NEW APPROACHES IN DRUG DISCOVERY: **EXPANDING HORIZONS FOR THERAPEUTIC SOLUTIONS**

XXI

NATIONAL MEETING
of the Spanish Society of
MEDICINAL CHEMISTRY
JUNE 15-18, 2025 · SEVILLE

Sociedad Española de
Química Terapéutica
SEQT

BOOK OF ABSTRACTS

INDEX

WELCOME

Dear Colleagues,

It is our great pleasure to invite you to the XXI National Congress of the Spanish Society of Medicinal Chemistry (SEQT), which will take place from June 15th to 18th, 2025, in the beautiful city of Seville, Spain.

This congress will bring together leading scientists from around the world to share their latest research and insights into the most cutting-edge areas of medicinal chemistry. The event will cover a wide range of topics in drug discovery, with a focus on translational medicinal chemistry and sustainable solutions to global health challenges. The scientific program will include plenary and keynote lectures, oral presentations, poster sessions, and discussions on emerging topics in our field, fostering collaboration and the exchange of ideas among experts and young researchers alike.

The program will be enriched by a trade exhibition and a vibrant social agenda. Seville, with its stunning monuments such as the Giralda, the Alcázar, and the Plaza de España, offers an inspiring backdrop for this event. Its rich cultural heritage, combined with its lively atmosphere and renowned Andalusian hospitality, will make your stay both scientifically rewarding and culturally enriching.

We look forward to welcoming you to this exceptional event, where scientific excellence and cultural discovery will go hand in hand. Your participation will contribute to the success of this important event, and we encourage you to engage actively in what promises to be an unforgettable experience.

Warm regards,

The Organizing Committee

BACK TO MAIN INDEX

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BACK TO MAIN INDEX

OPENING CONFERENCE

DISCOVERY AND DEVELOPMENT OF A MALE PILL BY TARGETING THE RETINOID SIGNALING PATHWAY WITH YCT-529 FOR EFFECTIVE, REVERSIBLE ORAL CONTRACEPTION

Gunda I. Georg [1]

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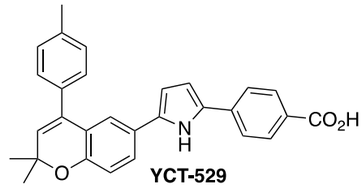
To lower the high levels of unintended pregnancies observed worldwide, additional effective contraceptive methods for women and men are desirable. Multiple contraceptive methods are available for women; however, male contraception options are limited to condom use and vasectomy. A novel male birth control method would provide an alternate method for family planning and lessen the gender gap in contraceptive responsibility. Hormonal male contraceptives have been investigated for many years, but no drug has reached the market yet. Therefore, investigations have been initiated in several laboratories to discover non-hormonal contraceptive agents. The talk will discuss the discovery and development of a selective retinoic acid receptor alpha antagonist, including preclinical efficacy studies of the clinical candidate YCT-529 in mouse and non-human primates and initial results from the first non-hormonal male contraceptive to reach the clinical stage.



YCT-529

	α	β	γ
IC_{50} (nM)	9.7	> 3500	>35000
	no agonist activity		

Acknowledgements

We would like to acknowledge for funding support the National Institutes of Health, NICHD Contraception Research Branch, USA, and Your Choice Therapeutics, USA.

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PLENARY LECTURES

PL - 02

PRECISION TOOLS IN IMMUNOTHERAPY OF HEMATOLOGICAL MALIGNANCIES: ADVANCES IN CAR-T CELL THERAPIES AND SYNTHETIC SINGLE-DOMAIN ANTIBODY DEVELOPMENT

Franco Bernasconi-Bisio [1, 7], Vianca Ibarra-García [1, 7], Federica Rochira [1, 7], Inés Ibáñez [1, 7], Iñigo Azagra [1, 7], Javier Marañón [1, 7], Eva Molina [1, 7], Saray Rodriguez-Diaz [2], Rebeca Martinez-Turrillas [2, 8], Lucia Vanrell [3, 4], Juan J. Lasarte [6, 7], Ana Alfonso-Pierola [5, 7, 8], Paula Rodriguez-Otero [5, 7, 8], Jesus San Miguel [5, 7, 8], Juan R. Rodriguez-Madoz [2, 7, 8], Felipe Prosper [2, 5, 7, 8], **Antonio Pineda-Lucena** [1, 7]

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Chimeric Antigen Receptor (CAR) T-cell therapies have revolutionized the landscape of hematological malignancy treatment, yet challenges remain in achieving durable responses and expanding their applicability. Our research addresses these critical needs by exploring novel CAR-T constructs and developing a versatile synthetic single-domain antibody (sdAb) library.

A significant part of our work has focused on improving CAR-T efficacy against Acute Myeloid Leukemia (AML) by targeting CD33. We have identified and characterized several novel sdAb-based CAR-T cells with varying affinities for CD33. Crucially, these sdAb-based CAR-T cells demonstrated superior anti-tumoral efficacy *in vivo* compared to traditional scFv-based CAR-T cells currently undergoing clinical evaluation. Interestingly, our findings suggest that CAR-T cells with moderate to high affinity exhibit better anti-tumoral responses. These results highlight the potential of sdAb-based CAR-T cells as a promising therapeutic option for AML.

In parallel, we have investigated innovative sdAb-based CAR-T cells targeting BCMA for the treatment of Multiple Myeloma (MM). Our studies have shown that certain sdAb-based CAR-T cell candidates not only matched but, in some cases, surpassed the anti-tumoral efficacy of currently approved BCMA-directed CAR-T therapies like ide-cel and cilta-cel, leading to improved survival rates in preclinical models. Mechanistic insights from affinity studies and single-cell transcriptomics reveal distinct expansion kinetics and gene programs underlying their differential functionality. Unexpectedly, combining multiple sdAbs into a biparatopic construct, while effective for existing therapies, can lead to reduced efficacy in our sdAb-based CARs due to altered binding kinetics. This underscores the importance of carefully designed and characterized binders for optimal CAR-T performance.

Underpinning these advancements is our ongoing endeavor to generate a comprehensive synthetic library of sdAbs. This innovative approach aims to provide a novel platform for the rapid and efficient discovery of high-affinity binders suitable for diverse immune-based therapies, including Antibody-Drug Conjugates (ADCs) and next-generation CAR-T cell constructs. This synthetic library holds the promise of accelerating the development of precision immunotherapies by offering a vast repertoire of specific and potent targeting agents.

This lecture will delve into the detailed preclinical data supporting these findings, discuss the mechanistic insights gained, and outline the future directions for translating these advanced CAR-T strategies and synthetic sdAb tools into effective clinical treatments for patients with hematological malignancies. We believe these developments represent a significant step forward in the quest for more precise and durable immunotherapeutic interventions.

PL - 03

UNLOCKING TARGETED PROTEIN DEGRADATION FOR NEGLECTED TROPICAL DISEASES

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Neglected tropical diseases (NTDs), continue to pose significant public health challenges in developing regions, as emphasized by the WHO's 2021–2030 Roadmap on NTDs. Leishmaniasis, an infectious NTD caused by *Leishmania* parasites, manifests primarily in two forms: cutaneous leishmaniasis (CL), and visceral leishmaniasis (VL), which is potentially fatal if left untreated. VL presents a critical health threat in low-income areas and is increasingly spreading to due to environmental changes to Southern Europe. With approximately one million new cases annually and limited treatment options, leishmaniasis remains severely underfunded, highlighting the urgent need for novel drug development.

Similarly, other vector-borne NTDs caused by Flaviviruses—such as Dengue, West Nile Virus, and Zika—can trigger severe illnesses and even epidemics. Despite their public health impact, efforts to develop effective treatments or vaccines for these infections have been minimal. Without proactive mea sures, these viruses risk escalating into future pandemics, echoing the global crisis witnessed with COVID-19.

In response to the urgent need for intensified drug discovery, academia plays a crucial role by pursuing innovative and high-risk approaches to uncover novel therapeutic strategies for NTDs. One such promising avenue is the use of Proteolysis Targeting Chimeras (PROTACs)—bifunctional molecules capable of selectively degrading target proteins through the ubiquitin–proteasome system (UPS).[1] PROTACs have shown success in degrading various proteins, including those involved in viral infections, primarily by harnessing the human UPS machinery. However, their application to a broader range of pathogens and diseases, including parasitic infections, remains largely unexplored.

In this presentation, we introduce a proof-of-concept chemical strategy employing PROTAC-like bifunctional molecules to induce targeted degradation of TR proteins in *Leishmania infantum* by engaging the parasite's own UPS. Additionally, we propose a novel application of the PROTAC approach to target the viral NS2B-NS3 protease—offering a potentially transformative strategy in the fight against flavivirus infections.

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BACK TO MAIN INDEX

KEYNOTE LECTURES

KN - 01

CASE STUDIES IN MEDICINAL CHEMISTRY: THE DISCOVERY OF WEE1 AND BRPF1 INHIBITORS

Tilly Bingham [1] Mandy Watson [2], Tom Pesnot [2], Andrew Scott [2], Anthony Huxley [2], Gary Nelson [2], Montserrat Shelbourne [2], Jen Morton [2], Sandeep Pal [2], Zandile Nare [2], Vincenzo A. Rao [2], Brian O. Smith [3], Ian Morrison [2], Edward A. Fitzgerald [4]

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The medicinal chemistry discovery of tool compounds which can be used to interrogate the biological significance of a receptor in disease is a vital part of drug discovery. This talk will highlight two case studies which take different approaches to the task of identifying a novel inhibitor; rational design or machine learning.

TP53-deficient cells depend on WEE1 to arrest the cell cycle which allows for DNA repair and survival. Inhibiting WEE1 can selectively sensitize these tumors to DNA-damaging therapies. Adavosertib, a WEE1 inhibitor, has been widely used to study WEE1 biology. However, adavosertib shows unexpected single-agent antiproliferative activity and our hypothesis was that this could be due to off-target activity at PLK1. Through structure-based drug design, we developed novel WEE1 inhibitors with high selectivity over PLK1, allowing clearer differentiation of WEE1-specific effects. These findings suggest that adavosertib's action is not solely WEE1-dependent.

In a contrasting approach we developed BioPhysical and Active Learning Screening (BioPALS); a rapid and versatile hit identification protocol, combining AI-powered virtual screening with a GCI driven biophysical hit confirmation workflow. Its application to the BRPF1b bromodomain afforded a range of novel micromolar binders with favorable ADMET properties. Binding kinetics were determined, and binding topologies predicted for all hits.

Acknowledgements

This work was performed at Concept Life Sciences.

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KN - 02

FIRST SELECTIVE NANOMOLAR INHIBITORS OF ERAP2 IN AUTOIMMUNE DISEASES

Rebeca Deprez

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ERAP1 and ERAP2 are zinc aminopeptidases playing a key role in the antigen presentation pathway. These enzymes trim peptide precursors resulting from proteins degradation by the proteasome and generate mature antigens for presentation by major histocompatibility complex class I (MHCI) molecules. The cytotoxic T-cells recognition of the cell surface peptidome triggers immune response. Thereby ERAPs are major regulators of adaptive immune responses acting upstream current therapeutic strategies targeting cytokines, immune checkpoints or downstream signalling pathways.

In particular, ERAP2 is a risk factor for three MHC-I associated diseases: ankylosing spondylitis, birdshot chorioretinopathy and psoriasis. Also, ERAP2 expression in tumors can facilitate immune evasion and predicts the overall survival in cancer and low levels of ERAP2 can be associated with improved response to anti-PD-L-treated patients.

We describe hereafter the discovery of the first ERAP2 ligands by Kinetic-target guided synthesis and the optimization leading to the unprecedented nanomolar ERAP2 inhibitors with outstanding selectivity. Potency and selectivity data are interpreted using 3 X-ray structures of enzyme-complexes of inhibitors with increasing potency and selectivity. Cellular activity and target engagement as well as in vivo pharmacokinetics and pharmacodynamics qualify the best compounds from this series for use as new therapy in autoimmune diseases.

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BACK TO MAIN INDEX

KN - 03

STRUCTURE-GUIDED DESIGN OF GLYCOPEPTIDES FOR CANCER DIAGNOSIS AND THERAPY

Francisco Corzana

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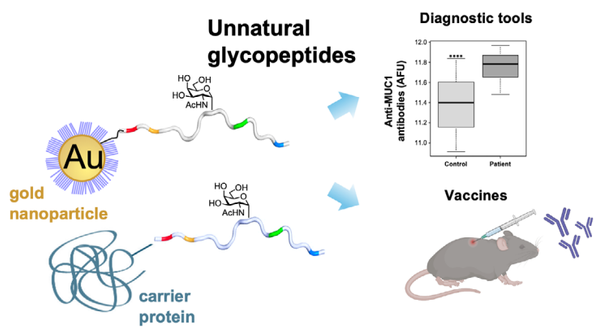
Mucin-1 (MUC1) is a transmembrane glycoprotein that is highly *O*-glycosylated and is predominantly expressed on the surface of epithelial cells. In healthy tissue, MUC1 is characterized by a dense arrangement of complex oligosaccharide structures. In malignant cells, however, both the expression and the glycosylation profile of MUC1 are significantly altered: The protein is overexpressed and exhibits predominantly simple, truncated carbohydrate units[1]. Recent studies have demonstrated the presence of anti-MUC1 antibodies in patients with early stage cancer[2]. To exploit this potential, we have developed artificial MUC1 glycopeptides using a structure-guided approach with artificial amino acids and chemically modified carbohydrates. Our strategy integrates NMR, molecular dynamics simulations, X-ray crystallography and binding assays to optimize both the antigenicity and structural stability of the glycopeptides. The selected modified glycopeptides are conjugated with gold nanoparticles or carrier proteins. These conjugates serve a dual purpose: as cancer vaccine candidates that elicit robust immune responses in mouse models[1,3], and as diagnostic probes for the detection of pancreatic cancer with higher sensitivity and specificity compared to currently available clinical biomarkers[2].



Acknowledgements

We would like to acknowledge for the funding support to *Agencia Estatal de Investigación* (AEI, RTI2018-099592-B-C21, PDC2022-133725-C21), the AECC (INNOVA 2023 and PhD contracts) and Universidad de La Rioja (REGI22/47 and REGI22/16).

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KN - 04

GLYCANS AS REGULATORS OF IMMUNE RESPONSE IN INFLAMMATION, AUTOIMMUNITY AND CANCER: FROM DISEASE PREDICTION TO THERAPEUTIC OPPORTUNITIES.

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The mechanisms underlying the genesis of the loss of immunological tolerance in autoimmunity or the creation of immunosuppressive networks in cancer are still elusive. Glycans have been highlighted as essential determinants that integrate the regulatory networks that guide both innate and adaptive immune responses (Pinho, Cell Mol Immunol 2023). Glycans act as master regulators of the inflammatory response being fundamental molecular determinants for the discrimination between “self” and “non-self” (Alves, FEBS Lett 2022). Our results in Systemic Lupus Erythematosus (SLE), a classical autoimmune disease, revealed that patients with lupus nephritis exhibit at kidney cell surface a unique glycan signature characterized by an increased abundance and spatial distribution of unusual mannose-enriched glycans (Alves I, et al. Arthritis and Rheumatology 2021) that was found to be recognized by specific glycans-recognizing receptors, expressed by gdT cells, culminating in the activation of pro-inflammatory pathways associated with autoimmunity (Alves I, et al. Science Trans Med 2023). Accordingly, our recent results in Inflammatory Bowel Disease (IBD), in which a series of preclinical serum samples were analyzed up to 6 years before IBD diagnosis, revealed the identification of a unique glycosylation signature on circulating antibodies (IgGs) characterized by lower galactosylation levels of IgG Fc domain that was detected many years before diagnosis. This specific IgG Fc glycan trait correlated with increased anti-microbial antibodies, specifically with anti-Saccharomyces cerevisiae antibody (ASCA) levels, pinpointing a glycome-ASCA hub, detected in serum, that predates by years the development of CD. Mechanistically, we demonstrated that this glycoform of ASCA IgG, elicits a pro-inflammatory immune pathway through the activation and reprogramming of innate immune cells (such as DCs and NK cells), via FcγR-dependent mechanism, triggering NF-kB and CARD9 signaling and leading to inflammasome activation. Adoptive transfer of ASCA IgG to recipient WT mice resulted in increased susceptibility to intestinal inflammation that was recovered in recipient FcγR KO mice (Gaifem, Rodrigues, et al Nature Immunology, 2024). Together these results unlock the identification of a pathogenic glyco-hub that may constitute a promising new serum biomarker for CD prediction and a potential target for disease prevention.

