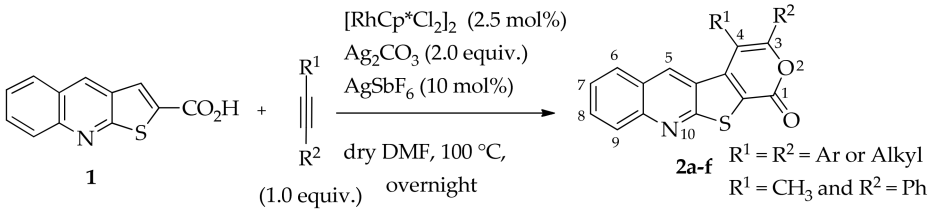


Figure 45. Synthesis of tetracyclic lactones.

The antiparasitic activity the compounds prepared was evaluated against *Trypanosoma brucei* and *Leishmania infantum (L. infantum)* promastigotes. The most promising compound was the derivative of the 5-decyne, presenting IC_{50} = 19 µM against *L. infantum*. The toxicity of the compounds was evaluated using THP-derived macrophages.

Thanks are due to FCT-Portugal for financial support to CQ-UM and COST Action 21111 OneHealthDrugs.

7.17. Application of Bacterial Autodisplay for the Evaluation of Ligand Binding to the HCN2 CNBD Using Flow Cytometry

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Hyperpolarization-activated and cyclic nucleotide-gated (HCN) ion channels are a family of voltage-gated pore loop channels permeable to a mixed sodium (Na^+) and potassium (K^+) current called $I_{f\ (funny)}$ or $I_{h\ (hyperpolarization\text{-}activated)}$. Often referred to as pacemaker channels, HCN channels are strongly involved in the rhythmic activity in heart and brain. Dysfunctional HCN channels on the other hand are associated with a number of channelopathies such as epilepsy or cardiac arrhythmia. Currently, only one HCN-selective channel blocker (Ivabradine) has been approved for treatment of angina pectoris and stable chronic heart failure [226], leaving much room for further development.

Structurally, an HCN channel consists of four pore-forming subunits where both homo- and heterotetrameric channels exist. Four isoforms of the HCN monomer have been identified (HCN1-4), each with distinct tissue distribution, activation kinetics and

sensitivity to cyclic nucleotides such as cyclic adenosine monophosphate (cAMP). Binding of cAMP to the cyclic nucleotide binding domain (CNBD) hereby typically leads to a shift of the activation voltage to more depolarized potentials and faster activation kinetics of the channel [227]. Considering the different affinities and responses of the HCN isoforms to cAMP, the modulation of cyclic nucleotide binding to the CNBD provides a promising approach for both disease research and drug development. Here, an application of the bacterial secretion system type V (autodisplay) is presented, which allows the determination of binding affinities and screening for novel ligands without the requirement for protein purification. Binding of a fluorescent cAMP derivative (8-Fluo-cAMP) to the autodisplayed HCN2 C-Linker-CNBD is measured by flow cytometry. Displacement of the fluorescent ligand with increasing concentrations of a competitor leads to a concentration dependent decrease in fluorescence intensity. This enables the calculation of IC_{50} and K_i values of the competitor [228]. Additionally, point mutations can be introduced into the autodisplayed protein to further characterize the interaction between protein and ligand [229].

7.18. Synthesis, Structure Elucidation, Antimicrobial and Antiparasitic Activities of New Piperidinhydrazide-Hydrazone Derivatives

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Benzyl-*N*′-benzylidenepiperidine-4-carbohydrazide derivatives are compounds with important bioactivities in medicinal chemistry. These activities include antimicrobial and antiparasitic activities [230,231], as well as acetylcholinesterase and butyrylcholinesterase enzyme inhibitory activities against Alzheimer's disease [232].

In the view of this reported literature information, new benzylidene piperidine-4-carbohydrazide derivatives were designed (Figure 46). Starting from the ethyl piperidine-4-carboxylate structure, piperidine-4-carbohydrazide-hydrazone structures with substituted benzyl and substituted aldehyde derivatives were synthesised in four steps. Spectroscopic methods were used to confirm the expected chemical structures and their purity. The antimicrobial activities of the compounds were determined using the broth microdilution method on *Mycobacterium smegmatis* ATCC 14468 strain with levofloxacin as a positive control [233]. The antiparasitic activity was tested on promastigotes of *Leishmania tropica* promastigote strain [234].

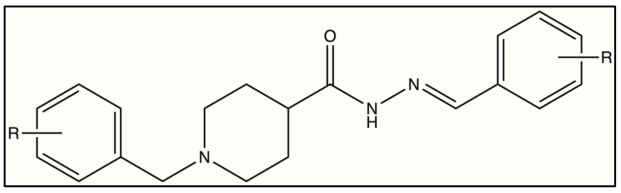


Figure 46. General structure of synthesised compounds.

The MIC values of the compounds ranged from 250 μM to 100 μM. Based on these results, we are continuing to work on more active and selective antimycobacterial/antiparasitic compounds. In silico studies are also underway to elucidate the mechanism of action of the compounds.

7.19. Design, Synthesis, and Biological Evaluation of Bridged Melanostatin Derivatives

Ivo E. Sampaio-Dias [1], Hugo F. Costa-Almeida [1], Xavier C. Correia [1], Beatriz L. Pires-Lima [1], Sara C. Silva-Reis [1], Ana Reis-Mendes [2], Vera M. Costa [2,3], Xerardo García-Mera [4] and José E. Rodríguez-Borges [1]

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Melanostatin is a short endogenous neuropeptide that acts as a positive allosteric modulator (PAM) with high selectivity towards the dopamine D_2 receptors (D_2R), exhibiting high clinical potential for the treatment of dopamine-related disorders of the central nervous system, including depression, drug abuse, obesity, tardive dyskinesia, restless leg syndrome, and Parkinson's disease (PD) [62,235]. Preliminary studies have shown that the replacement of the L-proline residue of MIF-1 with L-pipecolic acid provides bioactive derivatives [1].

In this work, we further explore the role of the L-proline residue in the PAM activity of Melanostatin neuropeptide by fusing the structures of L-proline and L-pipecolic acid into a bridged chimera scaffold, namely (1*R*,3*S*,4*S*)-2-azanorbornane-3-carboxylic acid. To this end, a series of 16 bridged Melanostatin derivatives were synthesized and pharmacologically evaluated by functional assays at the D_2R. In these assays, four compounds were found to promote a 6.6-fold improvement of dopamine potency in the subnanomolar range (0.01 nM), denoting potent PAM activity. Moreover, toxicological studies in human dopaminergic SH-SY5Y neuronal cells demonstrate that these compounds display safe neurotoxicological profiles up to 200 μM and enhanced pharmacokinetic properties in comparison with the parent neuropeptide.

These findings open a new avenue for the discovery of highly potent and selective PAM of the D_2R with clinical potential for application in dopamine-related disorders.

Funding: This work received financial support from PT national funds (FCT/MCTES, Fundação para a Ciência e a Tecnologia and Ministério da Ciência, Tecnologia e Ensino Superior) through project 2023.14440.PEX (DOI: 10.54499/2023.14440.PEX). **Acknowledgments:** FCT is also acknowledged for supporting projects 2022.01175.PTDC, UIDB/50006/2020, and UIDP/50006/2020. I.E.S.-D. thanks FCT for funding through the Individual Call to Scientific Employment Stimulus with reference 2020.02311.CEECIND/CP1596/CT0004 (DOI: 10.54499/2020.02311.CEECIND/CP1596/CT0004). V.M.C. thanks the financial support and her grant funded by national funds from FCT, in the scope of the projects UIDP/04378/2020 and UIDB/04378/2020 (UCIBIO), and the project LA/P/0140/2020 (i4HB). H.F.C.-A., X.C.C., B.L.P.-L., and S.C.S.-R. thank FCT for the Ph.D. grants UI/BD/154888/2023, 2024.02245.BD, 2022.14060.BD, and SFRH/BD/147463/2019, respectively. X.G.-M. thanks Xunta de Galicia for financial funding with reference GPC2020/GI1597.

7.20. Synthesis of New 1,3-bis[(4-(Substituted-Aminomethyl)Phenyl)methyl]benzene and 1,3-bis[(4-(Substituted-Aminomethyl)Phenoxy)methyl]benzene Derivatives, Designed as Novel Antimalarial Ligands

Sandra Albenque-Rubio [1], Jean Guillon [1], Patrice Agnamey [2], Céline Damiani [2], Solène Savrimoutou [1], Luisa Ronga [3], Romain Mustière [2], Tshering Zangmo [3], Noël Pinaud [4],

Stéphane Moreau [1], Jean-Louis Mergny [5], Mathieu Marchivie [6], Serge Moukha [7], Pascale Dozolme [7], Pascal Sonnet [2] and Anita Cohen [8]

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3 Université de Pau et des Pays de l'Adour, E2S UPPA, CNRS, IPREM, Pau, France
4 ISM, CNRS, Bordeaux INP, UMR 5255, University of Bordeaux, Talence, France
5 LOB, Institut Polytechnique de Paris, Ecole Polytechnique, CNRS, INSERM, Palaiseau, France
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8 Aix Marseille University, INSERM, SSA, MCT, Marseille, France

By taking into account our previously described series of new 1,3,5-*tris*[(4-(substituted-aminomethyl)phenyl)methyl]benzene compounds [236] and 1,3,5-*tris*[(4-(substituted-aminomethyl)phenoxy)methyl]benzene derivatives [237], a series of new 1,3-*bis*[(4-(substituted-aminomethyl)phenyl)methyl]benzene and 1,3-*bis*[(4-(substituted-aminomethyl)phenoxy)methyl]benzene derivatives was designed, synthesized, and evaluated in vitro against *Plasmodium falciparum* (chloroquine-sensitive 3D7 and chloroquine-resistant W2 strains) (Figure 47).

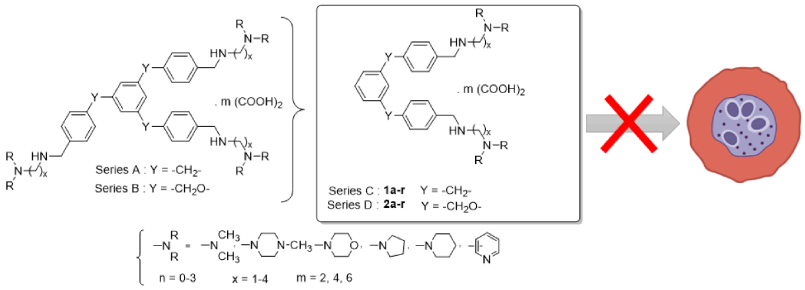


Figure 47. General structure of target compounds.

Biological results showed antiprotozoal activity with IC_{50} values in the μM range. In addition, the in vitro cytotoxicity of these novel original molecules was assessed with human HepG2 cells. It has been previously described that the telomeres of the various parasites could constitute interesting and potential targets; thus we have also investigated the possibility of targeting *Plasmodium* telomeres by stabilizing the *Plasmodium* G-quadruplex sequences using FRET melting assays with these novel synthesized derivatives.