At the other pole of the immune response, in a cancer context, where immunosuppressive networks promote cancer progression, we also demonstrated the immune-regulatory properties of glycans. We showed that complex branched N-glycans structures, typically overexpressed by cancer cells, are used by colorectal tumor cells to escape immune recognition, by instructing the creation of immunosuppressive pathways through inhibition of IFNγ production. The removal of this “glycan-mask” was found to expose immunogenic glycans that potentiate immune recognition through DC-SIGN-expressing immune cells resulting in an effective anti-tumor immune response (Silva M & Fernandes A, et al. Cancer Immunology Research 2020). In summary, glycans exert powerful immunoregulatory properties governing both innate and adaptive immune responses with important roles in the pathogenesis of major diseases such as cancer and autoimmunity, pinpointing glycans as key checkpoints with promising clinical and therapeutic applications in autoimmune diseases and cancer.

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BACK TO MAIN INDEX

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Cancer Immunol Res. 2020 Nov;8(11):1407-1425.

KN - 05

DISCOVERY AND OPTIMIZATION OF A NEW CLASS OF RIPK1 INHIBITORS ENABLED BY LATE-STAGE PHOTOREDOX CATALYSIS

María Méndez Pérez

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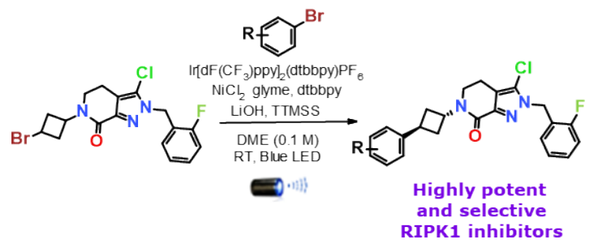
Receptor Interacting Protein Kinase 1 (RIPK1) plays a crucial role in regulating necroptosis and inflammation and the potential therapeutic benefits of RIPK1 inhibitors are being investigated in several clinical trials.[1,2] We will describe the discovery and optimization of a new series of highly potent and selective RIPK1 inhibitors, that were identified by combining structure-based approaches, free-energy perturbation (FEP+) and state-of-the-art machine learning approaches for property predictions. Using X-ray crystallography, we could confirm that the inhibitors bind as allosteric type III inhibitors, thereby not contacting the kinase hinge region. We will illustrate how a C(sp^3)-C(sp^2) photochemical transformation was a key enabler for the efficient SAR exploration and profile optimization.



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BACK TO MAIN INDEX

KN - 06

ADVANCES IN AUTOMATED SYNTHESIS: THE ROLE OF AI IN DRUG DEVELOPMENT

Carolina Alhambra

Director Research and Group Leader of Automated Synthesis and Analytical Technologies en Eli Lilly

Small molecule drug discovery involves demanding physical sample processing and data management. While areas like Sample Management and Quantitative Biology have significant standardization and laboratory automation, chemical synthesis, workup, and purification have fewer technology platforms due to the complexity and variability in generating new molecular matter. At the Eli Lilly Alcobendas site, the Global Discovery Automation Group has designed and implemented the Optimization and Parallel Synthesis Laboratory (OPSL), combining liquid handling automation platforms, custom-developed hardware, and bespoke software to enable workflows that facilitate rapid, efficient, and cost-effective SAR exploration and chemical synthesis optimization.

In recent years, the integration of artificial intelligence (AI) into automated synthesis workflows has significantly transformed drug discovery. AI-driven platforms enhance the efficiency and accuracy of chemical synthesis processes by optimizing reaction conditions, predicting successful synthetic routes, and automating purification processes. The combination of AI and automation in chemical synthesis is paving the way for more streamlined and scalable workflows, driving innovation and accelerating drug discovery.

KN - 07

QUANTUM DOTS AND PEPTIDE-BASED PROBES FOR THE UNDERSTANDING OF NEURODEGENERATIVE DISEASES

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Neurodegenerative diseases, characterized by a progressive neuronal loss, present complex molecular mechanisms and pose significant challenges for the discovery of effective therapies.[1] Due to the heterogeneity of each of the diseases and the lack of biomarkers of cellular functionality, the discovery of effective therapies is a remarkable challenge. The use of models of disease derived from patients enable to study in a personalized manner the pathologies and find tailored effective treatments.[2]

Recent advances in nanotechnology and chemical biology offer new opportunities to unravel these complexities, both for disease characterization and drug-candidate evaluation. In this talk, I will discuss the development and application of Quantum Dots (QDs) and peptide-based probes as innovative tools for investigating neurodegenerative processes. QDs, with their exceptional luminescent properties and versatility in biomolecular conjugation, enable real-time visualization of molecular targets and dynamic monitoring of enzyme activity within neural environments.[3] Complementing these, peptide-based probes enhance the specificity and efficacy of molecular imaging. Finally, the combination with state-of the art models of disease, derived from patients, provides a powerful platform to study disease and disease-modifying drug candidates. By integrating these approaches, our research aims to provide deeper insights into disease mechanisms and facilitate the discovery of novel therapeutic strategies for neurodegenerative disorders.

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BACK TO MAIN INDEX

KN - 08

TRYPANOSOME ALTERNATIVE OXIDASE INHIBITORS WITH BROAD-SPECTRUM ACTIVITY AGAINST AFRICAN ANIMAL TRYPANOSOMES: FROM ORTHOSTERIC TO ALLOSTERIC INHIBITION

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Trypanosomes are protozoan parasites of humans and livestock which, depending on the species, cause human African trypanosomiasis (HAT or sleeping sickness) and/or Animal African Trypanosomiasis (AAT). HAT and AAT are diseases with major clinical and economic impacts in many parts of sub-Saharan African countries; both can be fatal if not treated. AAT on the other hand is not limited to tropical regions of Africa, but is also endemic in South America, and parts of Asia. It is caused by several trypanosome species notably *T. b. brucei, T. congolense, T. vivax, T. evansi, and T. equiperdum.* While human trypanosomiasis and most animal trypanosomiasis in Africa is transmitted by tsetse flies, *T. vivax*, *T. equiperdum* and *T. evansi* do not depend on tsetse vectors and consequently have a wide range of distribution throughout the world.[1]

Throughout their life cycle, the energy metabolism of trypanosomes adapts to the available nutrients in their environment. Consequently, the procyclic forms of the parasite, located in the midgut of the tsetse fly vector (a glucose-poor environment), have a fully functional respiratory chain and synthesize ATP via oxidative phosphorylation in the mitochondrion. In contrast, the long slender bloodstream trypomastigotes of *T. brucei*, present in the mammalian bloodstream, depend entirely on glycolysis for their energy production.[2]

The glucose-dependent respiration of bloodstream forms of the parasite *Trypanosoma brucei* depends on an unusual and essential mitochondrial electron-transport system, consisting of glycerol-3-phosphate dehydrogenase and the trypanosome alternative oxidase (TAO). Because TAO has no counterpart in any mammalian host, and because it is essential for the viability of bloodstream trypanosomes, TAO is considered an excellent target for chemotherapy.[3]

Our efforts to develop potent mitochondrion-targeted TAO inhibitors based on simple chemical structures such as 2,4-salicylhydroxamate (SHAM) and dihydroxybenzoate (2,4-DHB)[2,4-7] scaffolds were rewarded with the discovery of a TAO inhibitor displaying broad-spectrum activity against African Animal Trypanosomes. Mode of action studies revealed a surprising new allosteric mode of inhibition.[8]

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KN - 09

COMBINATION THERAPY FOR CHAGAS DISEASE – PYRROLOPYRIMIDINE SERIES

Maria Marco [1], Stéphanie Braillard [2], John Thomas [3], Richard Wall [3], Sandra Carvalho [3], Lorna MacLean [3], Christy Paterson [3], Laste Stojanovski [3], Susan A. Charman [4], Martine Keenan [5], Vicky M. Avery [6], John Kelly [7], Manu De Rycker [3], Susan Wyllie [3], Timothy J. Miles [1], Eric Chatelain [2], Kevin Read [3] and Silvia Gonzalez [1]

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Chagas disease or American trypanosomiasis is a potentially life-threatening disease caused by *Trypanosome cruzi*. It is estimated that 6-7 million people are infected with *T. cruzi*, mostly in Latin American countries where the disease is endemic.

T. cruzi infection is curable if treatment is initiated soon after infection, during its acute phase, benznidazole and nifurtimox being the only available treatments. However, treatments are long (up to 2 months), efficacy diminishes the longer a person has been infected and nearly all of treated adult patients suffer from adverse reactions, some of which can lead to interruption of the treatment. Additionally, neither benznidazole nor nifurtimox should be taken by pregnant women nor people with kidney or liver failure. Hence, oral, efficacious, shorter and safer treatments for Chagas disease are urgently needed. Combination therapy is attractive since it can

- Improve treatment efficacy
- Reduce dose and/or duration resulting in fewer adverse effects for current standard of care
- Is a validated approach for anti-infectives

In our search for novel and shorter treatments for Chagas disease, and in collaboration with university of Dundee and Drugs for Neglected Diseases initiative (DNDi), we optimized a chemical series that originated from our phenotypic *in vitro* screening of 1.8M molecules [Peña, I *et al. Sci Rep* 5, 8771 (2015) that led to the identification of TCMDC-143610. This pyrrolopyrimidine series is active across different kinetoplastid parasites, such as *Leishmania spp* and *T. cruzi* with a novel mechanism of action. Initial hit was optimized improving its potency and metabolic stability profile enabling progression to a bioluminescent Chagas *in vivo* model [Lewis, M. D *et al*. *Cellular microbiology* vol. 16,9 (2014): 1285-300]. Compounds from this chemical series were able to show no relapse in mice after just 5 days of treatment in combination with a suboptimal dose of benznidazole opening the door to short treatments for Chagas disease.

"All animal studies were ethically reviewed and carried out in accordance with Animals (Scientific Procedures) Act 1986 and the GSK Policy on the Care, Welfare and Treatment of Animals."

Keywords:
Chagas, combination, *cruzi*, pyrrolopyrimidine

BACK TO MAIN INDEX

KN - 10

IMPROVING NATURE'S ANTIBIOTICS THROUGH (SEMI) SYNTHESIS

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The discovery and development of next-generation antibiotics with enhanced activity, reduced toxicity, and the capacity to overcome resistance is a challenge of growing societal significance. In addressing this challenge, the Martin group applies chemistry-based strategies to enhance the properties of structurally diverse naturally occurring antibacterials. To this end we recently reported a new class of highly potent semisynthetic glycopeptide antibiotics with enhanced activity against a range of Gram-positive pathogens including clinically relevant strains of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile*.[1]

This lecture will cover the design and synthesis of these improved antibiotics as well as the biochemical and biophysical techniques used to characterize their mechanisms of action. In addition, assessment of the *in vivo* activity of these new antibacterial agents in established infection models will also be presented.

Acknowledgements

Financial support provided by the European Research Council (ERC CoG to NIM, grant agreement no. 725523), Netherlands Scientific Organization (NWO NACTAR project number 18504), and the German Research Foundation (DFG, Project-ID 398967434 – TRR 261).

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KN - 11

PUT A GUANIDINIUM IN YOUR LIFE (OR HOW WONDERFUL IS THE GUANIDINIUM CATION FOR DIFFERENT APPLICATIONS!)

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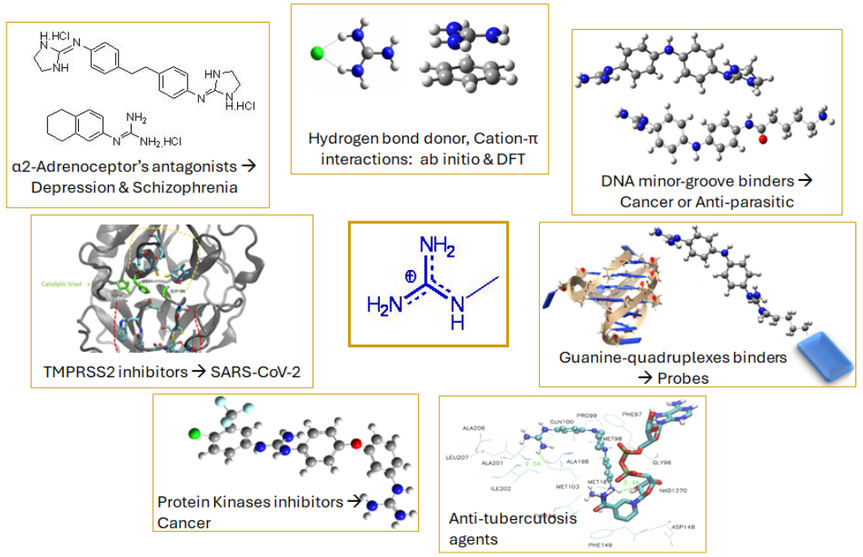
Guanidinium is a very versatile cation with very interesting properties. On the one hand, in physiological conditions is a strong base with pK_{aH} values between 8-10 (the simple guanidinium cation has a pK_{aH} of 13.6).[1] Besides, its structure is planar around the central C atom and like a propeller for the six H atoms attached to the N atoms. This cation is present in many drugs in clinic such as metformin, zanamivir, chlorhexidine, or guanabenz and its derivatives have found application as anticancer, antibacterial, antifungal, antiprotozoal, antithrombotic and antiviral therapeutics. In this communication, the design, preparation and evaluation of different guanidinium derivatives are presented framed within different therapeutic applications, i.e. alpha2-adrenoceptor ligands, DNA binders (in the minor groove or in G-quadruplexes) with application in cancer or antiparasitic activity, kinase inhibitors or anti-tuberculosis therapies.[3]



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BACK TO MAIN INDEX

KN - 12

COMPUTATIONAL INSIGHTS INTO BIOLOGICAL PROCESSES

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The computational simulation of biological processes is a complex task which requires the combination of different quantum and classical mechanical approaches to describe the intermolecular interactions and the molecular motion. In this contribution, different biological events recently investigated by our research group MoBioChem will be discussed, including the permeation of small molecules across lipid membranes and the binding of drugs to DNA and proteins.

KN - 13

SUGARS MEET SULFUR: FROM SMALL MOLECULES TO FUNCTIONAL GLYCO- NANOMATERIALS / QUIMIOTECA CSIC (QCSIC)

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Carbohydrates are vital biopolymers involved in numerous biological processes, including cell signaling, adhesion, immune response, and tumor progression. A hallmark of carbohydrate- mediated recognition is its dependence on weak, non-covalent interactions—particularly carbohydrate–carbohydrate and carbohydrate–protein binding—which are significantly amplified through multivalent presentation. Replicating this multivalency is a central goal in glycodrug design. Simultaneously, the biological performance of nanomaterials is strongly influenced by their size, shape, and surface properties. Yet, achieving precise synthetic control over these features remains a major challenge.

In this talk, we present our modular design strategies using thioglycosides as versatile building blocks for the controlled synthesis of nanostructured glycomaterials. These include glyconanotubes,[1] liposomes, micelles,[2] hydrogels,[3] metal-organic frameworks (MOFs),[4] and a novel class of disc-shaped structures called glyconanosomes.[5] These architectures mimic the multivalent glycan display of cell surfaces, enabling selective interactions with biological receptors. As a result, they show promise in pathogen detection, 3D cell culture, and targeted theranostics for liver and prostate cancers.