7.21. Derivatization of Carboxyl Group of Commercial NSAIDs as a Strategy for Enhancing COX-2 Activity

Maja Miličević [1], Milkica Crevar [2], Vladimir Dobričić [2], Jelena Bošković [2] and Jelena Savić [2]

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Non-steroidal anti-inflammatory drugs (NSAIDs) are well-known therapeutic agents primarily used to relieve pain and inflammation. However, some epidemiological studies have highlighted their potential benefits in cancer treatment and prevention [238]. These findings have driven research into the interplay between inflammation and cancer and have led to the development of new selective cyclooxygenase COX-2 inhibitors with additional antineoplastic properties. Based on our previous research, we decided to derivatize the carboxyl group of several commercial NSAIDs into an amide to investigate their effect

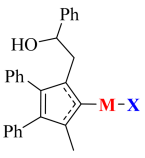
on COX-2 activity and antineoplastic activity. We converted eight commercial NSAIDs with carboxyl group (flufenamic acid, mefenamic acid, ketoprofen, flurbiprofen, diclofenac, ibuprofen, indomethacin, and naproxen) into amides using 3-amino-5-methylpyarazole. The products were obtained in high yields in a coupling reaction with EDCI and HOBt. All compounds were tested using the COX-2 kit (catalogue number: ab283401, Abcam, United Kingdom) at a concentration of 100 µmol. The lowest percentage of inhibition was observed for naproxen and ibuprofen amide (40.6 and 46.5%). All other compounds showed an inhibition of about 70%. The amide of mefenamic acid showed the highest percentage inhibition of the COX-2 isoform (74.7%). The results showed that obtained amides showed good inhibitory potential towards COX-2 isoform, with the exception of amides of ibuprofen and naproxen. The strategy of derivatization of carboxyl group of nonselective NSAIDs that have at least two nonfused aromatic rings in the structure into an amide by adding the aromatic pyrazole ring could enhance their selectivity towards COX-2. The prediction of activity against different cell lines in the software PASS 2.1 (Prediction of Activity Spectra for Substances) showed a high probability for the colon carcinoma cell line (HCT-116) indicating that these compounds should be tested on this cell line to investigate their antineoplastic potential.

7.22. New Ag(I)- and Au(I)-NHC α-Amino Acid Complexes as Anti-Breast Cancer Agents

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In the last decade, the research on *N*-heterocyclic carbenes (NHCs) complexes with transition metals has attracted scientists' interest for their applications in organometallic catalysis and for their versatile functionalization in medicinal chemistry [239]. Additionally, amino acids represent excellent ligands for transition metals, including silver and gold, although their use in this area remains quite unexplored [240]. Herein, we investigated a new series of Ag(I)- and Au(I)-NHC complexes, bearing halogen, acetate or carboxylate salts of *tert*-butyloxycarbonyl(Boc)-*N*-protected glycine (Gly), phenylalanine (Phe) or proline (Pro) as anionic ligands (Figure 48). All the complexes were studied for the anticancer activity against two breast cancer cells (MCF-7 and MDA-MB-231) and the identification of the target(s) and the mechanism(s) of action are ongoing. Moreover, their anti-inflammatory and antioxidant potential are being evaluated.



1 M= Ag X= I
2 M= Ag X= OAc
3 M= Ag X= GlyBoc
4 M= Ag X= PheBoc
5 M= Ag X= ProBoc
6 M= Au X= Cl
7 M= Au X= OAc
8 M= Au X= GlyBoc
9 M= Au X= PheBoc
10 M= Au X= ProBoc

Figure 48. Structures of the studied Ag(I)- and Au(I)-NHC metal complexes.

This work was supported by PRIN PNRR P20222BLAZ, Enhanced pharmacological activity of noble metal carbene-N-heterocyclic complexes by oligopeptide counterion (CUP MASTER: C53D23004490001; CUP: H53D23007840001).

7.23. Pyrrolidine-Based Nucleosides as Potential Mimics of the Riboxacarbenium Transition State

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Neglected tropical diseases (NTDs) encompass various infections caused by microorganisms like bacteria (e.g., Buruli ulcer), fungi (e.g., chromoblastomycosis), viruses (e.g., rabies), and protozoa (e.g., Human African trypanosomiasis, Chagas disease, leishmaniasis). These diseases are labelled "neglected" because they historically received minimal attention from pharmaceutical companies, despite their significant impact on public health and economic development. Around 200,000 people die from NTDs annually, and over 1.7 billion require treatment each year. Existing therapies suffer from limited efficacy, resistance development, side effects leading to treatment discontinuation and non-oral administration etc. [241]. In contrast to mammals, virtually all parasitic protozoa are purine auxotroph, meaning that they rely on the acquisition and processing of pre-formed purines from their host(s) [242]. As part of their purine salvage, a number of crucial enzymes are able to lyse (NH, PNP and MTAP) or construct (PRT) the glycosidic bond between sugar and the purine. Importantly, all these enzymes catalyse conversion via a riboxacarbenium transition state, as shown in Figure 49. Immucillins have been specifically designed to mimic this transition state, featuring a ribosyl moiety bearing an aminocation and a 9-deazapurine base [243]. Their therapeutic relevance is evidenced by the development of Galidesivir (R = OH, Y = NH_2), approved for Hepatitis C and other viral infections, and Forodesine (R = OH, Y = OH), used in the treatment of acute leukemia [244]. Inspired by these findings, we aimed to replicate the transition state using pyrrolidine-based nucleoside analogues. This poster will present their design rationale, synthesis, and preliminary biological evaluation.

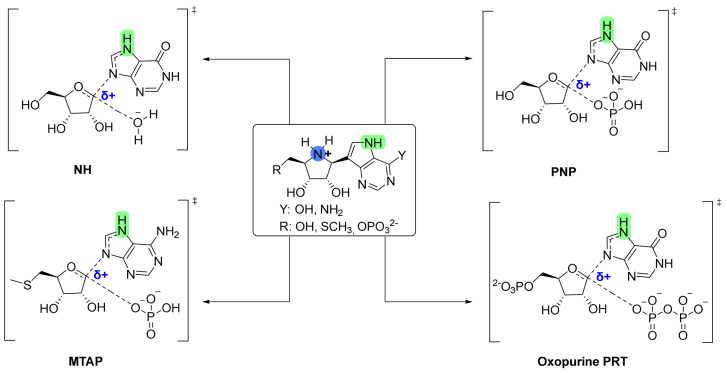


Figure 49. Transition state of the purine salvage enzymes. NH: Nucleosides hydrolase, PNP: Purine nucleoside phosphorylase, MTAP: Methyl thio-adenosine phosphorylase, PRT: Phosphoribosyl transferase.

7.24. Exemplification of Donecopride Family: Synthesis and Biological Evaluation of Novel MTDL with Potential Interest in the Treatment of Alzheimer's Disease

Cédric Lecoutey [1], Julien Lalut [1], Audrey Davis [1], Florence Gaven [3], Stacy Largillière [2], Gérald Née [2], Sophie Corvaisier [1], Jana Sopkova de Oliveira Santos [1], Marc Since [1,4], Thomas Freret [2],

Romain Legrand [5], Noëlle Callizot [6], Sylvie Claeysen [3], Michel Boulouard [2], Patrick Dallemagne [1] and Christophe Rochais [1]

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2 Université Caen Normandie, Normandie Univ, Mobilités: Vieillissement, Pathologie, Santé (COMETE), INSERM UMR-S 1075, F-14000 Caen, France
3 IGF, Univ. Montpellier, CNRS, INSERM, F-34094, Montpellier, France
4 PRISMM Platform, PLATON Service Unit, Caen, Université de Caen Normandie, France
5 RONOMA Pharma, 31 rue Léon Delille F-76800 Saint Etienne du Rouvray, France
6 Neuro-Sys, 410 chemin départemental 60, F-13120 Gardanne, France

We previously described donecopride as a promising Swiss-army knife, Multi Target-Directed Ligand (MTDL) exerting both acetylcholinesterase (AChE) inhibitory and 5-HT_4 receptor agonist activities, two targets of interest in Alzheimer's disease (AD) [25,27]. This compound is currently in regulatory preclinical trials and was also the subject of an intensive medicinal chemistry work, in order to achieve its declination into various derivatives, even perhaps more clinically relevant. In this work, we focused on the modulations on the aromatic moiety to exemplify the "copride" family of drug candidates able to both inhibit AChE and to activate 5-HT_4 receptors (Figure 50).

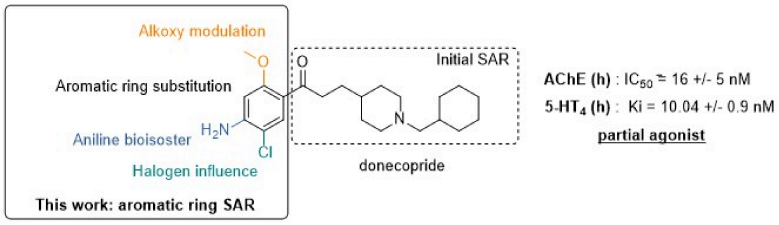


Figure 50. General strategy for the modulation of donecopride.

Twenty-one analogs of donecopride were then synthesized exploring the influence on the biological activities of the substituents carried by its phenyl ring. One of them, the flucopride displayed both anti-amnesiant and promnesiant activities in mice. These two activities, associated with an increased release in vitro of the neurotrophic protein sAPPα, account for a potential interest of flucopride towards AD.

This work was funded by Normandie Valorisation (Preclinicalz program) and the Fondation Vaincre Alzheimer.

7.25. Computational Modeling, Chemical Synthesis and Biological Evaluation of Compounds Targeting Viral Neuraminidase

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Influenza A viruses (IAVs) are major respiratory pathogens with pandemic potential. IAVs are subdivided into different subtypes based on the distinct surface glycoproteins hemagglutinin (HA) and neuraminidase (NA) isozymes, of which the H1N1 subtype are endemic in humans, circulating continuously in the population and causing seasonal outbreaks [245]. Neuraminidase (N or NA) plays a critical role in the viral life cycle by cleaving sialic acid residues from glycoproteins. Neuraminidase (NA) facilitates virion release, prevents viral aggregation, and promotes infection spread, making it a validated

antiviral target whose inhibition remains key to treating and preventing influenza [246]. In this study, we directed our research efforts toward N1 subtype of neuraminidase, a key enzyme in H1N1 viral strains, due to its clinical relevance and widespread circulation. The primary objective of our research was to identify and characterize novel inhibitory compounds specifically targeting the N1 neuraminidase enzyme through an integrated computational and experimental workflow. Our methodological approach began with the development of a structure-based pharmacophore model by analyzing multiple crystal structures of NA in complex with known inhibitors to identify key binding features. The model was subsequently subjected to rigorous validation protocols to assess its discriminatory power and ability to accurately distinguish active inhibitors from inactive compounds, thereby confirming its predictive value. Then, we implemented a virtual screening using an in-house compound library (CHIME24) to retrieve plausible candidates matching the pharmacophore features. Compounds identified through the virtual screening process were subjected to molecular docking studies to assess their potential binding interactions within the NA active site. The validation of our docking protocol was performed by comparing computationally predicted binding poses with experimentally determined crystallographic conformations of known inhibitors, which demonstrated excellent alignment of key functional groups and interaction networks, thus confirming the reliability of our computational approach. To further refine our understanding of inhibitor-enzyme interactions, we conducted extensive molecular dynamics simulations on the most promising protein-ligand complexes. In the last phase of our research, we selected several compounds possessing different chemical scaffolds and binding modes; these compounds were selected to pursuit the synthesis and biological evaluation.

This work was supported by research fellowships awarded by "HANAIN project" (CODSOG S5.P0005). "Tackling Influenza Viruses by optimized hemagglutinin (HA) and/or neuraminidase (NA) inhibitors" -in "One Health Basic and Translational Research Actions Addressing Unmet Needs on Emerging Infectious Diseases" Codice identificativo PE00000007 finanziato dall'Unione Europea—Next Generation EU" PNRR MUR—M4C2" –Investimento 1.3.- CUPB53C20040570005".

7.26. Standardized In Vitro Screening for Neglected Tropical Diseases: Evaluating Efficacy and Cytotoxicity of Drug Candidate

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Neglected tropical diseases (NTDs), such as Sleeping Sickness, Chagas Disease, and Leishmaniasis, continue to afflict millions of people worldwide. With the goal of identifying safer and more effective medications, this research project focuses on establishing standardized in vitro screening tests for the development of prospective drug candidates. These tests are being carried out on 96-well plates, following established protocols to ensure result reliability. The activity of every compound is quantified by its IC50 value, which is the concentration required to halt the growth of the parasite by 50%. Drugs such as Suramin and Melarsoprol are used as reference standards to compare relative performance. Cytotoxicity assays are also conducted using human lung fibroblasts (MRC-5) to examine the toxic levels of these compounds on human cellular structure. Compounds with high toxicity (IC_{50} < 10 μM) are eliminated from further consideration, and those with less toxicity (IC_{50} > 30 μM) are selected for further development. This rigorous and methodical process is critical in identifying new treatments that are not only efficacious but also safe for patients.

This work was carried out at the Laboratory of Pharmacology and Pharmacotherapy (LPHM), University of Antwerp, with a focus on drug discovery and pharmacokinetics. I

would like to express my sincere gratitude to Prof. Guy Caljon for his support, mentorship, and for sharing the screening protocols used in this research. Special thanks to eCampus University for their academic guidance and to the COST Action CA21111 network, which made this experience possible through a Short-Term Scientific Mission (STSM). Their collaborative framework has been a great opportunity to grow as a young researcher and contribute to the fight against neglected tropical diseases.

7.27. Synthesis and Molecular Docking Study on Mycobacterium Tuberculosis InhA of New N-acyl-hydrazones of 2-(2-Methyl-4-oxoquinazolin-3(4H)-yl)acetohydrazide

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Tuberculosis (TB) continues to be a leading cause of death worldwide and long-term, expensive therapy with significant side effects underscore for development of new therapeutic options [247]. Quinazoline ring is frequently used in drug design due to its diverse pharmacological actions [248]. Bedaquiline, a quinoline-based drug used in the treatment of multi-drug resistant TB. Hydrazone compounds have shown significant potential in the treatment of tuberculosis, isonicotinohydrazides being such examples [249]. Combining these two pharmacophores, we designed and synthesized a series of new *N*-acyl-hydrazones of 2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)acetohydrazide. Molecular docking analysis was performed in order to evaluate the binding modes of selected ligands within the active site of *Mycobacterium tuberculosis* enoyl reductase (InhA).

The compounds were obtained by microwave irradiation using different aromatic aldehydes and characterized physicochemically and spectrally (FTIR, ^{1}H-NMR, ^{13}C-NMR, UV-Vis). The 3D structures of the ligands were prepared by Spartan'24 and the molecular docking study was performed using CLC Drug Discovery Workbench and Molegro Virtual Docker. The crystal structure of the target protein was downloaded from Protein Data Bank (PDB ID: 4TZK).

The new compounds were evaluated using density functional theory. *N*-acyl-hydrazones have smaller energy gaps than starting acetohydrazide, making them more reactive. They also present higher eletrophilicity index which indicates reactivity towards protein targets and they comply with Lipinski rule of five for druglike molecules. Docking results showed increased predicted affinity for *Mycobacterium tuberculosis* enoyl reductase (InhA) compared with acetohydrazide. The keto group of the quinazolinone moiety forms hydrogen bonds with nicotinamide-dinucleotide phosphate (NAD) co-factor, whereas the amide-hydrazide group interacts with Tyr158. The substituents of the aldehyde part influence orientation of the molecule in the binding pocket, forming interactions with hydrophobic amino acids (Ile16, Met103, Pro156, Ala157, Ile215, Leu218).

Thus, the quinazolinone ring and the hydrazone group are key structural features implicating in bonding with the active site of *Mycobacterium tuberculosis* enoyl reductase. The antimycobacterial activity of the synthesized compounds must be further investigated in vitro.

7.28. 3-Heteroarylcoumarins as Potential Therapeutic Agents for Neurodegenerative Diseases: Synthesis, Molecular Modeling and Biological Insights

Manuel Novás [1], Cynthia N. Pereira [1], Lorenzo A. Mateos [1], Nuria B. López [1], Sara Mocka [1], Davide Crucitti [2,3], Sela González [1], Dolores Viña [3,4] and Maria J. Matos [1]

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2 Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain
3 Department of Pharmacology, Pharmacy and Pharmaceutical Technology, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain
4 Physiology and Pharmacology of Chronic Diseases (FIFAEC) Center for Research in Molecular Medicine and Chronic Diseases (CiMUS), University of Santiago de Compostela, 15782 Santiago de Compostela, Spain

Neurodegenerative diseases represent a complex therapeutic challenge, with currently available drugs primarily providing symptomatic relief. The development of new coumarin derivatives for the treatment of these diseases follows three main strategies: (1) modifying the coumarin scaffold to create compounds that inhibit MAO-B and cholinesterases, (2) introducing heteroaromatic rings at position 3 to enhance selectivity and potency, and (3) adding hydroxyl groups to confer antioxidant properties similar to those of naturally occurring molecules, such as resveratrol, which share a close structural relationship with 3-arylcoumarins [250–252]. The synthesis of 3-heteroaryl-6/7-hydroxycoumarin derivatives integrates these strategies to provide a multitarget approach to treating neurodegenerative diseases (Figure 51). This was achieved through the Perkin-Oglialoro reaction and a modified deacetylation of the acetyl groups using thionyl chloride, resulting in reaction efficiency and high yields. Computational studies and preliminary pharmacological screening show promising interactions with key therapeutic targets, low cytotoxicity, and effective MAO-B inhibitory activity.

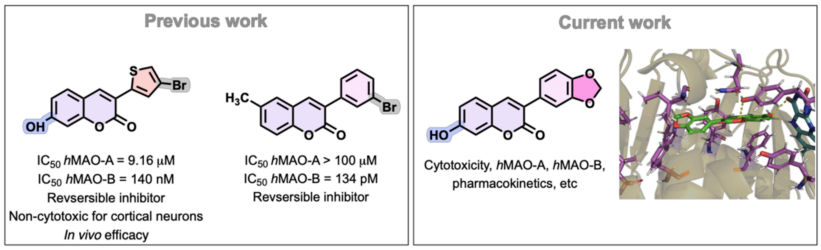


Figure 51. Overview of previous findings and key results presented in this study.

7.29. Synthesis and Antiparasitic Evaluation of Thieno[2,3-b]pyrazine Derivatives

Maria F. Martins [1], Nuno Santarém [2], Anabela Cordeiro-da-Silva [2,3] and Maria-João R. P. Queiroz [1]

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Thieno[2,3-*b*]pyrazine derivatives constitute a significant class of aromatic heterocyclic compounds, largely due to the important biological activities exhibited by some of their derivatives. Recently, in our research group, diheteroarylamines in the thieno[2,3-*b*]pyrazine series were prepared by Buchwald-Hartwig C-N coupling, and

evaluated as potential antitumor compounds [253]. Herein the Pd/Cu-catalyzed Sonogashira coupling [254] of methyl 7-bromothieno[2,3-*b*]pyrazine-6-carboxylate (**1**) with (hetero)arylalkynes to give Sonogahira products **2a-g**, is reported. Additionally, the 9-chloro 6-*endo-dig* lactone **3** was prepared from the Sonogashira phenyl derivative using $CuCl_2$ and NCS [255] (Figure 52).

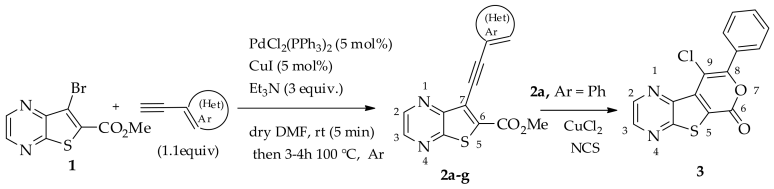


Figure 52. Synthesis of Sonogashira products in the thieno[2,3-*b*]pyrazine series and 9-chloro *6-endo-dig* lactone.

The compounds prepared were submitted to anti-parasitic evaluation against *Trypanosoma brucei* and *Leishmania infantum.* The results were promising for the Sonogashira product derivative of 2-pyridine with IC_{50} = 6.43 µM against *T. brucei* and IC_{50} = 16 µM for *L. infantum*, and for the 9-chloro tricyclic lactone **3** with IC_{50} = 10.80 µM against *T. brucei*. The toxicity of the compounds was evaluated using THP-derived macrophages.

Thanks are due to FCT-Portugal for financial support to CQ-UM and COST Action 21111 OneHealthDrugs.

7.30. A Collaborative Work in the Field of Medicinal Chemistry with CHEM-Symbiose, as a Devoted Custom Synthesis Platform

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Open to new collaborative opportunities?

Located at CEISAM laboratory (Nantes Université, UMR CNRS 6230), CHEM-Symbiose is a fully equipped platform dedicated to the elaboration of simple or advanced organic molecules (milligram to gram preparation scale) for academic research programs in life sciences and health [256,257], food and nutrition [258], and agriculture and environment, including marine environment. Thanks to its expertise in lots of chemistry fields, beyond its role as a supplier of organic molecules based on the state of the art, CHEM-Symbiose platform also supports collaborative works with biologist partners for establishing proof of concept of innovative research projects. CHEM-Symbiose is labeled by regional and national scientific networks Biogenouest and IBiSA. Our platform is also an active member of ChemBioFrance (Figure 53).