The final part of the lecture will highlight the CSIC Chemolibrary (QCSIC), a strategic academic platform for drug discovery

Acknowledgements

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BACK TO MAIN INDEX

KN - 14

STRUCTURE-, VALENCY-, AND STIMULI-RESPONSIVE GLYCOMIMETICS IN BIOLOGY AND MEDICINE: TARGETING ENZYMES, LECTINS, AND IMMUNE MEDIATORS

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Glycomimetics incorporating the endocyclic nitrogen of iminosugars into a pseudoamide linkage, exhibiting pronounced sp^2 hybridization, are termed *sp^2-iminosugars*. This structural modification enables glycosidation-like reactivity via acyliminium intermediates, allowing these compounds to mimic not only the structure but also the reactivity of natural monosaccharides. Their "chemical mimicry" expands their potential to modulate enzyme affinity with high precision and to target receptors and antibodies that recognize glycans and glycohybrid biomolecules, including glycopeptides or glycolipids. Beyond structural design, sp^2-iminosugars can be adapted into stimuli (pH, light, temperature)-responsive platforms, enabling fine-tuned interactions with pharmacological targets requiring strict spatiotemporal regulation. Their capacity to reproduce multivalency, a hallmark of carbohydrate-protein interactions, further enhances their biological relevance. Recent applications include therapeutic strategies in neurodegenerative diseases such as lysosomal storage disorders Alzheimer's disease, recognition of tumor-associated carbohydrate antigens, selective targeting of human C-type lectins in antigen-presenting cells, and modulation of innate immune responses. This presentation will highlight representative examples that illustrate the broad potential of sp^2-iminosugars as structure-, valency-, and stimuli-responsive glycomimetics in biology and medicine.[1-5]

Acknowledgements

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KN - 15

DESIGN AND BIOLOGICAL EVALUATION OF NEW HETEROCYCLIC FAMILIES OF TOPOISOMERASE I INHIBITORS WITH ANTIPROLIFERATIVE POTENTIAL

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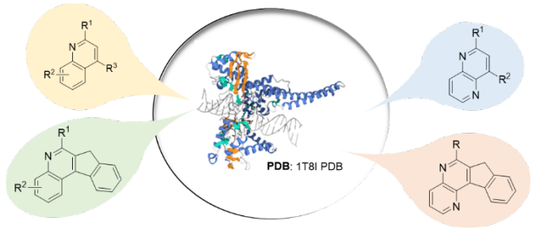
Over the years, a great effort has been made to discover and develop new anticancer drugs. And among those, topoisomerase I (Top1) inhibitors have gained attention due to their effectiveness in targeting cancer cells, which often overexpress Top1—a crucial enzyme involved in DNA replication and transcription.[1] Among the natural anticancer drugs targeting Top1, the most representative one is camptothecin (CPT)[2], however, its clinical potential has been limited by poor pharmacokinetic properties.[3]

To address these limitations, our research group has focused on designing, synthesizing, and evaluating new heterocyclic compounds that target Top1. Inspired by camptothecin, we explored various chemical scaffolds, including quinoline, naphthyridine, pyridopyrimidine, and phenanthroline derivatives. Through structure-activity relationship (SAR) studies, molecular modeling, and a range of in vitro biological assays—such as enzyme inhibition, DNA interaction, and cell viability tests—we assessed the antiproliferative potential of these compounds.

This comprehensive approach led to the identification of the most promising structures, which now serve as lead candidates for further optimization and preclinical development. The integration of chemical, biological, and computational data has been key in deepening our understanding of Top1 inhibition and guiding the design of next-generation anticancer agents with improved efficacy and safety.



Acknowledgements

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BACK TO MAIN INDEX

KN - 16

INHIBITION OF PLASMEPSIN X: A PROMISING STRATEGY AGAINST MALARIA

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Malaria remains a serious mosquito-borne disease, with an estimated 263 million cases and 597,000 deaths worldwide in 2023, predominantly affecting small children in Africa [1]. The constant need for novel antimalarial medicines is driven by the emergence of resistance to existing therapies. PMX, an essential aspartyl protease of the malaria parasite, has been identified as a potential multistage drug target. It plays a crucial role in parasite egress, invasion of erythrocytes, development of functional liver merozoites, and blocking transmission to mosquitoes [1].

UCB, in collaboration with Medicines for Malaria Venture (MMV), identified UCB7362, a potent, orally available PMX inhibitor with *in vivo* antimalarial activity [2]. However, preclinical assessments revealed a suboptimal dosing paradigm relative to the current standard of care. Subsequent molecular property optimization led to the identification of a biaryl chemical series with improved metabolic stability and pharmacokinetic parameters, offering a promising alternative for malaria treatment [2].

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KN - 17

NEW DIRECTIONS IN DRUG DISCOVERY: EXPANDING EXPLORATION OF CHEMICAL SPACE

Juan Miguel Jimenez

Executive Director Discovery Chemistry, Johnson & Johnson Innovative Medicine

In this presentation, we will provide an engaging overview of Johnson & Johnson's key initiatives aimed at identifying and expanding Chemical Space in drug discovery.

We will begin by showcasing our screening advancements that enable us to access and explore expanded chemical spaces using multiple innovative platforms. We'll highlight specific case studies that illustrate the success of these methods.

Next, we will explore how we are enhancing the efficiency of molecule design cycles through the integration of artificial intelligence and high-throughput experimentation. This modern approach allows us to evaluate vast libraries of potential compounds with remarkable speed and accuracy, drastically shortening the timeline for drug discovery.

Our discussion will also emphasize how we are addressing challenging targets in drug discovery. We will focus on our innovative methodologies and rigorous validation processes. To wrap up our session, we will summarize some key takeaways and offer insights into the future perspectives of drug discovery.

BACK TO MAIN INDEX

ORAL COMMUNICATIONS

OC - 01

PREDICTED SMALL MOLECULE FMLH INHIBITORS OF UROPATHOGENIC ESCHERICHIA COLI-INDUCED ADHESION TO TREAT URINARY TRACT INFECTIONS

Priyanka Samanta[1 §] and **Robert J. Doerksen**[1, 2]

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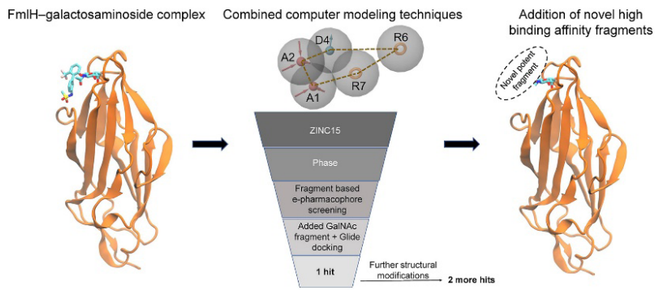
Urinary tract infections (UTIs) affect nearly 50% of women in their lifetime. A major cause of UTIs is uropathogenic Escherichia coli (UPEC), which expresses F9/FmI pili tipped with the protein FmlH that specifically bind to terminal galactoside and galactosaminoside units in glycoproteins on kidney and bladder cells, enabling colonization of host tissues. The extensive use of traditional antibiotics has led to the rise of various antibiotic-resistant strains of UPEC. An alternative therapeutic approach prevents the initial bacterial attachment on the host cells using competitive FmlH-binding inhibitors. We have used physics- as well as machine learning-based modeling approaches to identify novel glycomimetics that are predicted to bind strongly to and inhibit UPEC FmlH. Using receptor-based and ligand-based scaffold hopping combined with e-pharmacophore virtual screening, molecular docking, molecular dynamics simulations and binding free energy calculations we have predicted novel FmlH-binding glycomimetics with high chemical synthesizability[1-2]. Additionally, utilizing highly accurate global machine-learning models, we have predicted the ADMET properties of the molecules. This can aid in mitigating pharmacokinetics liability of the promising drug-like compounds. The hybrid screening protocol developed here could be utilized for the design of ligands for other homologous protein targets in several disease indications that can benefit from such an anti-adhesion therapy approach. The studies have the potential for reshaping the process of drug discovery. The modeling approaches we used here could be helpful for rapid identification of diverse, potent, target-selective drug-like compounds for novel protein targets.



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OC - 02

A FIRST-IN-CLASS TET2 ACTIVATOR AS A NEW THERAPEUTIC STRATEGY AGAINST CANCER

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In this presentation I will introduce ONR-7B, a first-in-class small molecule that allosterically, directly, and specifically activates TET2—a tumor suppressor and master epigenetic enzyme—leading to tumor cell cycle arrest and cell death, representing a completely novel mechanism of action.

Activation of TET2 by ONR-7B has demonstrated strong antitumor effects in both leukemia and melanoma models. Notably, this novel approach shows potential efficacy across all stages of the disease, from treatment-naïve primary tumors to recurrent, refractory, and metastatic cancers.

To elucidate the specific mechanism of action of ONR-7B, we have conducted multi-omics analyses—including methylome and gene expression profiling—as well as biochemical studies using melanoma patient-derived cells and leukemia cell lines treated with varying concentrations of the compou

BACK TO MAIN INDEX

OC - 03

MULTIPLE PATHWAYS FOR LANTHANIDE SENSITIZATION IN SELF-ASSEMBLED AQUEOUS SOLUTION FOR BIOIMAGING APPLICATIONS

Amparo Navarro [1], Álvaro Ruiz-Arias [2], Francisco Fueyo-González [3], Carolina Izquierdo-García [3], Marta Gutiérrez-Rodríguez, [3 4], Rosario Herranz [3], Chiara Burgio [5], Antonio Reinoso [5], Juan M. Cuerva [6], Juan A. González-Vera [2] and Angel Orte[2]

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The development of lanthanide complexes containing luminescent antenna ligands is crucial for the progress of areas such as luminescent bioprobes and medical diagnostics. The emission from the lanthanide emitter is characterized by narrow emission bands and very long photoluminescent lifetimes which makes them especially interesting for use in biological media. To achieve this, a prior process must occur which is the energy transfer from antennas acting as emitters to the lanthanide. On the other hand, biocompatible applications require luminophores that are stable in aqueous media. However, in most lanthanide-based emitters, the emission is usually quenched through the vibrational relaxation of water molecules bonded to the lanthanide in aqueous solution. In this study, we present a luminophore, 8-methoxy-2-oxo-1,2,4,5-tetrahydrocyclopenta [de]quinoline-3-phosphonic acid which is able to dynamically self-assemble in water, coordinate with Tb(III) and Eu(III), and surprisingly act as a sensitizing antenna for photoluminescent emission from lanthanides in aqueous media.[1] This system has been tested to determine the degree of photobleaching in human embryonic kidney (HEK)-293 cells.[2] An in-depth photophysical and time-dependent density functional theory (TD-DFT) computational study has revealed different sensitization mechanisms for Eu(III) and Tb(III) in which stable complexes are formed in water. The knowledge of the photophysical mechanisms behind this behavior is key for the development of applications of lanthanide antennas specifically designed to PLIM microscopy in cellulo.

Acknowledgements

We would like to acknowledge for the funding support Ministerio de Ciencia, Innovación y Universidades PID2023-148243OB-I00, PID2020-114256RB-I00, Grant PID2022-137214OB-C22 funded by MICIU/AEI/ 10.13039/501100011033 and by "ERDF/EU".

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OC - 04

DEVELOPMENT OF INHIBITORS OF THE HA-CD44 INTERACTION AS A NEW STRATEGY FOR CANCER TREATMENT

Meriem Chayah [1, 2, 3], Jose M. Espejo-Román [1], Rosario M. Sánchez-Martín [1, 2, 3], Olga Cruz-López[1 2, 3], Ana Conejo-García[1 2, 3]

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Hyaluronic acid (HA) plays a crucial role in the growth, migration, and invasion of malignant tumors. Its functions are primarily mediated by interactions with cluster of differentiation 44 (CD44) and other hyaladherins. The binding of HA to CD44 is implicated in various pathological processes, including cancer progression and angiogenesis. Under pathological conditions, post-translational modifications promote the expression of CD44 receptor isoforms with enhanced HA-binding capacity, thereby increasing tumorigenicity.[1]

Crystallographic and Nuclear Magnetic Resonance (NMR) studies have provided a detailed characterization of the CD44 structure, particularly the HA-binding domain (HABD), which is located in the N-terminal region of the receptor's extracellular region of the receptor. Biophysical binding assays, fragment screening, and crystallographic analyses have identified an inducible pocket adjacent to the HA-binding groove, suggesting a potential site for small-molecule interaction. The tetrahydroisoquinoline (THIQ) fragment was identified as a key pharmacophore, offering a starting point for further optimization. However, initial THIQ derivatives exhibited only low millimolar affinity for CD44-HABD, and their antitumor activity remained unexplored.[2]

To address this limitation, our research group has developed novel *N*-aryl[3] and *N*-alkylTHIQ[4,5] derivatives with the ability to interact with CD44 (Figure 1). Computational studies suggest that these compounds bind to CD44-HABD in a manner consistent with previously reported crystal structures. These findings were validated through fluorescence competitive binding assays conducted on the CD44++ MDA-MB-231 breast cancer cell line. The lead compound demonstrated an EC_{50} of 0.59 μM, effectively disrupting the integrity of cancerous spheroids and reducing MDA-MB-231 cell viability in a dose-dependent manner (Figure 1).

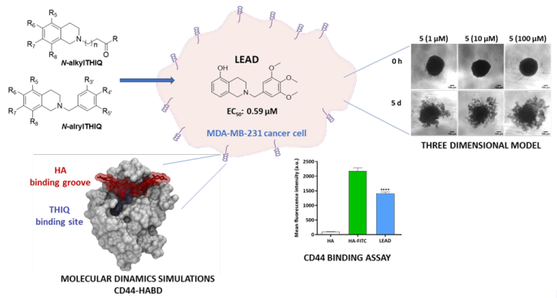

Figura 1. *General structure of the synthesized compounds and overview of the antitumor effect by inhibition of the HA-CD44 interaction of the lead compound.*

Acknowledgements

We would like to acknowledge for the funding support of the project PID2021.128109OB.I00 financed by MICIU/AEI/10.13039/501100011033, and the project P18-RT-1679 financed by the Consejería de Universidad, Investigación e Innovación of the Junta de Andalucía and by ERDF A way of making Europe.

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BACK TO MAIN INDEX

OC - 05

A NEW NMR APPROACH ASSISTED BY MACHINE LEARNING TO ACCELERATE FRAGMENT SCORING

Juan C. Muñoz-García [1], Ridvan Nepravishta [2], Kenneth Cameron [2], Jesús Angulo[1] and Dusan Uhrin [3]

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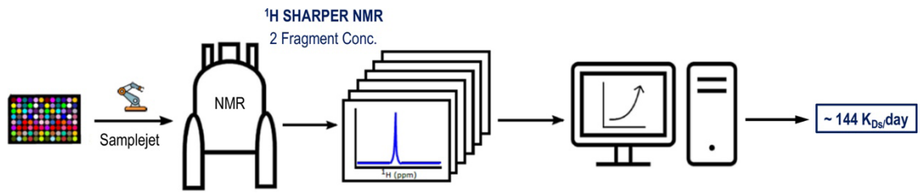
Fragment-Based Drug Discovery (FBDD) is a powerful approach employed in medicinal chemistry for the design of new therapeutics. FBDD consists of screening low molecular weight fragments against a target protein, where interactions are generally characterized by a low affinity. Nuclear Magnetic Resonance (NMR) spectroscopy is of common use in FBDD because it is well suited to detect and characterise weak protein-ligand[1] interactions. However, while NMR performs well in fragment screening, the determination of binding affinities (i.e., K_D) and, hence, fragment scoring, is labour-intensive and time-consuming. This creates a bottleneck in the drug discovery process. To tackle this important challenge, we have developed an innovative approach that integrates the ^{1}H SHARPER NMR experiment[2] with machine learning techniques[3] to increase the efficiency of fragment scoring. ^{1}H SHARPER NMR reduces dramatically the data acquisition times through multifold increases of the signal-to-noise ratio of the acquired spectra, allowing faster and more accurate quantification of fragment binding. Machine learning algorithms were employed to analyse the NMR data, accelerating the scoring process. Thousands of theoretical binding curves covering a range of K_D values from 50 μM to 2 mM were generated and two data points from each curve were then used for training the machine learning models. The new approach led to a significant reduction of experimental time, determining the K_D of 144 fragments in 24h, compared to only a 4-7 K_{Ds} using traditional approaches, using a 600 MHz QCI cryoprobe. This new methodology will significantly accelerate the drug discovery process by quickly providing a reliable scoring of tens to hundreds of fragments, thus allowing informed decision-making and faster progression from hit to lead compounds.