Figure 53. CHEM-Symbiose platform labels.

7.31. Analysis of the Structural Diversity of Heterocycles Amongst EMA Approved Pharmaceuticals (2014–2023)

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Heterocycle diversity amongst medicines with new active substances (NAS) approved by the European Medicines Agency in the last 10 years (2014–2023) was analysed. A total of 380 medicines were approved that contain a NAS, of which 160 products contained one or more NASs with a heterocycle (164 NAS in total). Of the 164 NASs, 76% contained more than one heterocycle (Figure 54). The majority (59%) of the 164 active substances contained at least one fused heterocycle. The most common bicyclic rings were quinoline, indole, benzimidazole, and purine. Tricyclic and polycyclic fused rings were observed but were rare. There were 28 distinct monocyclic heterocycles, consisting of 3, 4, 5, and 6 membered rings. 5-Membered rings were the most diverse as 15 of the 28 heterocycles were 5-membered rings. 6-Membered rings ranked second with 12 heterocycles. There was one 3-membered ring and one 4-membered ring seen. The five most common monocyclic heterocycles were pyridine, piperidine, pyrrolidine, diazinane, and pyrimidine. Nitrogen was by far the most common heteroatom in both monocyclic and fused heterocycles. Oxygen, sulfur and boron appeared in monocyclic heterocycles, whilst oxygen, sulfur and phosphorous were noted in fused heterocycles.

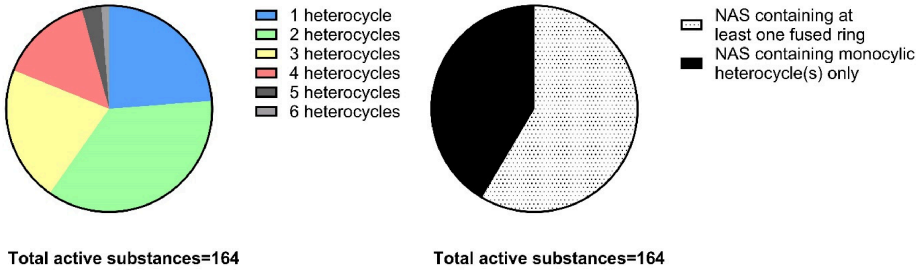


Figure 54. (**Left**) Number of heterocycles per NAS; (**Right**) Proportion of NAS containing at least one fused heterocycle compared to NAS containing only monocyclic heterocycle(s).

7.32. Synthesis of cis-4-Hydroxy-L-Prolyl Amides for Application in Medicinal Chemistry

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cis-4-Hydroxy-L-proline (*cis*-Hyp, Figure 55) is a rare but highly valuable isomer of 4-hydroxyproline, present in natural products such as phallotoxins from *Amanita* mushrooms. Due to its unique stereochemistry, *cis*-Hyp is a privileged scaffold in medicinal chemistry, enabling the design of conformationally restricted peptides and peptidomimetics with enhanced biological activity, metabolic stability, and receptor selectivity. However, its limited availability and classification as an advanced intermediate have hindered its widespread application in drug development. Moreover, existing synthetic strategies for

the preparation of *cis*-Hyp are often lengthy, low-yielding, and poorly suited for efficient peptide synthesis.

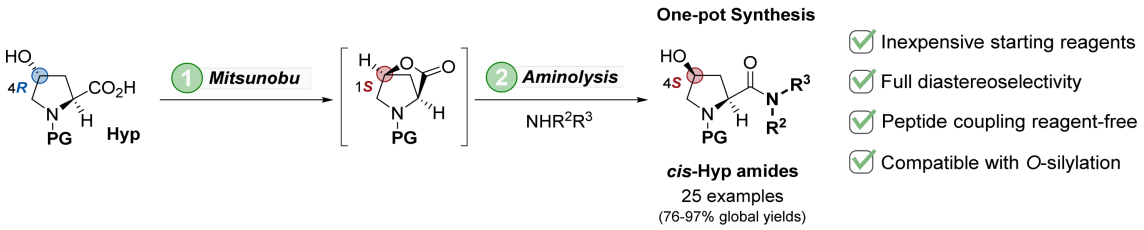


Figure 55. A Sustainable and telescoped one-pot strategy for the assembly of *cis*-Hyp amides from Hyp.

In this work, we introduce a novel one-pot methodology for the direct synthesis of *cis*-Hyp amides from readily available *trans*-4-hydroxy-L-proline (Hyp, Figure 1), without the need for peptide coupling reagents or capping steps [259]. This approach enabled the synthesis of 25 *cis*-Hyp amides in good to excellent yields (76–97%) with full diastereoselectivity, as verified by variable temperature NMR and HPLC [259]. The method is scalable (up to 91% yield) and adaptable to a three-step one-pot process including *O*-silylation (83% overall yield) [259]. The synthetic utility of this methodology is showcased by the formal synthesis of a bioactive compound with antiamnesic properties [259]. This streamlined, sustainable protocol enhances access to *cis*-Hyp-based building blocks, paving the way for their broader use in medicinal chemistry and the development of structurally refined peptide therapeutics.

Funding: This work received financial support from PT national funds (FCT/MCTES, Fundação para a Ciência e a Tecnologia and Ministério da Ciência, Tecnologia e Ensino Superior) through project 2023.14440.PEX (DOI: 10.54499/2023.14440.PEX).

Acknowledgments: FCT is also acknowledged for supporting projects 2022.01175.PTDC, UIDB/50006/2020, and UIDP/50006/2020. I.E.S.-D. thanks FCT for funding through the Individual Call to Scientific Employment Stimulus with reference 2020.02311.CEECIND/CP1596/CT0004 (DOI: 10.54499/2020.02311.CEECIND/CP1596/CT0004). X.C.C., H.F.C.-A., B.L.P.-L., and S.C.S.-R. thank FCT for the Ph.D. grants 2024.02245.BD, UI/BD/154888/2023, 2022.14060.BD, and SFRH/BD/147463/2019, respectively. R.S. thanks FCT for her research grant through project 2023.14440.PEX. X.G.-M. thanks Xunta de Galicia for financial funding with reference GPC2020/GI1597.

7.33. Towards More Water-Soluble Coumarin Photocages: A 7-Position Divergent Synthesis Approach

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Selectivity in drug activity, whether in space (targeted delivery) or time (controlled activation), is desirable for treating diseases such as cancer and epilepsy. In anticancer therapy, for instance, a cytotoxic drug should be activated/released only at the tumor site to minimize harm to healthy tissues. Similarly, an antiepileptic drug should function only when a seizure arises, ensuring precise therapeutic action while reducing side effects [260,261]. A strategy for achieving spatiotemporal control is the incorporation of a photolabile protecting group (PPG), which temporarily disrupts a drug's key interaction with its biological target and allows for reactivation via light irradiation [262] (Figure 56). One of the most widely used PPGs is 7-(diethylamino)-4-(hydroxymethyl)coumarin (Figure 1). However, its biological compatibility is limited due to its poor water solubility and uncaging occurring at 405 nm. To address these challenges extensive modifications to the coumarin core have

been explored [263,264]. One strategy to enhance water solubility is the replacement of the diethylamine moiety with more hydrophilic groups, such as morpholine or piperazine. However, the synthesis of 7-substituted coumarins remains challenging, as current methods rely on convergent approaches [265]. To overcome this limitation, we developed a versatile methodology that enables the incorporation of a hydrophilic side chain at the 7-position as a final-step modification, streamlining the synthetic process. As a proof of concept, we successfully introduced a 4-piperazine-L-phenylalanine moiety onto the coumarin core. This modification not only enhances water solubility but may also engage the LAT-1 transporter, potentially facilitating blood-brain barrier penetration for applications in neurological diseases [266].

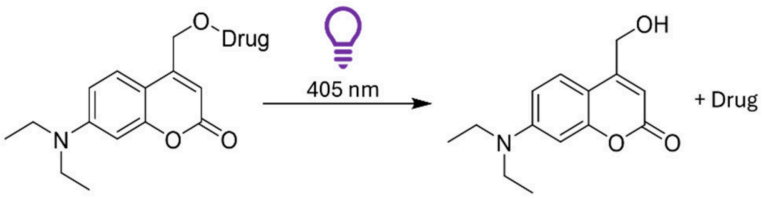


Figure 56. Uncaging of a drug under light irradiation with 7-(diethylamino)-4-(hydroxymethyl)coumarin as photocage.

7.34. Computational Design and In Vitro Anticancer Activity of a D-Glucose-Derived Anopyranoside

Rodrigo R A Caiana [1], Maria E B da Silva [1], Yasmim M Silva [1], Juliano C R de Freitas [2] and Teresinha G da Silva [3]

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Cancer is one of the top ten causes of death worldwide, with ~20 million new cases and 9.7 million deaths [267]. Limitations of current chemotherapy, particularly toxicity, are driving the search for new agents [268]. In this context, the present study aimed to develop an enopyranoside compound, through in silico rational design, with in vitro anticancer activity. The enopyranoside derived from D-glucose (Figure 57A) was selected from the synthetic compound library of the Laboratory of Organic Synthesis and Medicinal Chemistry (LASOQuim—UFCG/Brazil) and evaluated using the cheminformatics platforms PASSonline and Osiris Property Explorer to determine its anticancer potential, drugability, and toxicity risk. The anticancer potential of the enopyranoside was evaluated through the in vitro MTT assay on human colon cancer cells (HT-29). The enopyranoside showed high pharmaceutical potential in the computer-aided drug design step. The PASSonline evaluation showed an 85.8% likelihood of antineoplastic activity, while the Osiris program indicated a low/no risk of chronic toxicity. The MTT assay confirmed its antineoplastic potential (Figure 57B), with an IC_{50} of 1.35 μg/mL (0.91–1.79 μg/mL), which is in the highly active range as reported in the literature (IC_{50} values < 5 μg/mL) [269]. The high in vitro anticancer activity and low in silico toxicity of enopyranoside support future efforts focused on novel derivatives within this chemical class to identify new drug candidates with favorable pharmacological and toxicological profiles.

Acknowledgement to Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

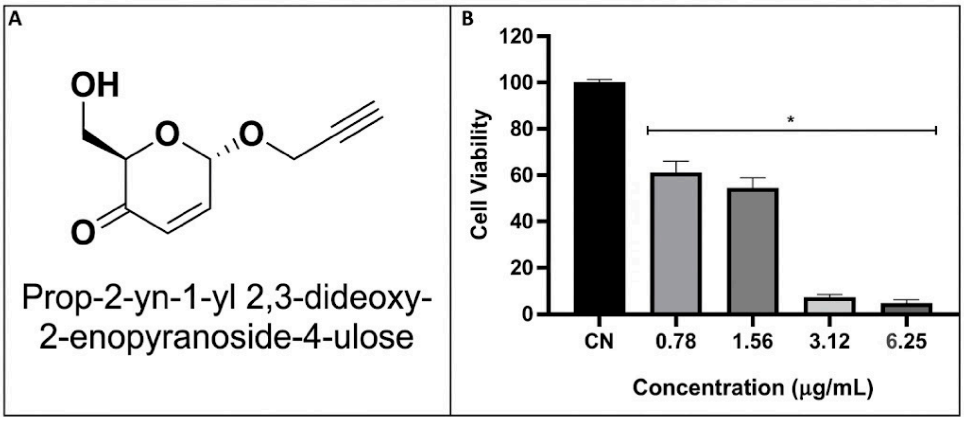


Figure 57. (**A**) Chemical structure of the D-glucose-derived enopyranoside; (**B**) Cell viability of HT-29 cells exposed to different concentrations of the enopyranoside. * indicates a statistically significant difference ($p < 0.0001$) compared to the Negative Control (CN) in the ANOVA test followed by Dunnett's post hoc test.