Acknowledgements

We acknowledge the financial support of the Junta de Andalucía for the EMERGIA program (DGP_EMEC_2023_00169) and the Ministerio de Ciencia, Innovación y Universidades for the grant PID2022-142879NB-I00.

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OC - 06

LEAD OPTIMIZATION OF NOVEL PROTEIN AGGREGATION INHIBITORS WITH NANOMOLAR ANTIPLASMODIAL POTENCIES AND FAVORABLE DMPK PROPERTIES

Ana Mallo-Abreu [1, 2], Elsa M. Arce [1], Pau Reolid [1], Antonino Nicolò Fallica [3, 4], Claudia Camarero-Hoyos [3, 4], Yunuen Avalos-Padilla [3, 4], Lucía Román-Álamo [3, 4], Inés Bouzón-Arnáiz [3, 4], Miriam Ramírez [3], María Isabel Loza [5], José Brea [5], Xavier Fernàndez-Busquets [3, 4, 6], Diego Muñoz-Torrero [1 2,]

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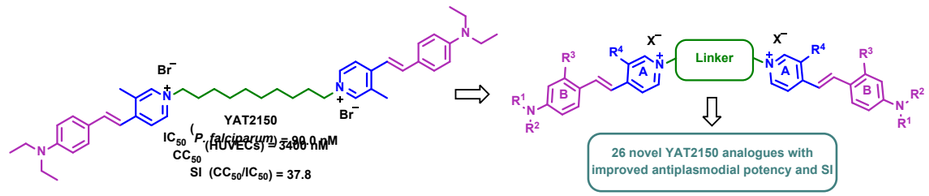
According to the World Health Organization, 263 million cases and 597,000 deaths from malaria occurred across 83 countries in 2023. Furthermore, the increasing emergence of resistance to the current therapeutic arsenal has led to an incessant search for new drugs capable of eradicating the parasite. Recently, a high content of protein deposits has been reported in all *P. falciparum* stages, emerging as a potential new target for the development of novel antimalarial agents.[1] YAT2150 can bind to these aggregates at all stages of the parasite inhibiting its growth with nanomolar potency.[2] Herein we report a hit-to-lead optimization campaign pursuing novel analogs with improved potency, selectivity, and physicochemical and pharmacokinetic properties. We have identified leads with IC_{50} values down to 33 nM and selectivity indices up to 1692, which emerge as promising antimalarial drug candidates.



Acknowledgements

The project that gave rise to these results has received funding from the “la Caixa” Foundation under the grant agreement LCF/PR/HR24/52440003. It was also supported by grants PID2020-118127RB-I00, PID2021-128325OB-I00, and PDC2022-133085-I00 from MICIU/AEI/10.13039/501100011033, and 2021SGR00357 from AGAUR.

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BACK TO MAIN INDEX

OC - 07

DECIPHERING ALLOSTERIC MODULATION AT DOPAMINE D2 RECEPTORS: FUNCTIONAL AND STRUCTURAL INSIGHTS FROM MELANOSTATIN-INSPIRED LIGANDS

Rubén Prieto-Díaz [1], Carlos Rodríguez-García [1], Xerardo García-Mera [1], María I. Loza [2], Jose Brea [2], Ivo E. Sampaio-Dias [3], Javier García-Nafria [4], and Eddy Sotelo.[1]

[1] Center for research in Biological Chemistry and Molecular Materials (CiQUS), and [2] Center for research in Molecular Medicine and Chronic Diseases (CiMUS). University of Santiago de Compostela, Santiago de Compostela, Spain. [3] Department of Chemistry and Biochemistry, Faculty of Sciences, University of Porto, Portugal. [4] Institute for Biocomputation and Physics of Complex Systems (BIFI). University of Zaragoza, Spain.

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Allosteric modulation of G protein-coupled receptors (GPCRs) represents a promising strategy to achieve receptor subtype selectivity and fine-tune signaling pathways while improving pharmacological profiles. The dopamine D_2 receptor (D_2R), a central target in the treatment of neuropsychiatric disorders such as Parkinson's disease and schizophrenia, is allosterically modulated by the endogenous tripeptide melanostatin (also known as MIF-1 or PLG). This peptide enhances dopamine binding and function at D_2R without affecting D_1R or D_3R activity. Inspired by the mechanism of melanostatin,[1] we developed an innovative multicomponent synthetic platform enabling the generation of a focused library of over 100 MIF-1 analogues, primarily via Ugi and PADAM-based sequences. This approach allowed systematic exploration of structural diversity, bioisosteric replacements, and the topology of this D_2R allosteric site. Targeted modifications at three key regions of the MIF-1 scaffold were combined with structural biology and computational modeling to elucidate SAR governing allosteric modulation at D_2R (Figure 1). Functional assays revealed distinct profiles (PAMs and NAMs), with several analogues exhibiting superior efficacy compared to melanostatin. Selected ligands demonstrated improved physicochemical properties, addressing key pharmacokinetic limitations of MIF-1.

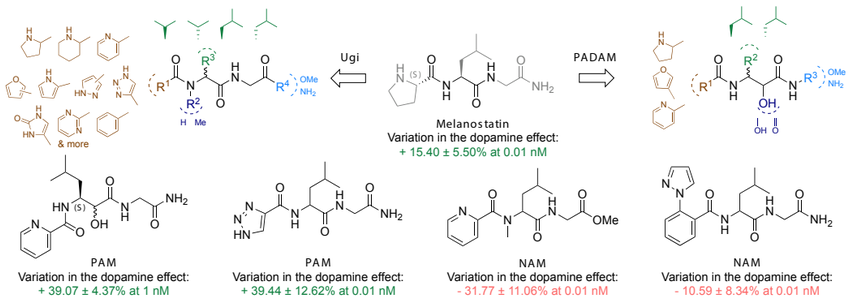

Figure 1. Multicomponent-driven modifications on the melanostatin scaffold

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OC - 08

FIRST-IN-CLASS TREX2 INHIBITORS: A BREAKTHROUGH KERATINOCYTE-TARGETED THERAPY FOR PSORIASIS

Ouldouz Ghashghaei [1#], Ingrid Filgaira [2, 3#], Serena Piticchio [4#], María Martin [2, 3], Daniel López-Ramajo [2, 3], Marc López-Cano [2, 5], Sara Preciado [2, 3], Josep Maria de Anta [2], Cristina Diaz-Perlas [6], Benjamí Oller-Salvia [6], Jordi Juárez-Jimenez [4], Francisco Ciruela [2, 5], Rodolfo Lavilla [1], Xavier Barril [4], Concepció Soler [2, 3]

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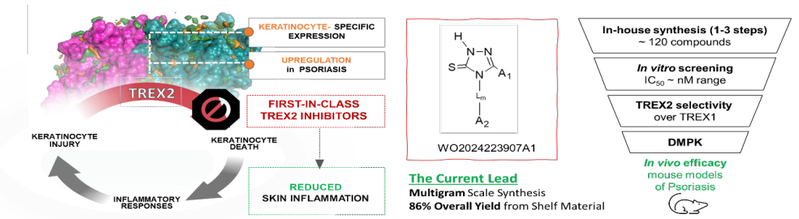
Psoriasis is a chronic inflammatory disease driven by abnormal keratinocyte function and immune cell activation. Current treatments primarily target immune components, often leading to immunosuppression, organ dysfunction, and treatment resistance. In this context, a promising alternative is the development of keratinocyte-targeted therapies. Our team has identified the keratinocyte-specific exonuclease TREX2 as a novel therapeutic target, as its deficiency reduces psoriasis-related inflammation.[1] We discovered a druggable hotspot site in the TREX2 protein, upon which we developed the first-in-class small molecule TREX2 inhibitors. These allosteric inhibitors feature high potency (nM range), specificity, and selectivity over the closely related TREX1.[2] Preclinical data demonstrate that they significantly reduce inflammation in several mouse models of psoriasis. Our current Lead also exhibits a remarkable pharmacokinetic and safety profile, making it a strong candidate for clinical translation. This novel approach may offer safer, more effective, and long-term treatment alternatives for psoriasis and other TREX2-driven diseases, improving patients' health and quality of life.



Acknowledgments:

We acknowledge the grants PID2020-114477RB-I00, PDC2021-120879-I00, PID2023-148121OB-I00 (MICIU/AEI/10.13039/501100011033 and the "European Union NextGenerationEU/PRTR), 2020 Discovery Grant (National Psoriasis Foundation), F2I-FVal_2020-013 (Fundació Bosch i Gimpera-UB), CI20-00169 ("la Caixa" Foundation), NEA21-IMP164, NEA22-IMP175 (National Eczema Association), 2023 INNOV 00012 and 2024 PROD 00106 (AGAUR).

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BACK TO MAIN INDEX

OC - 09

TARGETED DEGRADATION OF MASTL KINASE

Sonsoles Rodríguez-Arístegui, J.A. Torres, L. de Andrés, A. Cebriá, M. I. Albarrán, C. Varela, E. Gómez, A. B. García, L. Cañizares, E. Hernández, M. San Martín, C.A. Gómez, E. González, S. Martínez, C. Blanco and J. Pastor*

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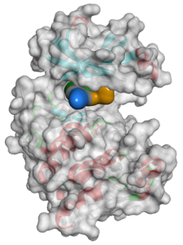
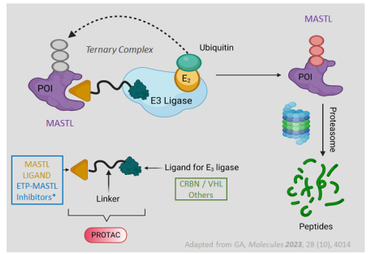
Chromosomal instability (CIN) is a hallmark of cancer characterized by an abnormal number or structure of chromosomes. CIN results from defects in mitotic checkpoint control, chromosome attachment to the spindle, and/or DNA damage repair pathways, among other factors. The resulting genomic instability can lead to the accumulation of genetic alterations that promote tumor development and progression, including metastasis, and resistance to targeted therapies.

Overexpression of MASTL kinase has recently been unveiled as a CIN tolerance mechanism and therapeutic vulnerability in therapy-refractory metastatic lethal prostate cancer. Similarly, MASTL overexpression is highly correlated with CIN levels in a cohort of breast tumors and has been associated with poor patient survival. Knockdown of MASTL showed therapeutic effects in this context [1]. Although the correlation between MASTL and CIN has not been addressed, the genetic depletion of MASTL also compromised the viability of tumor cells in other types of cancers such as, leukemia, hepatic, gastric, colon, and pancreatic [2]. Notably, MASTL controls and promotes “checkpoint recovery”, and its upregulation represents a common mechanism for cancer cells to escape DNA-damaging therapies, leading to drug resistance and potential cancer recurrence [3]. The genetic depletion of MASTL in cancer cells showed additive/synergistic effects in combination with some DNA damaging therapies. All these precedents justified the selection of MASTL kinase as therapeutic target in cancer. We will describe the discovery and optimization of “first-in-class MASTL degraders”, and present our current lead molecules that exhibit potent MASTL-degrading activity, high proteome-wide selectivity, and in vivo bioavailability.



Proprietary MASTL Inhibitors (SAR)
Exit Vector to Solvent Exposed Area



*Full length recombinant human MASTL

Acknowledgment.

Ministerio de Ciencia, Innovación y Universidades (PID2023-150522OB-I00) & Centro Nacional de Investigaciones Oncológicas (CNIO) for financial support.

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NOTE: The full structures of the described molecules will not be disclosed due to patent limitations.

OC - 10

DISCOVERY OF NOVEL MGLUR2 NAM DERIVATIVES. FROM HIT IDENTIFICATION TO IN VIVO ACTIVITY IN A RODENT’S MODEL OF COGNITION

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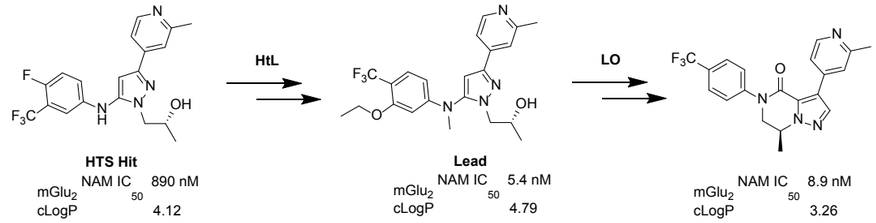
Metabotropic glutamate receptors 2 ($mGluR_2$) play a vital role in the central nervous system (CNS) by mediating the levels and effects of the neurotransmitter glutamate. These receptors are primarily located in brain regions involved in key functions such as learning, memory and mood regulation. Preclinical data support the therapeutic potential of negative allosteric modulators (NAMs) of the $mGlu_2$ receptor in neuropsychiatric disorders such as depression and improvement in cognitive function in disorders like Alzheimer Disease.

In this communication a medicinal chemistry overview of our search for new and selective $mGluR_2$ NAMs will be presented. It will describe the initial discovery of a 1,3,5-trisubstituted pyrazoles series as $mGluR_2$ NAMs with single digit nanomolar potency after a focused optimization of a starting pyrazole hit identified from a high throughput screening (HTS) campaign with moderate potency.[1]

Subsequent evaluation of the pyrazole series, focused on reducing lipophilicity by means of a cyclization strategy, led to the discovery of the 6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one series with improved drug-like properties.[2] Further optimization resulted in the improvement in the $mGluR_2$ NAM potency and subsequent selection of a compound for in-depth evaluation based on its overall profile including selectivity and ADMET properties. Additionally, results of this compound in a V-maze study as an *in vivo* rodent’s model of cognition will be presented.



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BACK TO MAIN INDEX

OC - 11

ALLOSTERIC INHIBITION OF THE HOST NEUTRAL SPHINGOMYELINASE 2 AS A NOVEL APPROACH TOWARDS ANTIVIRALS AGAINST FLAVIVIRUSES

Eva-María Priego [1], Hadrián Álvarez-Fernández [1], Patricia Mingo-Casas [2], Ana-Belén Blázquez [2], Flavia Caridi [2], Juan Carlos Saiz [2], Miguel A. Martín-Acebes [2] and María-Jesús Pérez-Pérez [1]

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Orthoflavivirus comprises globally emerging and re-emerging pathogens such as Zika virus (ZIKV), Dengue virus (DENV) and West Nile virus (WNV), among others[1]. Although some vaccines are available, there is an unmet medical need, as no effective antiviral treatment has been approved for any flaviviral disease. The development of host-directed antivirals (HDAs), targeting host factors that are essential for viral replication cycle such as the lipid metabolism, offers the opportunity for the development of broad-spectrum antivirals[2]. In the case of flaviviruses, neutral sphingomyelinase 2 (nSMase2) plays a key role in WNV and ZIKV infection[3].

We have recently described the antiviral activity of the non-competitive nSMase2 inhibitor DPTIP against WNV and ZIKV virus. In addition, computational studies have been carried out to unravel the allosteric binding site of DPTIP in nSMase2 and the details of their interaction, revealing the involvement of H463 in the binding and that DPTIP could block the DK switch in nSMase2[4].