7.35. Evaluation of the Antifungal Activity of Formulations Containing Hybrid of 1,2,3-Triazole and Phthalimide for the Treatment of Vulvovaginal Candidiasis

Yasmim M. Silva [1], Rodrigo R. A. Caiana [1], Elizabeth F. de O. Borba [1], Marília G. de F. Silva [1], Natacha F. A. Paixão [1], George T. de Lima [1], Juliano C. R. de. Freitas [2], Silvania T. Paz [1] and Teresinha G. da Silva [1]

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Vulvovaginal candidiasis (VVC) is a fungal infection caused mainly by the yeast *Candida albicans*. This infection is classified as the second most frequent cause of vaginitis. Side effects associated with antifungal drugs and Candida resistance mechanisms have been described in the literature. Therefore, it is interesting to investigate promising molecules such as 1,2,3-triazoles and phthalimides [270]. For this study, 6 hybrid compounds were obtained resulting from the conjugation of the 1,2,3-triazole and phthalimide nuclei (Figure 58).

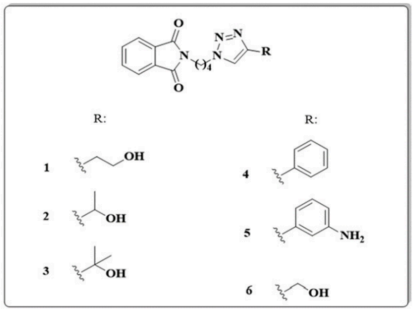


Figure 58. Structure of 1,2,3-triazole-phthalimide hybrids (1–6).

In the antifungal susceptibility test, all the hybrids (1–6) showed potent antimicrobial activity with minimum inhibitory concentration and minimum fungicidal concentration values (MIC, MFC) of 256 µg/mL. Hybrid 1 was incorporated into Polawax® cosmetic base cream at concentrations of 5% and 10% and administered to different groups of female mice for 14 days, after 24 h of administration of *C. albicans* suspension (2.5×10^6 cells/mL) by intravaginal route [271]. Nystatin cream was used as a positive control. Ethical committee number: 0057/2022 for the use of animals. Histopathological analysis of the vaginal tissue

showed structural destruction just in groups B and C. Vaginal cross-section of the groups of female mice evaluated: A (Sham); B (untreated control); C (Polawax®); D (Nystatin); E (5% cream); F (10% cream). The vaginal lumen (VL), stratum corneum (SC), stratified squamous epithelium (SSE), lamina propria (LP), inflammatory cells (black arrow). Staining: Hematoxylin-Eosin. Original magnification: 1000× (Figure 59).

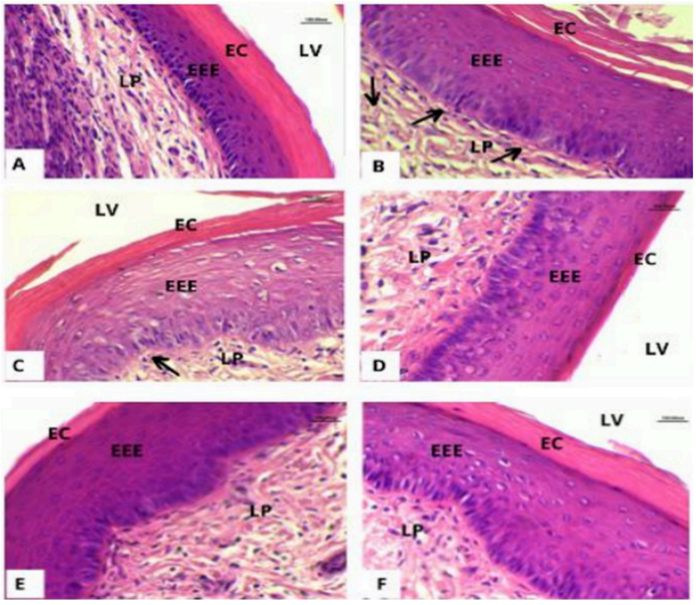


Figure 59. Photomicrographs of vaginal tissues. Vaginal cross-section of the groups of female mice evaluated: (**A**) (Sham); (**B**) (untreated control); (**C**) (Polawax®); (**D**) (Nystatin); (**E**) (5% cream); (**F**) (10% cream). The vaginal lumen (VL), stratum corneum (SC), stratified squamous epithelium (SSE), lamina propria (LP), inflammatory cells (black arrow). Staining: Hematoxylin-Eosin. Original magnification: 1000×.

7.36. Facile Epimerization of (+)-Sclareolide: A Versatile Experiment for Laboratory Education

Florence O'McCarthy [1], Jukka Saarinen [2], Amit Upadhyay [1,3], Chiara Zanetti [3], Emily A. Collins [1,3], Michelle O'Driscoll [1,3], Orla M. Lynch [1,3], Michael F. Cronin [3], Tobias Rüffer [4], Olha Antoniuk [5,6,7], Jari Yli-Kauhaluoma [2] and Vânia M. Moreira [2,5,6,7]

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4 Inorganic Chemistry, Faculty of Natural Sciences, Institute of Chemistry, Technische Universität Chemnitz, 09107 Chemnitz, Germany
5 Faculty of Pharmacy, University of Coimbra, Pólo das Ciências da Saúde, Azinhaga de Santa Comba, 3000-548 Coimbra, Portugal; vmoreira@ff.uc.pt
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7 Centre for Innovative Biomedicine and Biotechnology (CIBB), University of Coimbra, 3004-504 Coimbra, Portugal

An experiment to teach the concept of epimerization has been designed and developed starting from the naturally occurring sesquiterpene lactone (+)-sclareolide, and made available to the general community [272]. The parent compound suffered epimerization at position 8, under catalytic conditions, upon treatment with bismuth(III) triflate, in refluxing

acetonitrile. The facile experimental setup allowed the implementation of the experiment at two different locations, namely, the School of Pharmacy at the University College Cork (UCC), in Ireland and the Faculty of Pharmacy at the University of Helsinki (UHEL), in Finland. At both locations, students with only basic knowledge of stereochemistry and analytical techniques were able to prepare and isolate the epimer of (+)-sclareolide. Problem set questions helped the students to learn important concepts beyond epimerization, including carbocation-mediated reaction mechanisms and catalysis, as well as to apply the most current analytical techniques for structural elucidation, i.e., Nuclear Magnetic Resonance, High-Resolution Mass Spectrometry and X-Ray Crystallography. Overall, the students assessed the work positively and felt more confident to explore the concept of epimerization which can be challenging to grasp thorough theory alone. This presentation will provide an overview of the experiment which we hope will inspire the teaching of this topic by the broader community of educators in the field [272].

OA acknowledges the Portuguese Science and Technology Foundation (FCT) for a doctoral scholarship (2023.02956.BD). VMM acknowledges UIDB/04539/2020, UIDP/04539/2020.

7.37. Molecular Docking Analysis of a Novel Coumarin-Triazole-Isatin Hybrid with Cholinesterase Inhibitory Activity

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Development of novel Alzheimer's disease (AD) drugs remains a challenge, as current treatments provide symptomatic relief without altering disease progression. Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) play key roles in cholinergic neurotransmission, with AChE promoting amyloid-β aggregation and BChE contributing to plaque maturation. Coumarin and isatin scaffolds hold potential as cholinesterase inhibitors. An in silico study was conducted on compound **15**, a coumarin-triazole-isatin hybrid with the best inhibitory activity against both enzymes from a series of 21 previously synthesized compounds (Figure 60). The 3D structures of AChE (PDB ID: 5NAP) and BChE (PDB ID: 5K5E) were obtained from the Protein Data Bank (PDB). The active sites were prepared using MAKE Receptor 3.2.0.2 [273]. Ligand conformations were generated in OMEGA 2.5.1.4, while molecular docking was performed using the fast rigid exhaustive docking (FRED) tool in OEDocking 3.2.0.2 [273–275]. Moderate in vitro activity of compound **15** against AChE, compared to S-donepezil, could be attributed to key interaction differences. While S-donepezil forms strong π-π stacking with Trp84 and Trp279, a hydrogen bond with Tyr121, and π-σ/π-alkyl interactions with Phe330 and Phe331, compound **15** lacks π-π stacking with Trp279 and hydrogen bonding with Tyr121, which most likely reduces its AChE inhibitory activity. Compound **15** exhibited enhanced interactions with BChE, compared to both donepezil enantiomers, including π-π stacking with Trp82 and Phe329, π-π-T-shaped interactions with Trp231, and a hydrogen bond with Ser198. While a steric hindrance with Leu286 was noted, it likely had minimal impact due to the enzyme's flexibility. Donepezil enantiomers form weaker π-alkyl interactions with key residues Trp82 and Tyr332, which most likely contribute to their lower activity toward BChE. These findings could serve as a strong basis for the design of new coumarin-triazole-isatin hybrids with dual AChE and BChE inhibitory activity.

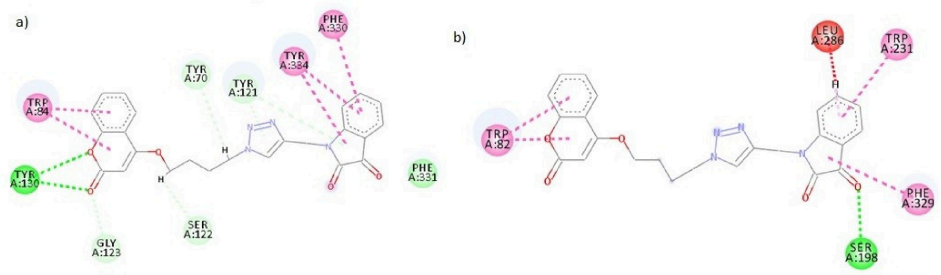


Figure 60. 2D presentation of interactions of compound **15** with AChE (**a**) and BChE (**b**).

7.38. Synthesis and Biological Evaluation of New Resinic Acid Derivatives from Biomass as Antitumor Agents

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Biomass has recently attracted considerable attention in the scientific community as a promising source of renewable and sustainable raw materials. In this context, colophony, a natural resin derived from pine trees, has been widely investigated for its chemical richness and its potential in the development of high-value added derivatives [276]. Numerous publications have reported the relevance of resinic acids particularly abietane-type diterpenes and their potential applications in medicinal chemistry, including antitumor and antiviral activities [12,13,277,278].

In this communication, we present the synthesis of several novel resinic acid derivatives obtained from colophony and the evaluation of their biological properties toward in vitro cancer models. Preliminary screening assays have shown that some of these derivatives induce significant inhibition of cell proliferation, highlighting the therapeutic potential of abietane-based compounds (Figure 61).

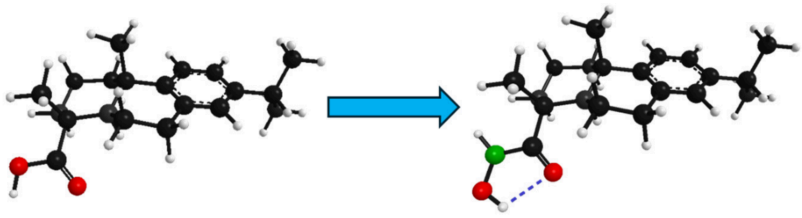


Figure 61. Synthesis of hydroamic acid derivative with potencial anticancer activity from resinic acid.

The authors acknowledge the Spanish government, the "Asociación Española Contra el Cáncer (AECC) de Santa Cruz de Tenerife" and the regional government of "Comunitat Valenciana" for their financial support.

7.39. Design and Optimization of Melanostatin Derivatives with Enhanced Bioavailability

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Melanostatin is an endogenous neuropeptide that acts as a positive allosteric modulator of the dopamine D_2 receptors, thus having the potential to be used in the treatment of several dopamine-related disorders (e.g., Parkinson's disease, depression, tardive dyskinesia, restless leg syndrome, obesity) [62]. Nevertheless, this neuropeptide fails to exhibit adequate pharmacokinetic properties due to its biochemical nature, hampering its clinical use [62].

This project fosters overcoming the pharmacokinetic drawbacks of melanostatin by developing azapeptides through the rational replacement of the proline residue with an aza-proline scaffold. This subtle yet effective approach was applied to assemble a library of 24 melanostatin derivatives. Pharmacological and toxicological assays demonstrated promising pharmacological properties by decreasing the EC_{50} of dopamine by up to 8.8 times, denoting better performance than the parent neuropeptide at 1 nM. In addition, the azapeptides did not reveal relevant cytotoxicity in differentiated SH-SY5Y cells at 100 μM, indicating a safe therapeutical window. Moreover, the azapeptides did not interact with *h*ERG channels. Proof of concept pharmacokinetic studies revealed improved microsomal stability by up to 4.7 times.

Funding: This work received financial support from PT national funds (FCT/MCTES, Fundação para a Ciência e a Tecnologia and Ministério da Ciência, Tecnologia e Ensino Superior) through project 2023.14440.PEX (DOI: 10.54499/2023.14440.PEX).

Acknowledgments: FCT is also acknowledged for supporting projects 2022.01175.PTDC, UIDB/50006/2020, and UIDP/50006/2020. I.E.S.-D. thanks FCT for funding through the Individual Call to Scientific Employment Stimulus with reference 2020.02311.CEECIND/CP1596/CT0004 (DOI: 10.54499/2020.02311.CEECIND/CP1596/CT0004). V.M.C. thanks the financial support and her grant funded by national funds from FCT, in the scope of the projects UIDP/04378/2020 and UIDB/04378/2020 (UCIBIO), and the project LA/P/0140/2020 (i4HB). H.F.C.-A., X.C.C., S.C.S.-R., and B.L.P.-L. thank FCT for the Ph.D. grants UI/BD/154888/2023, 2024.02245.BD, SFRH/BD/147463/2019, and 2022.14060.BD, respectively. X.G.-M. thanks Xunta de Galicia for financial funding with reference GPC2020/GI1597.

7.40. The GPER Protein as a New Target for the Control of Chemotherapy-Induced Peripheral Neuropathy: Towards Promising Therapeutic Perspectives in Oncology

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Drugs that are used for the control of chemotherapy-induced nociception are restricted to analgesics, antidepressants and anticonvulsants, with limited effects in 70% of cancer patients. The development of new approaches for the control of chemotherapy-related pain is, therefore, a priority of public health. Recently, we have developed the first peptidic GPER modulator (i.e., ERa17p), an inverse agonist that is issued from the hinge region of the human estrogen receptor alpha (ERa66, residues 295–311), and from the 123–139 region of the ERa36 isoform [279,280]. GPER, for G protein-coupled estrogen receptor, is a protein of 375 amino acids belonging to class A (rhodopsin-like) RCPG, which is involved, among other things, in nociception [281]. In a previous work and by using a murine CFA model, we have observed that the N-terminal part of ERa17p, the PLMI tetrapeptide, was responsible for a decrease of tactile hypersensitivity [282]. Here, we show that the PLMI peptide is capable of exerting GPER-dependant anti-nociceptive action, in a paclitaxel-induced pain mice model. This action is mediated by GPER at the peripheral, spinal and supraspinal levels of the nervous system. The chronic administration of this peptide reduces pain-like behaviors and protects against nerve conduction velocity deficits, without causing cognitive impairments or addiction. Importantly, the PLMI peptide also alleviates oxaliplatin- and bortezomib-induced neuropathic pain. In the light of these results, we have proposed a mode of binding of this peptide within the GPER ligand-binding pocket. This study highlights the functional role of GPER in chemotherapy-induced pain and suggests that targeting GPER could be promising, at least in our context. Our results further suggest that the use of GPER modulators could be an innovative approach to alleviate paclitaxel-induced peripheral neuropathy.

We are grateful to La Ligue Nationale contre le Cancer (Program "Lutte contre les douleurs liées au cancer" 2024) for its financial support.

7.41. Synthesis and Study of Novel Stilbene Disulfonate Compounds as RAD51 Inhibitors and Potential Chemosensitizer in Cancer Therapy

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DNA repair process is particularly important in maintaining genomic integrity. In proliferative diseases therapies such as radiotherapy or chemotherapy, this process can restore the DNA damaged with the treatment, making cancer cells less vulnerable. Homologous recombination (HR) is one of the two cellular pathways that repair DNA double-strand breaks (DSBs) [283]. It is catalyzed with RAD51 a highly conserved protein overexpressed in a wide variety of cancers and consequently contributing to drug resistance [284]. Elevated level of RAD51 expression is also associated with increased metastases and patients outcome.

Hence, RAD51 protein is a relevant biological target for modulating HR and thus achieving greater potency of antiproliferative treatments. Consequently, identification of small molecules exhibiting anti-recombinase activities has attracted increasing attention these last years. It has been discovered that certain small molecule inhibitors of the RAD51 protein (Figure 1) directly interfere with crucial steps in the recombinase activity of the RAD51 protein and thus prevent or limit the HR repair pathway. Among them the disulfonic compound 4,4′-diisothiocyanostilbene-2,2′-disulfonic acid (DIDS, Figure 62), has been identified with 50% effect around 1–2 μM, and we have recently selected several commercial analogues of DIDS to characterize the structural determinants involved in modulating RAD51 activity, with such sulfonic compounds [285].

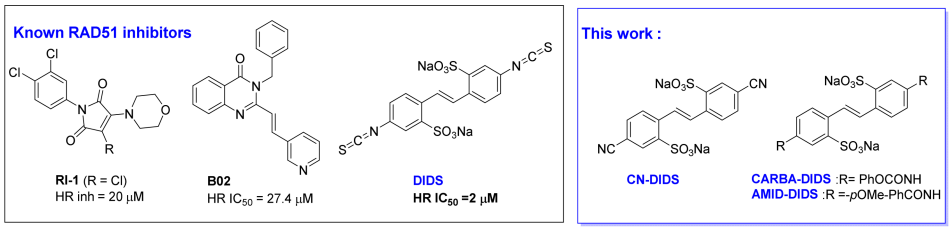


Figure 62. Known RAD51 inhibitors and our novel DIDS analogues.

To pursue this research program, a series of DIDS analogues were prepared in CEISAM laboratory and studied in US2B laboratory as potential RAD51 inhibitors, disrupting protein-protein interaction [286]. From in vitro to in cellulo bioassays, stable analogues of DIDS have been identified as effective inhibitors of RAD51 and potential sensitizers of prostate cancer cells to chemotherapy. The chemical and biological results will be detailed in this communication.

7.42. Drug Discovery of Pyrazolo-Piperidinone Inhibitors Targeting YAP:TEAD Interaction and Development of a Fluorescence Anisotropy Assay for High-Throughput Screening

Giulia Malpezzi [1,2], Laura Scalvini [3], Lorenzo Tagliazucchi [1], Annalisa Chiaravalle [3], Daniele Aiello [1], Giulia Saporito [1], Davide Illuminati [4], Salvatore Pacifico [4], Remo Guerrini [4], Cecilia Pozzi [5], Alberto Venturelli [1], Glauco Ponterini [1], Marco Mor [3], Sheraz Gul [6] and Maria Paola Costi [1]

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6 Fraunhofer Institute for Molecular Biology and Applied Ecology (IME)

The Hippo signaling pathway (HP) is a critical regulator of cell proliferation, apoptosis, and tissue homeostasis. Central to its oncogenic deregulation is the interaction between Yes-associated protein (YAP) and TEAD transcription factors (TEAD1–4), which drives the expression of genes involved in tumor progression. Disrupting the YAP:TEAD (Y:T) complex has therefore emerged as a valuable strategy in anticancer drug discovery, though few small-molecule inhibitors with validated activity exist. In this work, we describe the discovery and optimization of a novel class of pyrazolo-piperidinone derivatives designed to interfere with the Y:T complex. Structure-based virtual screening targeting Interface 3 of the TEAD surface yielded a focused set of candidate molecules, followed by synthesis and biological evaluation of over twenty derivatives. Several compounds exhibited micromolar IC_{50} values in colorectal and ovarian cancer cell lines, including drug-resistant models, and modulated the expression of key Y:T downstream targets such as CTGF and CYR61 as shown by RT-PCR and mass spectrometry-based proteomics. A key component of this study was the design and validation of a fluorescence anisotropy (FA) displacement assay to quantitatively assess compound binding at the YAP-binding domain (YBD) of TEAD4. The assay uses a tetramethylrhodamine-labeled peptide (P6-TMR) that mimics the YAP Ω-loop, whose anisotropy increases upon binding to TEAD4 and decreases upon displacement by candidate inhibitors. This approach enabled accurate determination of binding affinities

(Kd values) and offered a reliable readout of target engagement, with strong correlation to in vitro antiproliferative activity. Given its robustness, sensitivity, and quantitative nature, the assay has been selected for high-throughput screening (HTS) optimization at the Fraunhofer Institute for Translational Medicine and Pharmacology (ITMP) in Hamburg. The objective is to adapt it to screen large chemical libraries and accelerate the identification of next-generation Y:T complex inhibitors. Overall, this work introduces a promising new chemotype, validates a specialized assay for YAP:TEAD disruption, and lays the foundation for its application in large-scale screening campaigns to expand the repertoire of PPI-targeting oncologic drugs [287–291].