Based on our proposed bioactive conformation of DPTIP, we have now carried out a ligand-based virtual screening (LBSV) campaign for the development of new nSMase2 allosteric inhibitors. Computational methods, hit identification and optimization, along with enzymatic and antiviral evaluation will be discussed in detail.

Acknowledgements

This work was supported by the Spanish Ministry of Science and Innovation AEI/10.13039/501100011033 under Grants PID2019-105117RR-C21 (to MAMA), PID2019-105117RR-C22 (to MJPP), PID2022137372OR-C21 (to MAMA), PID2022-137372OR-C22 (MJPP and EMP).

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OC - 12

MEDINAMYCIN, FIRST MEMBER OF A NEW STRUCTURAL CLASS WITHIN THE PHOSPHOGLYCOLIPID ANTIBIOTICS

Ignacio Pérez-Victoria [1], Marina Sánchez-Hidalgo [1], Jesús Martín [1], Mercedes de la Cruz [1], José M. Quesada [1], Sandra Resa [1], Ignacio González [1], Hao Wang [2], José R. Tormo [1], Fernando Reyes [1], Terry Roemer [2] and Olga Genilloud [1]

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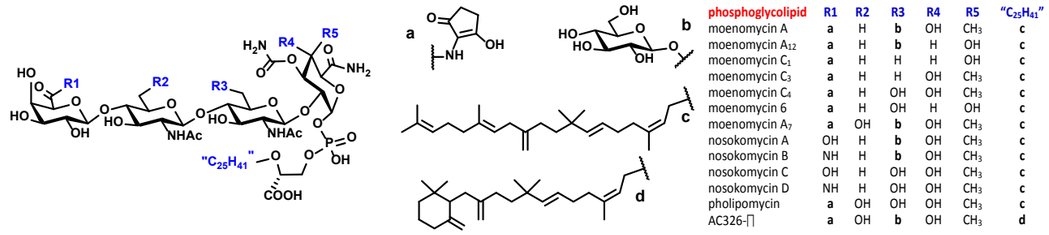
The phosphoglycolipid natural products are the only known antibiotics that inhibit the peptidoglycan glycosyltransferase domains (PGTs) of the Penicillin Binding Proteins (PBPs) involved in the bacterial cell wall biosynthesis.[1,2] This antibiotic family is rather compact in terms of chemical diversity, being Moenomycin A its archetypal member (Fig. 1). Despite, their extraordinary subnanomolar inhibition of PGTs, their use as therapeutic agents has been hampered by suboptimal pharmacokinetics.[1,2] Fortunately, recent reports highlighting the potent antigonococcal activity of Moenomycin A against drug-resistant *Neisseria gonorrhoeae*,[4,5] a gram-negative pathogen of significant concern, have boosted the revival of this antibiotic family.

In this communication, we will introduce Medinamycin, a novel phosphoglycolipid antibiotic. Medinamycin contains unique structural features that unveil a remarkable new class within this important family of antibiotics. Its discovery, structural elucidation, biosynthesis pathway and bioactivity profile will be presented herein, along with a discussion on its potential as lead antibiotic for further development.



phosphoglycolipid	R1	R2	R3	R4	R5	"$C_{25}H_{41}$"
moenomycin A	a	H	b	OH	CH_3	c
moenomycin A_{12}	a	H	b	H	OH	c
moenomycin C_1	a	H	H	H	OH	c
moenomycin C_3	a	H	H	OH	CH_3	c
moenomycin C_4	a	H	OH	OH	CH_3	c
moenomycin 6	a	H	OH	H	OH	c
moenomycin A_7	a	OH	b	OH	CH_3	c
nosokomycin A	OH	H	b	OH	CH_3	c
nosokomycin B	NH	H	b	OH	CH_3	c
nosokomycin C	OH	H	OH	OH	CH_3	c
nosokomycin D	NH	H	OH	OH	CH_3	c
pholipomycin	a	OH	OH	OH	CH_3	c
AC326-∏	a	OH	b	OH	CH_3	d

Figure 1. *Structural diversity of known (fully characterized) naturally occurring phosphoglycolipid antibiotics.*

Acknowledgements

We would like to acknowledge Ministerio de Ciencia e Innovación (PID2020-119559RB-I00 and PID2023-153331OB-I00) for funding support.

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BACK TO MAIN INDEX

OC - 13

EXPLORING FLUORINATED MAN5 GLYCOMIMETICS AS POTENTIAL INHIBITORS OF SARS-COV-2 VIRUS INFECTION.

Carmen Pérez-Alonso [1], Adrián Silva-Díaz [1], Jonathan Ramírez-Cárdenas [1], Michel Thépaut [2], Juan C. Muñoz-García [1], M. Carmen de la Fuente [1], Franck Fieschi [2], Jesús Angulo [1], Javier Ramos-Soriano [1], Javier Rojo [1]

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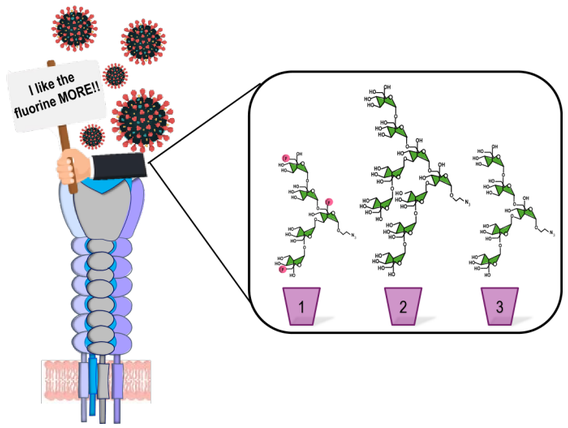
DC-SIGN, a homotetrameric C-type lectin receptor predominantly expressed on immature dendritic cells, have been identified as efficient trans-receptor for SARS-CoV-2 infection. This receptor recognizes high-mannose ($Man_9GlcNAc_2$) structures present on the spike protein of SARS-CoV-2, facilitating viral entry and transmission.[1] In this context, the development of glycomimetics to inhibit this infection through DC-SIGN blockade is an emerging approach. Over recent years, fluorinated compounds have been widely used to tailor the biological behaviour of drugs for enhancement of therapeutic efficacy disrupting the COVID infection.[2]

Herein, we present a library of fluorinated Man_5 glycomimetics (structural part of the natural epitope Man_9) with 2-OH and 6-OH substitutions as inhibitors on DC-SIGN/SARS-CoV-2 recognition processes. To investigate the impact of fluorine on affinity for DC-SIGN, SPR competition assays with the spike protein were performed. These experiments demonstrated a notable enhancement in inhibitory potency for the [6F,6F]-substituted compound, representing a 3.5-fold improvement compared to the non-fluorinated Man_5 analogue and a similar affinity to the natural epitope Man_9, synthetically more complex. Finally, through STD-TOCSYreF-NMR we also demonstrate that fluorine substitution has a critical influence on ligand accommodation within the binding site, with the C6-fluorine substitution favouring the engagement when is at D2 arm.



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OC - 14

TARGETING HEMATOLOGICAL CANCERS: SYNTHESIS AND EVALUATION OF NOVEL BENZOTHIAZOLE-BASED PPAR ANTAGONISTS

Nazaret Moreno-Rodríguez [1], Rocío Calderón [2], Rocío Recio [1], Antonio Laghezza [3], Fulvio Loiodice,3, Alessandra Ammazzalorso [4], José Antonio Pérez-Simón [2] e Inmaculada Fernández [1]

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Hematological cancers are aggressive and challenging to treat due to their high heterogeneity and resistance to conventional therapies. Peroxisome proliferator-activated receptors (PPARs), particularly PPARα and γ, play a role in regulating cellular pathways involved in the progression of these malignancies.[1] PPAR antagonists, such as benzothiazole-based compounds, show promise as potential therapeutic agents.[2] In this study, we synthesized a novel series of benzothiazole-based PPAR antagonists through nucleophilic addition of methyl benzothiazolyl sulfoxide to *N-tert*-butylsulfinylimines,[3] resulting in thiosulfinates, β-aminothiosulfonates, and enantiomerically pure disulfides and thiols (Fig. 1). The cytotoxic activity of these compounds was evaluated in hematological cancer cell lines, revealing important structure-activity relationships.

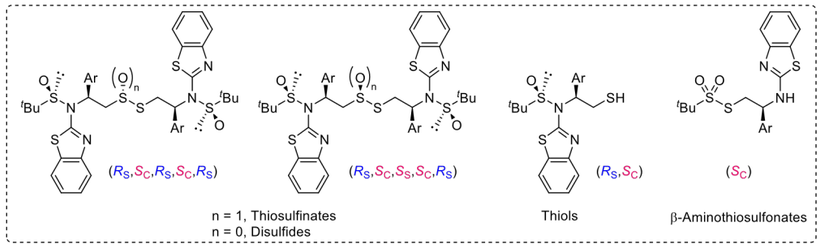

Figure 1. *Novel benzothiazole-based PPAR antagonists.*

Acknowledgements

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BACK TO MAIN INDEX

OC - 15

FOLATES CONJUGATES: A BREAKTHROUGH IN THE FIGHT AGAINST CANCER

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One of the greatest challenges in cancer therapy is minimizing toxicity caused by the non-specific distribution of anti-tumor agents. To overcome this limitation, various strategies are being developed to selectively target drugs to cancer cells. Among them, the use of tumor-specific ligand conjugates has gained significant attention. Folic acid (FA), an essential compound internalized via endocytosis through folate receptors (FRs) overexpressed on most cancer cells, represents a powerful targeting tool.[1]

Building on this approach, we have identified protein kinase CK2, a key enzyme overexpressed in multiple cancer types, [2] as a promising molecular target for the design of a novel class of folate conjugates (FCs). Given that FR expression increases with tumor progression, FCs are expected to achieve enhanced selectivity toward cancer cells, improving therapeutic efficacy while significantly reducing toxicity.[3]

In this study, we present the synthesis of an FA-based conjugate targeting CK2 using a convergent synthetic approach. Our design links the CK2 inhibitor CX-4945 to FA via a cleavable disulfide linker (Figure 1). Preliminary studies have yielded promising results: the CK2-targeting FC successfully releases CX-4945 quantitatively within five hours, confirming the potential of this strategy to improve the specificity and safety of anticancer treatments.

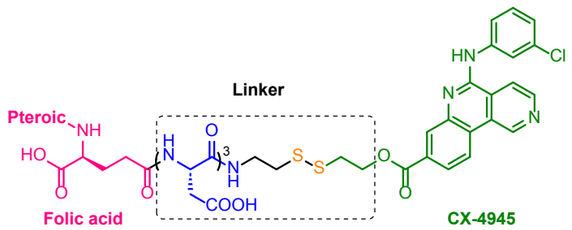

Figure 1. CK2 Folate conjugate

Acknowledgements

We would like to acknowledge the funding support from the Marie Sklodowska-Curie grant agreement No 101031883 and from PID2021-123786OB-I00 (MICIU/FEDER, UE).

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OC - 16

EU-OPENSCREEN – AN OPEN ACCESS INITIATIVE TO IDENTIFY NEW BIOLOGICAL ACTIVITIES OF YOUR COMPOUNDS

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Compounds and natural products synthesized by chemists represent a rich, untapped source of novel chemical diversity. In many cases, **chemists have limited opportunities to systematically test these compounds against a variety of drug targets**. These compounds are also often not readily accessible to the biologists who develop suitable assays.

In order to make the invaluable chemistry of local chemistry groups accessible to a broader scientific community, **EU-OPENSCREEN offers chemists the opportunity to make their compounds available**, in a regulated and transparent framework, to a wider community of biologists, who screen these compounds in suitable bioassays. This opportunity allows chemists **to expose their compounds to a range of biological/drug targets to screen for unknown bioactivities**, which would otherwise not be feasible in individual one-to-one-collaborations, thereby enabling novel collaborations with EU-OPENSCREEN users from across Europe and beyond.

The submitted compounds are centrally quality-controlled, stored, and reformatted at the EU-OPENSCREEN Central Compound Management Facility in Berlin. Submitted compounds are initially annotated in a suite of cell-based, biochemical and physicochemical assays to analyse their physicochemical and biological properties before being continuously tested and annotated in our screening campaigns. This **'bioprofiling' effort is free of charge to the chemist**, and the bioactivity data are shared with the respective chemist who submitted the individual compound.

After the initial 'bioprofiling', compounds are tested exclusively at official EU-OPENSCREEN partner sites and are not passed on to third parties without consent, so that the chemists retain control over the usage of their compounds.

EU-OPENSCREEN is a publicly funded international consortium of approximately 30 academic partner institutes across nine European countries. The consortium supports chemical biologists to implement their drug discovery projects by providing access to high-throughput screening platforms, screening collections and hit-to-lead optimisation support on a collaborative basis.

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BACK TO MAIN INDEX

FLASH COMMUNICATIONS

FC - 01 → P - 49* *correspondig poster

TARGETING TELOMERIC G-QUADRUPLEXES WITH CATIONIC CALIXARENES

Maria Cremonini [1], Alessandro Casnati [1], Francesco Sansone [1], Stefano Volpi [1]

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The telomeric regions of human chromosomes contain repeated guanine-rich (TTAGGG) sequences, which can fold into G-quadruplex (G4) structures. Telomeric G4s interfere with the activity of telomerase, an enzyme typically active in cancer cells and responsible for their uncontrolled proliferation. Thus, the stabilization of telomeric G4s has emerged as a promising anticancer strategy, leading to the development of several small molecules targeting these structures.[1]

Building on our recent findings regarding the interaction between calix[n]arenes and G4 models,[2] we designed and synthesized a library of calix[n]arene derivatives as potential telomeric G4 stabilizers (Fig. 1). The upper rim of these compounds was decorated with various amines to facilitate electrostatic interactions with the negatively charged DNA backbone, while their aromatic scaffold was expected to provide hydrophobic and stacking interactions. Additionally, macrocycle size and valency (n = 4, 6, 8) and functionalization of their lower rim (free vs methylated phenolic OHs) were modulated to investigate the impact of conformational mobility on G4 stabilization.

The binding properties of these compounds were initially evaluated via Förster Resonance Energy Transfer (FRET)-melting assays using a fluorophore-labelled model of the human telomeric G4.[3] Derivatives **1e-g**, **2e-f**, **3e-f** and **4g** exhibited the highest ability to stabilize the telomeric G4, highlighting the key role of cationic ammonium/guanidinium groups at the upper rim and macrocycle mobility in ligand efficiency. Further circular dichroism (CD) spectroscopy characterization provided insights into telomeric G4 binding, including preliminary binding affinity estimates and assessment of ligand-induced G4 structural rearrangements.

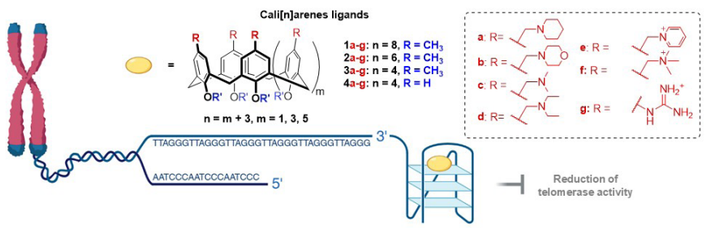

Figure 1: *telomeric G-quadruplex and the synthesized calix[n]arene ligands*

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FC - 02 → P - 55* *correspondig poster

INDOL DERIVATIVE COLCHICINE SITE LIGANDS: PROMISING ANTIMITOTICS AGAINST RESISTANT CANCER CELLS

Laura Gallego Yerga [1], Raúl Fuentes Martín [1], Raquel Álvarez [1], Pilar Ayuda-Durán [2] and Rafael Peláez [1]

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The lack of efficacy of some of the most important class of chemotherapeutics, such as the vinka alkaloids and the taxanes, is associated to cancer cells resistance. These drugs cause apoptotic cell death by interfering with tubulin dynamics but they are also substrates of multidrug resistance (MDR) pumps. Antimitotics acting at the colchicine biding site in tubulin have emerged as an alternative to overcome those mechanisms of resistance. The study of the structural requirements of these ligands to improve the interaction with the tubulin led to the identification of the best performing organic moieties in colchicine site ligands. We succeed to design and develop new families of molecules that behave not only as potent antimitotic compounds but also as vascular disrupting agents. Structure-activity relationship studies afforded that the best performing ligands consisted on the combination of trimethoxyphenyl or substituted pyridyl rings with indolyl rings linked by sulfonamides[1] or tetrazole bridges[2]. The new synthesized molecules revealed high antitumor potency against a broad panel of cancer cells, including resistant cells, together with high selectivity respect non-tumorigenic cells and improved pharmacokinetic profiles respect the reference drugs in clinical use. Tubulin polymerization inhibition assays, immunofluorescence experiments through confocal microscopy, and flow cytometry studies demonstrated that the compounds target tubulin and arrest the cell cycle at the G2/M phase followed by induction of apoptosis via caspase 3/7 activation. The substituents on the sulfonamide nitrogen appeared to determine different mechanistic results and cell fates. The docking experiments agreed with the interactions at the colchicine site and supported the structure–activity relationships. The described compounds are potential candidates for further clinical development, especially for the treatment of difficult-to-treat resistant tumors.

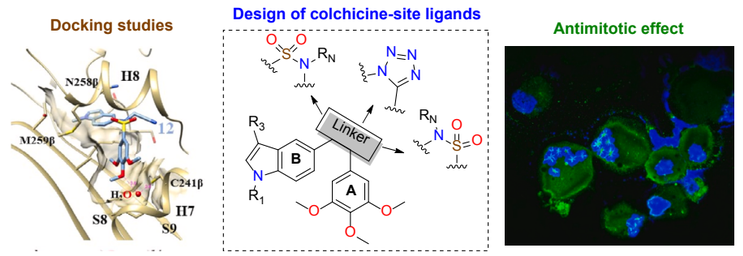

Figure 1. (A) General structure of antimitotic ligands.
(B) Docking at the colchicine site.
(D) Immunofluorescence images of treated MCF7 cells.

Acknowledgements.

Funding support: PIC2-2023-05 funded by University of Salamanca, PID2021-127471OB-I00 funded by MCIN/AEI/10.13039/501100011033 and ERDF by the "European Union.

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BACK TO MAIN INDEX

FC - 03 → P - 24*

*correspondig poster

TARGETING KIT-DRIVEN DISEASES: ML329 AS A PROMISING MITF PATHWAY INHIBITOR

Eva Serrano-Candelas [1], Elizabeth Proaño-Pérez[2], Mario Guerrero[2], Alfonso García-Valverde[3], Jordi Rosell[3], Laia Ollé[2], César Serrano[3] and Margarita Martin[2]

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Gastrointestinal stromal tumors (GISTs) account for approximately 80% of mesenchymal neoplasms in the gastrointestinal tract, with KIT (CD117) mutations playing a key role in their pathogenesis[1]. Although imatinib mesylate is the standard treatment, drug resistance necessitates alternative therapeutic strategies[2]. Mastocytosis is a myeloproliferative neoplasm characterized by excessive mast cell (MC) proliferation in tissues such as the skin, bone marrow, gastrointestinal tract, liver, spleen, and lymph nodes[3]. It presents with symptoms like flushing, pruritus, abdominal pain, diarrhea, hypotension, syncope, and musculoskeletal pain, resulting from increased MC mediator release and organ infiltration. A key driver of mastocytosis is the Asp816Val (D816V) KIT mutation, which occurs in the catalytic domain of the receptor tyrosine kinase KIT, promoting abnormal mast cell proliferation and survival. Microphthalmia-associated transcription factor (MITF) has emerged as a crucial regulator of pro-survival signaling and tumor growth in GISTs[4]. MITF is upregulated in mastocytosis by KIT oncogenic signals[5].

In this study, we examined the effects of MITF inhibition using ML329, an MITF pathway inhibitor, in GIST and HMC-1, a cellular model of mastocytosis. ML329 suppressed the growth of both imatinib-sensitive (GIST-T1) and resistant (GIST 430/654) cell lines, induced S-G2/M cell cycle arrest, and downregulated MITF targets such as BCL2 and CDK2. *In vivo,* ML329 was welltolerated and significantly reduced tumor growth in established GIST xenografts. Additionally, ML329 treatment reduced MITF expression and impaired viability and cell cycle progression in HMC-1 cells.

These findings highlight MITF as a critical player in KIT-driven GISTs and mast cell disorders, supporting its inhibition as a promising therapeutic strategy for both malignancies.

Acknowledgements

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FC - 04 → P - 64*

*correspondig poster

DISCOVERY OF PAN-CORONAVIRUS ANTIVIRALS WITH A NOVEL MECHANISM OF ACTION

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The COVID-19 pandemic has highlighted the urgent need for strategies to halt the spread of novel pathogens. Considering the severity of the infection provokes by coronavirus (SARS-CoV-1, MERS and SARS-CoV-2) and the lack of effective antiviral therapies, it is still required the development of novel therapeutic agents to treat infected individuals by pathogens.

Phenotypic screening of our chemical library against SARS-CoV-2 identified two hits with promising antiviral activity, both sharing structural features centered around the 1,2-diaminopropylbenzene scaffold.

Herein, we report the medicinal chemistry around the identify scaffold to develop lead compounds following an iterative design–synthesis–antiviral activity process. Four structural regions on the 1,2-diaminopropylbenzene scaffold - East, West, North and South - were systematically modified to optimize antiviral potency against SARS-CoV-2, explore the chemical space and improve DMPK properties. Structure–activity relationship (SAR) and structure–property relationship (SPR) studies enabled optimization of the series and selection of lead compounds with improved antiviral potency and drug-like properties.

The compounds showed selective activity against human coronaviruses such as SARS-CoV-2, HCoV-229E, and MERS-CoV, with no measurable activity against unrelated RNA viruses, suggesting potential pan-coronavirus activity.

We have also explored the potential pathways leading to compounds resistance, the molecular mechanisms involved, and the viral determinants. Preliminary studies have revealed that the selective pressure imposed by the compounds cluster together in a non-structural region of SARS-CoV-2 genome responsible for the formation of double membrane vesicles, the putative RNA replication compartment. To date, no drugs targeting this region have been identified.

Overall, our research would represent a significant step forward in developing new, innovative strategies for treating infections caused by emergent coronaviruses useful for combined therapies with protease or/and RNA polymerase inhibitors.

Acknowledgment

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BACK TO MAIN INDEX

FC - 05 → P - 42*

*correspondig poster

EXPLORING LARGE CHEMICAL SPACES FOR LEAD OPTIMIZATION

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The lead optimization stage of a drug discovery program generally involves the design, synthesis, and assaying of hundreds to thousands of compounds. The design phase is usually carried out via traditional medicinal chemistry approaches and/or structure-based drug design (SBDD) when suitable structural information is available. Two of the major limitations of this approach are (1) difficulty in rapidly designing potent molecules that adhere to myriad project criteria, or the multiparameter optimization (MPO) problem, and (2) the relatively small number of molecules explored compared to the vast size of chemical space.

To address these limitations, Schrödinger has recently spearheaded the development of workflows that combine large-scale synthetically aware de novo design methods (AutoDesigner[1]) with rigorous free energy-based scoring methods (Active Learning FEP+) for potency and selectivity optimization of small molecules. Recent developments of this technology move beyond R-group design to core exploration, enabling its expanded application to early stage hit identification efforts and the discovery of back-up series.

In this presentation, we will describe the workflows that have been developed and show how these technologies can impact and accelerate drug development programs.

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FC - 06 → P - 11*

*correspondig poster

POTENT DIPEPTIDYL PEPTIDASE 8/9 INHIBITORS DESIGNED VIA RELATIVE BINDING FREE ENERGY CALCULATIONS

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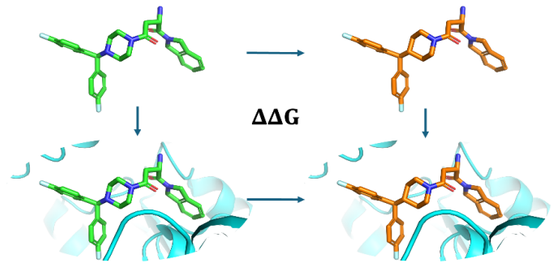
Dipeptidyl peptidases (DPP) 8 and 9 are proline-selective serine proteases that belong to the Dipeptidyl peptidase 4 Activity/Structure Homologues (DASH) family. These proteins are capable of processing different (oligo-)peptides containing proline at the penultimate position of the N-terminus. While DPP4 is the only fully validated drug target of the family, given its role in glucose homeostasis, DPP8 and DPP9 have recently attracted attention due to the finding that inhibition of DPP8/9 stimulates a proinflammatory form of cell death (pyroptosis) in monocytes and macrophages[1] which is considered as an interesting approach to treat acute myeloid leukaemia (AML). However, full biological characterisation and chemical development of selective inhibitors has been elusive due to the high degree of sequence homology between DPP8 and DPP9.

In this work, we optimize a well-known reference DPP8/9 inhibitor named 1G244[2], using relative binding free energy (RBFE) calculations. An initial retrospective, computational analysis of experimental structure-activity data of 1G244 and close structural analogues, guided the subsequent prospective design of novel inhibitors derived from the reference scaffold. Synthesis of the compound set and subsequent *in vitro* evaluation led to the identification of compound **21**, for which initial pharmacokinetic and pharmacodynamic studies were performed. This novel compound could be used as a tool to further clarify the role of DPP8 and 9 in cellular physiology.



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BACK TO MAIN INDEX

FC - 07 → P - 08* *correspondig poster

ORGANOSELENIUM IMINES: THEIR DUAL ROLE IN TREATING BACTERIAL INFECTIONS AND ALZHEIMER'S DISEASE

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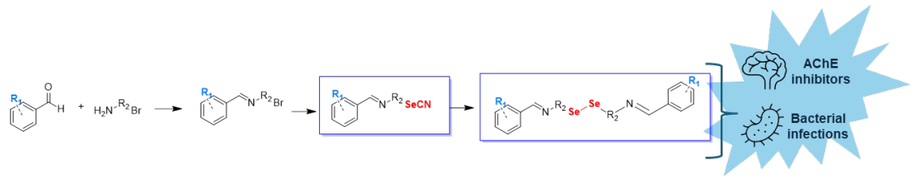
Microbial infections have become a globally significant concern, contributing to an estimated 700,000 deaths annually[1]. Additionally, Alzheimer's disease, a leading cause of dementia, represents a substantial socioeconomic and healthcare burden on society[2]. Consequently, the development of novel therapeutic treatments for both diseases is an urgent need.

In this context, several selenoderivatives have emerged as a promising strategy for the development of acetylcholinesterase (AChE) inhibitors [3], while others have demonstrated their potent antibacterial activity[4]. Based on this evidence, the design and synthesis of novel organoselenium compounds is proposed for the treatment of both diseases using a fragmentbased design. It is hypothesized that incorporating both the imine moiety and selenium within the same molecular structure, each of which has demonstrated activity against these diseases, will led to the development of novel and potent therapeutic agents. A total of 28 compounds were synthesized and their minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) were assessed against a panel of bacterial strains. Additionally, the Ellman method was employed to evaluate their AChE inhibitory activity at 1 μM.

Of the 28 compounds tested, 12 exhibited greater inhibitory capacity than the reference AChE inhibitor galantamine. Notably, two compounds demonstrated an inhibition percentage exceeding 60%. Regarding antibacterial activity, selenocyanate derivatives showed supperior inhibitory activity than their diselenides analogs, highlighting those compounds containing a fluor or nitro substituent in the structure, with MIC and MBC values of 25 μg/mL.

These findings indicate that incorporating Se and imines into the same organic molecule could yield compounds with a dual role as antibacterial agents and AChE inhibitors. Therefore, additional experiments will be conducted to explore the potential of these compounds.



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FC - 08 → P - 25* *correspondig poster

EXTENSIVE SAR STUDY LEADS TO THE DISCOVERY OF NANOMOLAR-POTENT LEISHMANICIDAL AGENTS

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Leishmaniasis is an infectious disease caused by parasitic protozoa of the genus *Leishmania*, responsible for between 30.000 deaths per year in more than 140 countries, making it the second most serious parasitic disease worldwide[1]. It is worth noting that no effective long-term vaccine for humans has yet been developed[2], whereas the currently available chemotherapeutic arsenal is limited and hampered by toxicity issues, lack of efficacy, emergence of drug resistances and still high costs[3]. Consequently, the discovery of innovative and effective agents for the treatment of leishmaniasis is an urgent and challenging need for the scientific community.

In this context, our research group during a focused screening campaign identified compound **AMPHI-8** as a *L. infantum* Tripanothione Synthetase (LiTryS) inhibitor with promising leishmanicidal activity against axenic amastigotes (EC_{50} =0.6 μM) and good safety profile (SI >35)[4] which lead us to consider **AMPHI-8** as a worthy prototype for further exploration in a SAR study.

In this communication, we report a general, optimized, and reliable synthetic route employed to obtain a library of over 50 compounds with structural modifications of the prototype **AMPHI-8**. This collection of derivatives was evaluated against LiTryS in an enzymatic assay and against axenic amastigotes. These studies led to the identification of six compounds exhibiting enhanced leishmanicidal activity (EC50 ~30 nM) while preserving a favorable safety profile (SI >80). Ongoing investigations are currently focused on elucidating the mechanism of action of these promising compounds.

Acknowledgements

The Spanish ministry of Science and Innovation AEI/10.13039/501100011033 (grants PID2022136307OB-C21 and PID2022-137372OR-C22 (MICINN/AEI/10.13039/501100011033/FEDER, UE)) are acknowledged for financial support.

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BACK TO MAIN INDEX

FC - 09 → P - 60* *correspondig poster

NOVEL PLATINUM-BASED CHEMOTHERAPEUTIC AGENTS AGAINST CHOLANGIOCARCINOMA BASED ON THE INDUCTION OF INTER-STRAND DNA BREAKS

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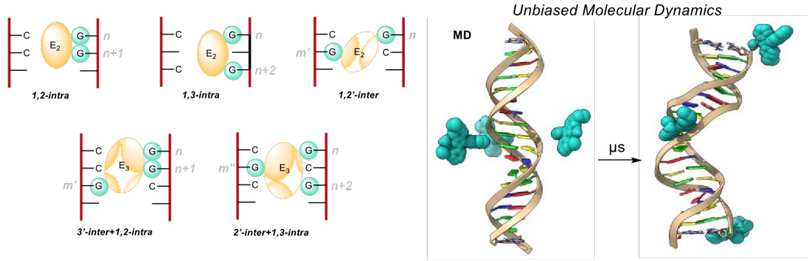
Cholangiocarcinoma (CCA) comprises a heterogeneous group of malignant biliary tumors characterized by a poor prognosis. First-line treatment for advanced CCA [cisplatin (CisPt) and gemcitabine][1] is considered palliative due to the high chemoresistance of this type of cancer, barely impacting on patients' overall survival.

This work presents the design, synthesis, and biological study of a new generation of platinum (Pt)-complexes (Auri-Pt#s) based on fused polyazaheterocycles. These compounds induce double-strand DNA breaks vs single-strand breaks induced by CisPt (Figure 1), resulting in increased cytotoxicity and apoptosis in cancer cells. These compounds have shown promising results in a variety of both naïve and CisPt-resistant cancers, including CCA, breast, and ovarian cancer. Their effectiveness, selectivity, and impact on the tumour microenvironment support their potential as therapeutic candidates in the fight against cancer.