7.43. Molecular Design of Fluorescence Probes Derived from the SOCE/Orai1 Modulator Delikine DAD3.473 for Cell Bio-Imaging in Pancreatic Cancer

Léa-Angélique Voli [1,2], Arnaud Asséké [1,2], Clarisse Dago [1,2], Pablo Even-Hernandez [1], Victor Marchi [1], Emmanuel Limanton [1], Lucie Paquin [1], Olivier Mignen [3], Yaya-Alexandre Békro [2], Janyl Mamyrbékova [2], Rémi Le Guével [4], Thomas Charlier [4] and Jean-Paul Bazureau [1]

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Calcium channel Orai1 is currently considered as an emerging and relevant target in cancer due to its indirect contribution, particularly in cell migration/invasion and metastatic spread. Therefore, the calcium channel Orai1 represents a promising therapeutic lead and accessibility to a selective inhibitor is a challenge for preventive treatment of metastases. During a **S**tructure **A**ctivity **R**elationship study around SKF-96365 [292] (a molecule used as reference for measuring calcium influx since 1991), delikine molecules were identified as a new family of selective inhibitors [293] targeting SOCE calcium influx controlled by the membrane protein Orai1. Thus, the delikine DAD3.4733 [294] was identified and patented in 2021 as an active "hit" on pancreatic carcinoma cells PANC1 and on breast carcinoma cells MDA-H321 during the RSA study. To date, the mechanism of action of industrial SOCE/Orai1 inhibitors (GSK-96365 and CM4620) in clinical studies, is not or is poorly controlled. In this context and to try to build proof of concept around this new SOCE/Orai1 inhibitor, we decided to develop fluorescence probes derived from the delikine DAD3.473. To achieve this objective, we opted for the use of a short linker (3 or 4 carbon atoms) so as not to disturb the intrinsic character of this SOCE inhibitor, and to graft it onto the West, East or North of this inhibitor. The terminal part of the linker comprises the fluorophore NBD (7-nitro-1,2,3-benzoxadiazole). For this 33rd annual GP2A Medicinal Chemistry Conference, the results of the multi-step syntheses of these fluorescence probes will be presented as well as the cell bio-imaging works in the poster presentation.

Funding: "Ligue Contre le Cancer" contracts 2018 and 2021, Ion Channel and Cancer Network contract 2012 from CGO, Corporate Foundation of BPO contract 2020, Scientific Challenges Contract 2020 of University of Rennes 1, Pre-maturation contract (2022) of Satt

Ouest-Valorisation. PhDs grants from : « Présidence de la République de Côte d'Ivoire » for V. L-A. , « Ministère de l'Enseignement Supérieur et de la Recherche Scientifique» for C.D., V.L-A. and A.A., « Total Raffinage Africa » for C.D. , « District d'Abidjan, CI » for V. L-A. within the framework of UR1-UBO-UNA cooperation contract 2019–2024.

7.44. Chalcones: A Potential Scaffold for the Development of AntiCancer Drugs

François-Xavier Toublet [1], Cécile Letulle [1], Aline Pinon [1], Aurélie Laurent [1], Aurélie Levêque [1], Catherine Fagnère [1], Yves Champavier [1], Bertrand Liagre [1] and Christelle Pouget [1]

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In LABC*i*S team, we have long been interested in the development of new therapeutic agents, mainly directed against two prevalent cancers: prostate cancer and colorectal cancer [268]. Natural products have always been considered to be invaluable sources of inspiration for drug design. Thus, chalcones are polyphenolic compounds belonging to the vast family of flavonoids, widely distributed in the plant kingdom, fruits and vegetables. Chalcones are open-chain molecules in which two aromatic rings (A and B) are joined by a three-carbon α,β-unsaturated carbonyl system. They received significant attention due to their wide range of biological activities, especially anti-cancer properties [295]. The in vitro antiproliferative activity against cancer cell lines has been mostly reported and is associated with interfering with the activity of several mechanisms and targets such as aromatase, VEGF, JAK/STAT signaling pathways, tubulin, topoisomerase-II [296].

Considering structure-activity relationship, a trimethoxyphenyl ring was demonstrated to be interesting for anticancer activity of chalcones, more precisely for inhibition of tubulin polymerization [297]. Therefore, some of our previous and ongoing works are devoted to the synthesis of original trimethoxylated chalcones through the pharmacomodulation of the B aromatic ring [298]. Biological activities of these compounds are investigated in vitro on colorectal and prostatic cancer cell lines.

Besides, many chalcones, like most anticancer compounds, suffer from a lack of selectivity leading to adverse side effects. Sometimes, they also have a low bioavailability due to a poor hydrosolubility. So, performing structural modifications on chalcone cores to enhance their selectivity towards cancer cells and their bioavailability appears to be a pertinent strategy. For example, a relevant methodology for anticancer drug vectorization is the use of polyamine-based vectors [299]. Thus, we designed and highlighted the potent of several chalcone polyamine conjugates [300].

7.45. Design and Synthesis of Chalcones with Anti-Herpesviridae Activity

François-Xavier Toublet [1], Maeve-Carmen Malanda-Samba [1], Manon Rouge [2], Sébastien Hantz [2], Sophie Alain [2] and Christelle Pouget [1]

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Flavonoids are natural compounds present in the plant kingdom and in our diet. They have numerous biological properties, including antioxidant, anti-infectious, anti-inflammatory and anticancer activities [298,301]. They comprise several classes, including chalcones which are the biosynthetic source of other flavonoids. Our research focuses on the design of new antiviral agents, against *Herpes simplex virus* (HSV) and *Cytomegalovirus* (CMV), from a chalcone base scaffold (Figure 63).

Currently the treatment of herpesvirus infections primarily relies on viral polymerase inhibitors. These molecules can have adverse effects, and their use can also lead to the emergence of resistance mutations. The recent development of antivirals such as letermovir

and maribavir against CMV, or pritelivir and amenamevir against HSV, provides avenues for research into the pharmacomodulation of chalcones by inhibiting other stages of the viral replication cycle.

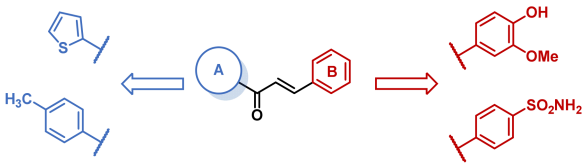


Figure 63. Pharmacomodulation of chalcones.

Many studies on flavonoids and chalcones (natural and synthetic) have demonstrated their effectiveness against Herpesviruses (including CMV and HSV) [302–304]. Thus, preliminary work carried out by the LABC*i*S team, in collaboration with the RESINFIT laboratory, enabled us to identify interesting groups on chalcone scaffold against the development of CMV [304]. Based on our previous results, tests involving the introduction of other substituents on the two aromatic rings are underway in order to identify key compounds that would be more active on HSV and/or CMV (Figure 63).

Authors are greatly thankful to University of Limoges for funding this project.

7.46. Biophysical Evaluation of IRE1α Inhibitors with Blood-Brain Barrier Permeability for Glioblastoma Adjuvant Therapy

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Glioblastoma (GB) is the most aggressive primitive cancer of the central nervous system (CNS). The current standard of care, the Stupp protocol, combines surgical resection when possible (~70% of patients), radiotherapy and temozolomide (TMZ)-based chemotherapy. However, cancer cells rapidly develop resistance to TMZ and tumor relapse, resulting in an average survival time of 12 to 18 months post-treatment [305]. Recent studies have highlighted the role of the unfolded protein response (UPR), an adaptive signaling pathway associated with the endoplasmic reticulum (ER) stress, in promoting cancer cell survival. This signaling pathway offers to cancer cells a mechanism to cope with cellular stress, notably through the main UPR sensor: the inositol-requiring enzyme type 1 α (IRE1) [306]. IRE1 is a highly conserved protein, which presents a dual serine/threonine kinase and endoribonuclease (RNase) activity. Inhibition of IRE1 activities has shown significant potential in resensitizing cancer cells to TMZ, making it a promising therapeutic target to overcome resistance in GB [306,307]. However, no IRE1 kinase inhibitor capable of crossing the blood-brain barrier (BBB) is currently available on the pharmaceutical market, partly due to the need for high membrane permeability—a critical requirement for effective drug delivery to the CNS.

In a previous study, our laboratories discovered and characterized Z4P as a first promising hit and first-in-kind BBB-permeable IRE1 inhibitor [308]. This compound demonstrated IRE1 inhibition in the micromolar range in vitro, prompted target engagement in vivo and most notably had a real impact as adjuvant with TMZ in an orthoptic xenograft murine GB model [308]. Chemical diversification around the Z4P scaffold was performed. However, in-house biological assays hindered the establishment of a clear mode of action and structure-activity relationships (SAR). We are currently focusing on developing complementary biophysical and biochemical assays applied to IRE1 to (1) provide insights into

its binding mode and (2) support the development of a quantitative SAR (QSAR) model, guiding the access to early lead based-Z4P analogs.

7.47. Applying Computer-Aided Drug Design (CADD) and Synthetic Methods to Target the NS3 Protein of West Nile and Zika Viruses

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Currently, zoonosis caused by Flaviviruses poses an ongoing global health threat. To date, no antiviral treatments are available [309]. The Flaviviridae family comprises many enveloped viruses, including Dengue (DENV, isoforms 1–4), West Nile, and Zika. These small spherical particles contain a single positive-sense genomic RNA that encodes three structural and seven non-structural proteins (NS) [310,311]. Among them, the NS3 complex (protease and helicase) is crucial for viral replication and represents a valid druggable target.

In our studies, we combine classical and advanced computational methods, such as structure- and ligand-based approaches, virtual screening (VS), conventional and accelerated molecular dynamics simulations (MDs), and dynophore, to identify new potential inhibitors capable of binding to different sites (catalytic or allosteric) and thereby altering the conformational equilibrium of the protein function. These multiple approaches mitigate the limitations of individual methods while enhancing the chemical diversity of the identified scaffolds. To date, we have identified more than 20 molecular hits exhibiting low micromolar inhibitory activity against the NS3 protease and helicase functions of both WNV and ZIKV viruses. This work represents a significant initial step in developing new broad-spectrum inhibitors for flaviviruses.

This research was supported by EU funding within the NextGenerationEU-MUR PNRR Extended Partnership initiative on Emerging Infectious Diseases (Project no.PE00000007, INF-ACT).