-Figure 1-

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FC - 10 → P - 01* *correspondig poster

NEW HYBRID COMPOUNDS DERIVED FROM NATURAL PRODUCT PODOPHYLLOTOXIN TARGETING CANCER CELLS WITH DUAL MECHANISM OF ACTION

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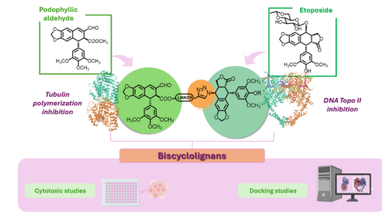
As cancer incidence remains growing, natural products still remain as valuable antitumor agents. Among them, the cyclolignan podophyllotoxin stands out. This compound presented important antitumor activity based on tubulin polymerization inhibition. However, despite this antitumor activity, it showed profound side effects but became a lead compound in the anticancer drug discovery field [1]. Structural modification of its skeleton, drove by chemical techniques such as molecular hybridization [2], lead to the synthesis of etoposide, which was approved as anticancer agent by FDA in 1983 against some lymphomas. Etoposide differs from podophyllotoxin in its mechanism of action, being an inhibitor of DNA-topoisomerase II enzyme. Nevertheless, side effects also limit the use of this drug in chemotherapy [3].

Herein, we report the synthesis and the in silico and *in vitro* evaluation of a new family of hybrid compounds, obtained through molecular hybridization strategies, named biscyclolignans. With these compounds, we try to combine in a single molecule the structure requirements to interact with both cellular targets, tubulin, and DNA-topoisomerase II, by joining two cyclolignans fragments through a heterocycle derived of 1,2,3-triazole, that acts as a linker. One of the fragments is derived from epipodophyllotoxin and the other from podophyllic aldehyde, a non-lactonic derivative obtained by our research group that showed better selectivity and cytotoxicity than podophyllotoxin against some human tumour cell lines [4]. The 1,4-disubstituted 1,2,3-triazole linker was synthesized following Click Chemistry procedures [5].



Docking studies have confirmed the potential dual mechanism of action of these compounds, obtaining similar affinity results as parental compounds. On their part, cytotoxic studies have shown interesting results relating to cytotoxicity and selectivity against some tumour cell lines, which manifest the improved properties of this family of compounds.

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BACK TO MAIN INDEX

FC - 11 → P - 19*

*correspondig poster

IMPLANTS THAT WORK SMARTER: THE ROLE OF BIOFUNCTIONAL COATINGS IN ADVANCING HEALTHCARE

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This comprehensive study examines various approaches developed within our research team for prosthesis development. These strategies include advanced coatings, biphasic titanium or ceramic implants, and 3D printing technology, all of which can be customized to meet specific patient anatomical and physiological needs. These strategies are designed to enhance osseointegration, provide antibacterial protection, and improve mechanical properties, integrating material science, biomechanic, and clinical considerations from a multidisciplinary and holistic perspective, Figure 1.

Titanium-based substrates with a specifically designed porous structure were utilized to fabricate prostheses, reducing stiffness and thereby minimizing stress shielding and promoting efficient bone ingrowth. Ceramic materials were also explored using 3D printing technology, enabling the creation of highly precise, customized structures that replicate the natural architecture of bone and cartilage. To enhance bioactivity at the implant interface, specific chemical treatments and state-of-the-art fabrication techniques were applied to intelligent and novel organic coatings. These coatings included different hydroxyapatites, bioglasses, crosslinked polymers such as chitosan, polyacrylate, polyacrylamide, and other PCL/PVA biocompatible materials or convenient composites containing nanoparticles.

Furthermore, we have endeavored to advance this cutting-edge knowledge into a largely unexplored field, pioneering high-quality research in tissue engineering to tackle the complex challenge of osteochondral defects. These investigations have been augmented with *ad hoc in vitro* and *in vivo* models, proteomic studies, and advanced virtual simulations to analyze and elucidate the molecular mechanisms governing interactions between implant systems and biological tissues, considering the intricate mechanical and chemical behaviors involved.

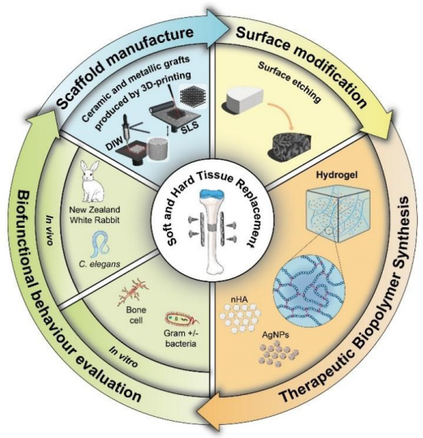

Figure 1.

Contributions and coordinated actions across different research areas, highlighting the group's collective impact on implemented prosthesis fabrication.

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This work is part of the project PID2022-137911OB-I00, funded by MICIU/AEI/ 10.13039/501100011033 and by ERDF/EU. Also, we would like to mention previous projects which laid the foundation for these investigations from Ministerio de Ciencia e Innovación Programa Estatal de I+D+*i* Retos de la Sociedad: Pruebas de Concepto (PDC2022-133369-I00) and Unión Europea: Proyectos I+D+*i* FEDER Andalucía 2014-2020 (US-1380878). D.C., G.M., E.J.D.-P. and M.B. would like to thank Ministerio de Educación y Formación Profesional, Plan Propio de Investigación Universidad de Sevilla and Ministerio de Universidades for their respective Beca de Colaboración, University of Seville (VII_PPITUS) and FPU21/06762 and FPU23/01664 grants.

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FC - 12 → P - 07* *correspondig poster

DISCOVERY OF NOVEL PROGERIN LIGANDS FOR PROTAC-BASED PROGERIA TREATMENT

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Hutchinson-Gilford Progeria Syndrome (HGPS), or progeria, is a rare disease that affects approximately 1 in 4 million newborns. It results in death at 14-15 years of age due to heart failure. This average life span can be extended up to 33% with lonafarnib administration, the only drug approved so far for treating progeria.[1] This modest efficacy, together with the fact that lonafarnib does not correct some of the main phenotypic hallmarks of the disease, [2] suggests the need to search for new approaches to the treatment of this disease. Progeria is caused by a mutant protein called progerin, whose accumulation in the nuclear membrane promotes permanent structural changes in cells. Recent studies have shown that reducing progerin levels in the nuclear membrane improves the phenotype of the disease. [3] Considering this, our research group has initiated a project aimed at directly reducing progerin levels through the development of proteolysis-targeted chimeras (PROTACs), heterobifunctional molecules capable of inducing degradation directed against a specific protein.

Previous work in our laboratory has successfully validated this approach with PROTAC UCM-18142,[4] based on (+)-decursinol (Figure 1A), the only progerin ligand described to date.[5] However, given the drawbacks associated with this natural product, such as its selectivity and limited pharmacological properties, the discovery of new progerin ligands is of utmost importance. Towards this end, cellular thermal shift assay (CETSA) has allowed us to identify compound UCM-91 as a new hit with affinity for progerin. In this work, we will present the medicinal chemistry program around this ligand (Figure 1B) to optimise the affinity for progerin and our efforts towards the development of new PROTACs targeting progerin with improved efficacy.

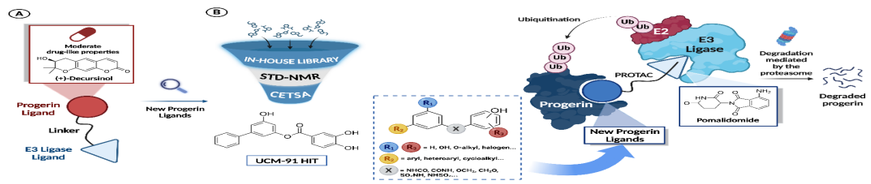

Figure 1. *(A) Schematic structure of a PROTAC based on (+)-decursinol. (B) Identification and structural exploration around hit UCM-91 and its application in the synthesis of new PROTACs directed to progerin.*

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The authors thank MCIN/AEI/FEDER (grant PID2022-138797OB-I00), The Progeria Research Foundation (grant PRF 2022-84) and Comunidad de Madrid (PIPF-2022/SAL-GL-24817 predoctoral contract to D.F.).

FC - 13 → P - 38* *correspondig poster

DUAL-MECHANISM PAIN MODULATION: SIGMA-1 ANTAGONISM AND SEH INHIBITION FOR ENHANCED ANALGESIA

Javier Sánchez [1, 2], Celia Escriche [1, 2], Eugènia Pujol [1, 2], José M. Entrena [3], Juan Martínez-López [1, 2], José M. Brea [4], Christophe Morisseau [5], Belén Pérez [6], Clara Bartra [7], Coral Sanfeliu [7], Bruce D. Hammock [5], María I. Loza [4], M. Carmen Ruiz-Cantero [8], Enrique J. Cobos [8] and Santiago Vázquez [1, 2]

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Chronic pain is a major global health issue. The limitations of conventional analgesics, alongside the opioid crisis, underscore the urgent need for alternative therapeutic strategies. This study presents the *first-in-class* **dual-acting analgesic compound**. Our approach focuses on compounds designed to simultaneously address the deficiencies of traditional analgesics by inhibiting **soluble epoxide hydrolase** (sEH) and antagonizing the **Sigma-1 receptor** (S1R).[1,2] By inhibiting sEH our compounds amplify epoxyeicosatrienoic acids, resulting in reduced pain response associated with neuropathy.[1] Furthermore, S1R is a key modulator of ion channels and receptor function in pain pathways, particularly by regulating calcium influx and influencing the activity of various pain-related signaling proteins, making it an attractive target for pain treatment.[2] Moreover, dual inhibition of S1R and sEH potentiates analgesic effects, offering a **synergistic and "opioid-free"** approach to pain management.[2]

Herein, we disclose a series of compounds that achieved **low nanomolar potencies** on both targets. A screening cascade with more than 200 compounds allowed us to identify a lead endowed with excellent potency and DMPK properties.[3] Subsequent *in vivo* assays in rodent models of pain showed that the lead compound **induced potent analgesia** without side effects through a dual mechanism of action. Additional *vivo* essays are currently ongoing.

Acknowledgements

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BACK TO MAIN INDEX

SEQT AWARDS COMMUNICATIONS

II Edición del Premio a la Mejor publicación SEQT (2022-2024)

OC - 17

MOLECULAR CHAMELEONICITY: NOVEL STRATEGIES IN THE bRo5 SPACE

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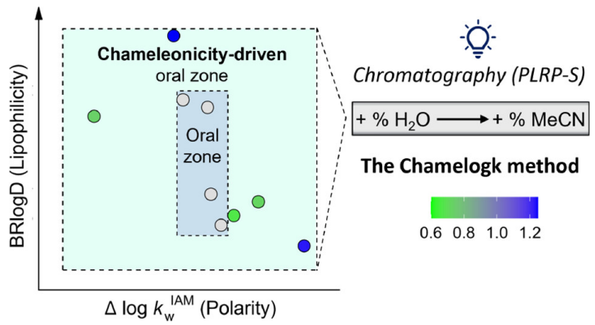
bRo5 (beyond-Rule-of-5) compounds such as PROTACs and macrocycles are highly interesting from a therapeutic potential but possess challenging physicochemical properties (i.e., extreme polarity and lipophilicity). As a result, they face *in vitro* ADME limitations (i.e., low water solubility and cell permeability) that impact their oral bioavailability. Nevertheless, nature has provided some examples of bRo5 molecules that can solve these issues by behaving as "molecular chameleons", i.e. by adapting to the surrounding environment. Nevertheless, the lack of bRo5-tailored property-based strategies slows down their development as oral drugs. [1]

In this context, a novel chromatographic method (RP-HPLC) to measure the chameleonicity of bRo5 compounds was recently disclosed by our group.[1] In practice, this method is able to capture the property change of compounds, when modifying the polarity of the environment. In addition to ranking of industrial candidates, its combination with other chromatographic descriptors (polarity and lipophilicity) and *in silico* studies, allowed to reveal structural patterns driving PROTAC chameleonicity (dynamic formation of IMHBs).

Overall, this work presents the latest advances on molecular chameleonicity, laying the foundation for their integration into property-based drug discovery strategies, particularly for the rational design of orally bioavailable bRo5 compounds.



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XXII Convocatoria premios para investigadores noveles: Premio Almirall

FC - 14 → P - 98*

*correspondig poster

INDUCING TARGETED PROTEIN DEGRADATION BY ALLOSTERIC MODULATION OF THE FBW7 E3 LIGASE

Andrea Bertran-Mostazo [1, 2], Míriam Martínez-Cartró [1, 2], Álvaro Serrano-Morrás [1, 2], Roger Castaño-Muñiz [1, 2], Salvatore Scaffidi [1, 2], Rosa Barrio [3], James D.Sutherland [3], Xavier Barril [1, 2, 4], Carles Galdeano [1, 2]

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E3 ligases are key regulators of the ubiquitin-proteasome system (UPS) and have emerged as attractive drug target candidates for precise therapeutic intervention. Additionally, their ligands are extremely valuable as handles for Targeted Protein Degradation (TPD). However, only a limited number of E3 ligases have been targeted with small molecules [1]. We applied an efficient approach to identify ligandable surfaces on 22 structurally diverse E3 ligases, revealing that they offer significant binding opportunities through allosteric pockets. As a proof of concept, we targeted an allosteric pocket identified in FBW7, leading to the discovery of the first potent small-molecule binders of this E3 ligase.

FBXW7 is one of the ~600 E3 ligases known in humans. Particularly, is one of the most deregulated proteins in human cancers (6% of cancers present mutations in the FBXW7 gene), resulting in an upregulation of its natural and oncogenic substrates such as c-Myc, cyclin E and Notch1 [2]. Although E3 ligases are attractive drug target candidates for specific and less toxic therapeutic intervention, the development of small-molecules against E3 ligases has been rewarded with limited success, and to date, no potent small-molecules targeting FBXW7 have been reported [3]. We identified several FBW7 allosteric binders with a K_D in the micromolar range. Biophysical and structural studies confirmed the binding site, while functional cell assays showed that some of these molecules act as allosteric enhancers of c-MYC and c-JUN degradation in an FBW7-dependent manner. These allosteric modulators of E3 ligases represent a novel mechanism of action in the TPD landscape and could be also used as PROTAC handles.

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We would like to acknowledge Almirall, S.A to award this work with the "Almirall Prize" in the "XXII Convocatoria Premios Para Investigadores Noveles En El Campo De La Búsqueda Y Desarrollo De Nuevas Terapias".

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BACK TO MAIN INDEX

XXII Convocatoria premios para investigadores noveles: Premio Johnson & Johnson

FC - 15 → P - 99*

*correspondig poster

UNVEILING THE THERAPEUTIC POTENTIAL OF THE INTEGRIN-LINKED KINASE WITH SMALL MOLECULES

Marta Durán Martínez [1], Mercedes Griera Merino [2], José Luis Aceña [1], Laura Calleros [3], Sergio de Frutos García [3], Diego Rodríguez Puyol [4], Javier García Marín[1]

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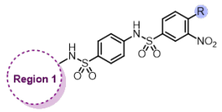
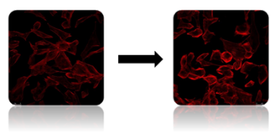
Integrin-Linked Kinase (ILK) is a pseudokinase that has been related to several prevalent diseases including chronic kidney disease (CKD), nephrogenic diabetes and diabetes mellitus. The first one is a pathology characterized by the accumulation of extracellular matrix in kidney cells and progressive acute kidney injury.

Despite its importance, ILK remains poorly understood due to its controversial catalytic role. Our research aims to deepen our understanding of ILK function and explore its potential as a therapeutic target for CKD. We have identified an ILK ligand, JGM416, capable of activating ILK function over the cell cytoskeleton. Since there are currently no drug-like molecules targeting ILK, we will report our progress in optimizing this compound with chemical, biological and computational approaches.