7.48. Ligand-Directed Labelling Probes for Covalent Labelling of A_1 Adenosine Receptors

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Ligand-directed (LD) labelling probes offer a novel approach to covalently label proteins of interest (POIs) using small molecules. An LD probe consists of three main components: a POI-selective pharmacophore, a cargo-transferring moiety, and a linker that connects these parts. The LD probe binds to the POI and transfers the cargo via nucleophilic substitution between a reactive moiety on the probe and a nucleophilic amino residue on the POI. After cargo transfer, the remaining probe dissociates from the POI, enabling a reporter system for further pharmacological assessment. Compared to self-labelling protein tags (e.g., SNAP-tag, Halo-tag) and fluorescent proteins (e.g., GFP), LD probes

eliminate the need for genetic engineering and offer smaller molecular tags, minimizing the impact on POI function. We synthesized two potent LD probes, based on Comeo's work (Figure 64), targeting A_1 adenosine receptors (A_1 ARs) with improved selectivity [312]. Covalent labelling was confirmed through in-gel fluorescent scans and confocal imaging. Additionally, we demonstrated that the orthosteric binding pocket of A_1 AR labelled with our probe remains accessible to other reversible fluorescent ligands and DPCPX (an A_1 AR selective antagonist) using bioluminescence resonance energy transfer (BRET) and fluorescence lifetime microscopy (FLIM). Furthermore, reversible fluorescent ligand affinity measured from NanoLuc-A_1 ARs with or without LD probe labelling showed no significant differences, indicating that our novel LD probes for A_1 ARs set a reporter without interfering with A_1 AR pharmacological characteristics.

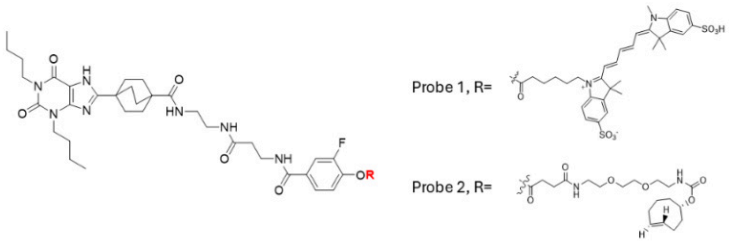


Figure 64. Ligand-directed (LD) probes synthesized by Comeo targeting adenosine A_1 receptors. The figure illustrates Comeo's original probes, which served as a template for synthesizing two analogues with improved selectivity.

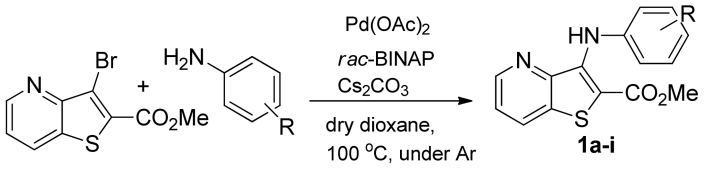
7.49. Synthesis of 3-(Arylamino)thieno[3,2-b]pyridines and Evaluation of Their Neuroprotective Activity on Transgenic C. Elegans for Machado-Joseph Disease

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Neurodegenerative diseases such as Machado-Joseph disease (MJD) are progressive clinical pathologies. MJD or spinocerebellar ataxia type 3 (SCA3) is the most common dominant inherited ataxia in the world and the second most common polyglutamine (polyQ) disease, after Huntington's disease. The genetic base of the MJD is the expansion of a polyQ tract within the protein ataxin-3 (ATXN3) [313]. Based on the antioxidant activity of di(hetero)arylamines, it was decided to prepare novel methyl 3-(arylamino)thieno[3,2-*b*]pyridine-2-carboxylates **1a-i**, by palladium-catalyzed Buchwald-Hartwig C-N cross-coupling (Figure 65) and evaluate their neuroprotective activity on transgenic *C. elegans* for MJD.



R = H, *o*-F, *m*-F, *p*-F; *o*-OMe, *m*-OMe, *p*-OMe; *o*, *p*-diOMe and *m*, *p*-diOMe

Figure 65. Synthesis of 3-(arylamino)thieno[3,2-*b*]pyridines by C-N Buchwald-Hartwig coupling.

The neuroprotective effects were tested in vivo using the nematode *Caenorhabditis elegans* (*C. elegans*) as model for MJD (AT3q130), where mutant ATXN3 leads to aggregation

and motility defects [314]. None of the di(hetero)arylamines were toxic to wild-type *C. elegans* at the tested concentrations. Only compounds with one OMe group in *ortho* or *para*, and two OMe groups in both positions, improved neuronal dysfunction caused by mutant ataxin-3 in *C. elegans* neurons, ameliorating the animals motor behavior using motility assays [314]. The dimethoxylated compound showed to be the most promising.

Thanks are due to FCT-Portugal for financial support to CQ-UM (UID/0686).

7.50. Synergistic Antifungal Effects of Dibenzofuran Derivatives and Fluconazole Against Resistant Candida Albicans

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Candida albicans is a major fungal pathogen causing serious infections in immunocompromised individuals and intensive care patients. Every year fungi are responsible for more than 1.5 billion infections worldwide. The limited arsenal of antifungal agents and the emergence of multidrug-resistant species necessitate the development of new therapies. One strategy is to find new compounds that improve or restore fungal susceptibility to existing antifungal agents [315,316].

Dibenzofurans are heterotricyclic organic complexes with furan ring ortho-fused across 2,3- and 4,5- positions of the two benzene rings. They have shown promise in antimicrobial and antifungal research [317]. In this study, we synthesized two original dibenzofuran derivatives [318], **CTN1381** and **CTN1382**, and evaluated their activity against six clinical isolates of *Candida albicans* using MIC determination, checkerboard assays for drug interactions, and in vitro PKC activity assays (Figure 66). *Galleria mellonella* model was used to confirm the synergistic effect between fluconazole and dibenzofurans in vivo.

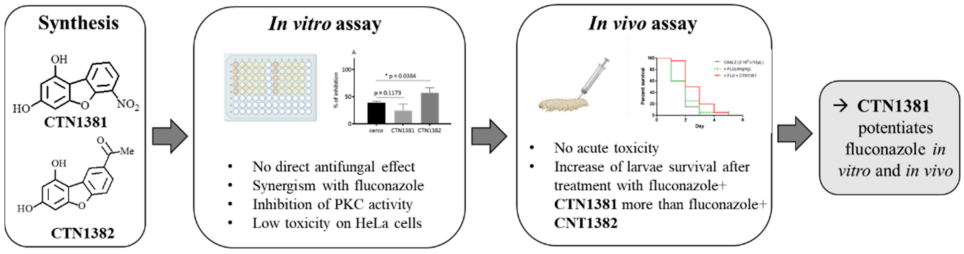


Figure 66. Schematic representation of the project main results.

Taken together, our results suggest that **CTN1381** and **CTN1382** potentiate the efficacy of fluconazole, possibly by inhibiting PKC, and offer a promising strategy against resistant *C. albicans* strains.

7.51. Bicyclic Lactams and Their Piperidine Analogues with Potent Antileishmanial Properties

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A major parasitic endemic that affects 98 countries, leishmaniasis remains one of the most neglected diseases in the world and affects the poorest populations, mainly in developing countries. Leishmaniases are chronic diseases with cutaneous (LC), mucocutaneous (LCM) and visceral (LV) manifestations [319,320]. According to estimates from the World Health Organization, 350 million people are at risk of contracting the disease and some 1.5 million new cases occur each year with a mortality of 30,000 to 40,000 people. In Senegal, in recent years, cases of canine leishmaniasis have been observed [321].

While leishmaniasis still represents a global scourge, new therapeutic tools are necessary to replace the current limited number of treatments that are expensive, difficult to administer, which induce numerous side effects and for which resistance is increasingly worrying. The main objective of this study is to synthesize new classes of low-toxic molecules with low side effects, low cost and greater speed of action. In the process of searching for new classes of antileishmanial molecules, we identified bicyclic lactams and their piperidine analogues as interesting and original central cores (Figure 67). To obtain these scaffolds, we have developed synthetic reactions involving asymmetric Michael reactions and lactamization. The compounds have been tested for their intramacrophagic antileishmanial properties on *L. major* (LC) and *L. donovani* (VL) strains and display promising activities associated with a low toxicity towards macrophages. In addition, their pharmacological and pharmacokinetic properties (ADME) were studied. All the encouraging results will be presented and discussed.

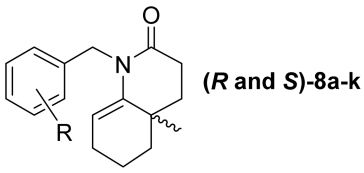


Figure 67. Structure of bicyclic lactams **8a-k**.

7.52. Modulation of Positions 2 or 8 of the Imidazo[1,2-a]pyrazine Lead CTN1122 Influences Its Antileishmanial Properties, L-CK1.2 Kinase Inhibition and Its 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** [322–324] which targets a specific *Leishmania* Casein Kinase 1 protein (L-CK1.2) and demonstrates strong antileishmanial properties. In this context, we have decided to synthesize **CTN1122** analogues to enhance the pharmacological activity profile with low toxicity (Figure 68).

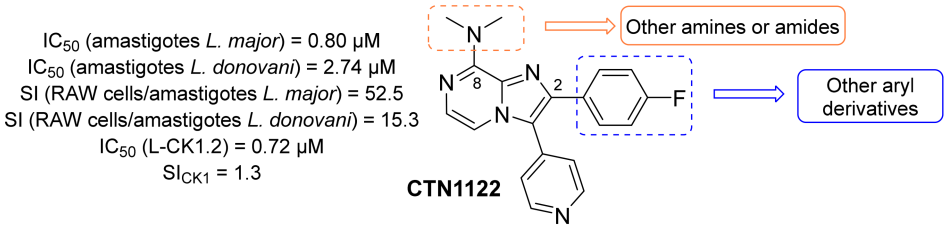


Figure 68. Modulations from the lead compound **CTN1122**.

8. Conclusions

For the first time, the GP_2A conference was jointly organized in collaboration with the COST Action OneHealth*Drugs* and the Paul Ehrlich MedChem Euro-PhD Network. This edition, returning to Nantes, France after an 11-year interval, was successfully held at the School of Pharmacy.

We acknowledge the outstanding support of our sponsors, namely Nantes Université, CEM, BUCHI, DDC–MDPI, AM Technology, RSC Medicinal Chemistry, RSC Pharmaceutics, AFECT, Atlanchim Pharma, Macherey-Nagel and Eurisotop.

The 34th GP_2A Conference on Medicinal Chemistry will be held at the Department of Chemistry and Molecular Biology at the University of Gothenburg, Sweden—26–28 August 2026.

The XVth Paul Ehrlich MedChem Conference has been held at the at the Hotel Flamingo Resort in Santa Margherita di Pula (CA), Italy, organized by the "CADD, Synthesis and Extraction of Bioactive Compounds MedChem" research group with the support of the University of Cagliari (UNICA)—20–22 May 2026.

Author Contributions: All authors contributed to compiling and formatting the conference abstracts and all authors approved the submission of the final manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data available on request from the respective authors.

Conflicts of Interest: The authors declare no conflicts of interest.

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