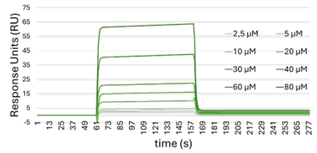
Structure-based design



Actin polymerization



Affinity assays



Acknowledgements

We would like to acknowledge the funding support of Comunidad de Madrid (INNOREN-CM/P2022/BMD-7221, CM/DEMG/2024-005 and FPI-CAM contract (A281)), Red Española de Supercomputación (BCV-2024-2-0037), Instituto de Salud Carlos III (RICORS2040-RENAL RD24/0004/0008 cofounded by European Union) and Johnson & Johnson (SEQT award)

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XXII Convocatoria premios para investigadores noveles: Premio Lilly

FC - 16 → P - 100*

*correspondig poster

DEVELOPMENT OF NEW MICROBIOTA-INSPIRED COMPOUNDS FOR THE VALIDATION OF NPM1 PROTEIN AS A THERAPEUTIC TARGET FOR ACUTE MYELOID

Anabel Sánchez-Merino [1], Miguel Ángel Navarro-Aguadero [2], Rafael L. Giner-Arroyo[3], Joaquín Tamargo-Azpilicueta [3], Irene Diaz-Moreno [3], Miguel Gallardo [2], María L. López-Rodríguez[1], Henar Vázquez-Villa [1], Bellinda Benhamú[1]

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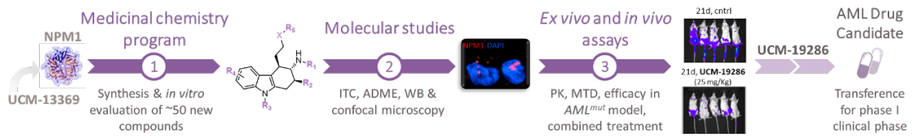
Acute myeloid leukemia (AML) is a disease caused by hematological myeloid cancer stem cells (CSC) with high mortality and a low 5-year survival rate (around 30%), especially for patients harboring critical nucleophosmin 1 (NPM1) genetic alteration.[1] However, no targeted approach to NPM1 mutation has yet been successfully translated into clinical practice. Recently, we generated a library of microbiota metabolite-inspired small molecules and identified the carbazole derivative **UCM-13369**, whose cytotoxicity against CSC was mediated by NPM1.[2] **UCM-13369** was characterized as an NPM1 inhibitor with promising efficacy in *ex vivo* and *in vivo* AML models, but observed toxicity precluded further development. In this work, we conducted a medicinal chemistry program around **UCM-13369** towards optimized inhibitors for the treatment of NPM1-AML.[3] Over 50 new analogues were synthesized and tested for NPM1 activity in AML cell lines and cytotoxicity in healthy fibroblasts. For compounds with optimal profiles, ADME properties were determined, and the mechanism of action was studied using western blot and confocal microscopy. Two candidates were selected for *in vivo* studies to evaluate pharmacokinetics, maximum tolerated dose and efficacy in a xenograft mouse model. **UCM-19286** treatment induced tumor reduction without toxicity, achieving a 70% increase in survival. Moreover, in e*x vivo* studies with AML patient and healthy donor samples **UCM-19286** showed a submicromolar IC_{50} and a 10-fold therapeutic window, supporting a strong potential as drug candidate. Ongoing preclinical evaluation aims to confirm the efficacy *in vivo* in a PDX model that will hopefully enable the advancement of **UCM-19286** as a first-in-class drug for NPM1-AML that addresses current therapy limitations.



Acknowledgements

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BACK TO MAIN INDEX

XXII Convocatoria premios para investigadores noveles: Premio Menarini

FC - 17 → P - 101*

*correspondig poster

NEW TUBULIN-INHIBITING ANTITUMOR AGENTS WITH DIARYLTETRAZOLE STRUCTURE: DESIGN, SYNTHESIS, AND BIOLOGICAL EVALUATION

Miguel Marín [1], Laura Gallego-Yerga [1], Dominik Fachet [2], Raúl Fuentes-Martín [1], Silvia Gonzalez-Pelayo [1], Simone Reber [2], Rafael Peláez [1]

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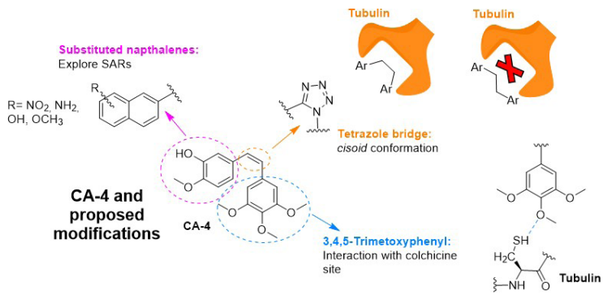
Agents that disrupt tubulin dynamics affecting its polymerization-depolymerization processes constitute an important class of antitumoral chemotherapeutics. Among these, Combretastatin A- 4 (CA-4) stands out for its potent activity and its dual role as a vascular-disrupting agent [1]. However, it suffers from poor solubility, isomerization issues, and susceptibility to multidrug resistance (MDR) pumps. In this study, we have synthesized a novel series of tetrazole compounds inspired by the structure of CA-4 (Figure 1): The B Ring was replaced with a naphthalene ring, incorporating various modifications to investigate its interaction with the colchicine binding site [2]. The Olefinic Bridge was replaced with a tetrazole bridge to enforce a *cisoid* conformation, essential for proper binding to the protein [1] [3]. The Trimethoxyphenyl Ring was retained, due to it is linked to strong cytotoxic activity.

Cytotoxicity assays against a broad range of cell lines were conducted, and the IC_{50} values of the most potent compounds showed nanomolar activity in the double-digit range. The most promising candidates were further evaluated through cell cycle analysis, cell death mechanisms, and in vitro depolymerization assays using functional tubulin. The synthesis and biological results will be presented, and the Structure-Activity Relationships (SAR) will be discussed.



Acknowledgements

Convocatoria de premios SEQT: Premio MENARINI. Funding support from Grant PID2021- 127471OB-I00, funded by MCIN/AEI/10.13039/501100011033, Junta de Castilla y León (SA0116P20), and "ERDF A way of making Europe" by the "European Union"

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XXII Convocatoria premios para investigadores noveles: Premio Ramón Madroñero SEQT

OC - 18

ATTACKING THE ACHILLES' HEEL OF THE INFLUENZA VIRUS: INHIBITORS OF VIRAL HEMAGGLUTININ FUSION.

Álvaro de la Cruz [1], Marina Serrano [1], Francisco J. Hermoso [2], Dr. Lieve Naesens [3], Dr. Francisco J. Luque [2], Dr. María José Camarasa [1], Dr. Sonia de Castro [1]

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The emergence of resistant Influenza strains undermines the efficacy of existing antiviral therapies, leaving few reliable treatment options. As a result, Influenza remains a leading cause of morbidity and mortality, imposing a substantial economic burden due to increased hospitalizations and healthcare costs. This urgent scenario demands novel antiviral strategies capable of delivering broad-spectrum efficacy.

One of the most promising strategies is the design of drugs targeting highly conserved viral regions, a strategy that could overcome viral resistance. In this pursuit, our research group has identified a novel class of **N-benzyl-4,4-disubstituted-piperidines**, the first molecules known to specifically inhibit the fusion process of **H1N1 Influenza A virus** by directly interacting with the fusion peptide of hemagglutinin (HA). These fusion inhibitors represent a revolutionary advance, as no other compounds have been reported to bind this critical viral component.

Mechanistic and computational studies on the peptidomimetic prototype **DICAM180** revealed that its antiviral activity is driven by interaction with a previously unexplored pocket in the HA2 subunit. This unique binding mechanism is mediated by a **direct π-stacking interaction with the Phe9 residue of the HA2 fusion peptide**, a key structural feature required for viral entry. By exploiting this weak spot of Influenza, our approach opens the door to a new class of broad-spectrum antivirals with the potential to overcome resistance.

Taking advantage of the **trimeric structure of hemagglutinin (HA)**, we have conducted structure-activity relationship (SAR) studies, complemented by molecular dynamics simulations, to optimize interactions and improve inhibitory potency. Our strategy aims to simultaneously target a second fusion peptide, an innovative approach designed to amplify antiviral efficacy and broaden the anti-influenza activity.

To further assess the drug development potential of the most promising candidates, we have conducted **stability, aggregation and ADME-Tox studies**, ensuring their suitability for pharmaceutical formulation. Additionally, we have explored **alternative delivery strategies** to optimize bioavailability and therapeutic efficacy. These efforts are essential to advancing our fusion inhibitors towards clinical application, reinforcing their potential as next-generation broad-spectrum anti-Influenza agents.

Acknowledgements:

Álvaro de la Cruz Potenciano expresses his gratitude to the S.E.Q.T. for awarding him the Ramón Madroñero Prize.

BACK TO MAIN INDEX

POSTERS

P - 02

THE ANXIOLYTIC, ANTI-DEPRESSIVE, AND ANTIOXIDATIVE EFFECTS OF LEMON VERBENA IN RAT RENDERED DIABETIC BY STREPTOZOTOCIN INJECTION

Oumaima Abouyaala[1], Mustapha El Aoufi[1], Soukaina Bougrine[1], Noura Rahmouny[1], Mohammed Yassine El Brouzi[1], Marouane El Arbaoui[1], Brahim Sow[1], Khadija Elmotia[1], Moulay Laarbi Ouahidi[1].

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Diabetes, is a metabolic pathology marked by chronic hyperglycemia, that leads to a multitude of long-term complications, adversely affecting various organ systems, including retinopathy, nephropathy, and peripheral neuropathy [1]. The brain could be affected by diabetes [2], which undergoes glycemic changes that may increase the risk of psychiatric disorders like depression, and anxiety [3, 4].

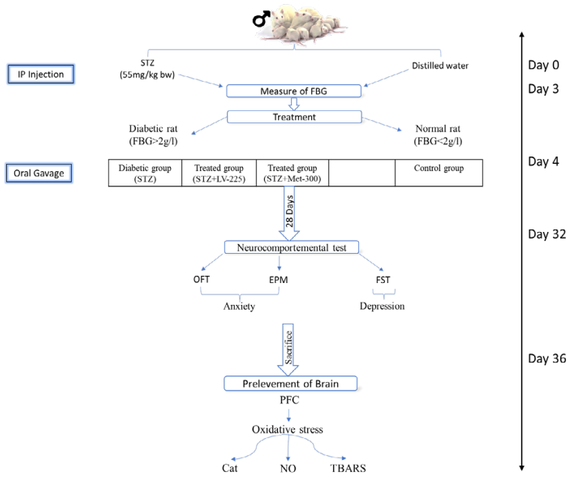
Many studies about the anxiolytic and antidepressant of Lemon verbena (LV) were found, but no studies delineated a direct link between affective disorders in diabetics and the mechanism of LV effect on neurobehavioral disorders. The current study aimed to investigate if treatment with Lemon Verbena methanolic extract (LVME) improves hyperglycemia-related affective disorders by mitigating oxidative stress in rats rendered diabetic by streptozotocin (STZ).

After intraperitoneal injection of STZ, experimental diabetes was induced and confirmed. Then, the normal rat received distilled water, however, three diabetic group rats were treated with LVME, Metformin, for 28 days respectively. The examination of affective disorders was assessed using the neurobehavioral test, and the prefrontal cortex (CPF) oxidative stress (OS) markers were evaluated also.

Our study revealed that treatment with LVME reversed the STZ effect on behavioral disorders in the OFT, EPM, and FST demonstrating their anxiolytic, and anti-depressive effects. The amelioration of antioxidant enzymes and reduction in oxidant markers at the PFC in the treated group with LVME can explain this. The Lemon verbena methanolic extract ameliorated the anxiety and depression-like effects in rats rendered diabetic by STZ- injection, which its antioxidant activity in the PFC region might explain.

Keywords:
LVME, Streptozotocin, anxiety, depression, oxidative stress.

Graphical abstract



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The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

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P - 03

VERSATILE NANOENCAPSULATION PLATFORM FOR THE STABILIZATION AND ORAL DELIVERY OF PEPTIDES

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Pharmaceutical research and development is shifting toward biopharmaceuticals such as peptide and protein drugs, but most remain injectable due to permeability barriers and gastrointestinal (GI) instability. Nanotechnology offers promising solutions for oral formulations. However, the efficacy, safety and reproducibility of many of these methods need to be improved[1].

To address these issues, we propose the IC-Tagging system patented in our laboratory as an advanced one-step, *in cellulo* nanosphere (NS)-encapsulation strategy for protein stabilization and oral delivery. This technology allows the production of NS loaded with any protein of interest without affecting its folding or function[2]. Recently, a highly active version of AvPAL (a candidate enzyme to treat phenylketonuria) was produced to which nanoencapsulation provides formidable thermostability, long-term storage stability, resistance to acidic pH and proteolytic degradation protection. This latter characteristic, essential for oral delivery, is further enhanced by coating the NS with chitosan. Thus, a similarly nanoencapsulated and chitosan coated luciferase displays sustained enzymatic activity through the entire GI transit when administered orally in mice, indicating the high protective capability of the system while maintaining the availability (**Fig.1**).

Overall, these results highlight the potential and versatility for peptide-based oral delivery applications of this innovative methodology not only in the field of enzyme replacement therapies (AvPAL), but also for other therapeutic peptides/proteins (e.g. insulin, GLP1, antifibrotics, etc.).

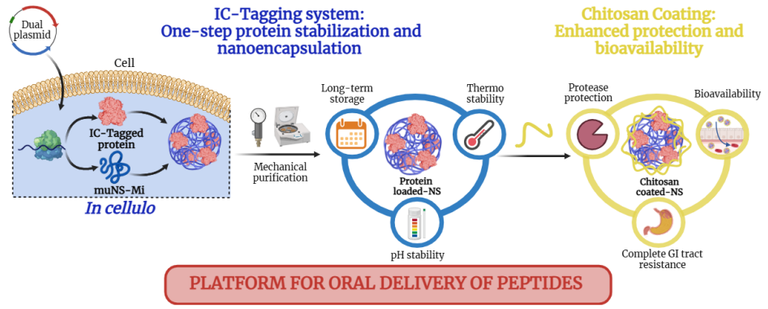

Fig.1. Representative diagram of the proposed methodology.

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BACK TO MAIN INDEX

P - 04

MULTIFUNCTIONAL COMPOUNDS FOR PREVENTING SEVERE SKIN DISEASES: SYNTHESIS, TYROSINASE INHIBITION, ANTIOXIDANT ACTIVITY, AND SPF EVALUATION

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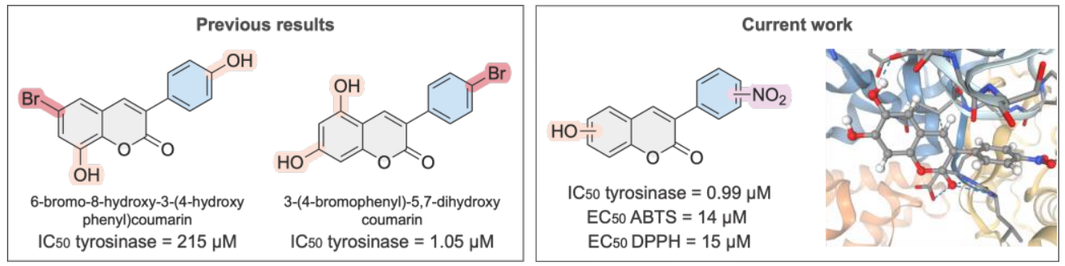
The biosynthesis of melanin involves a series of oxidative reactions, with the amino acid tyrosine serving as a substrate in the presence of the enzyme tyrosinase. Consequently, excessive activity of this enzyme can result in dermatological conditions such as age spots, melanoma, and areas of actinic damage. Differently substituted 3-phenylcoumarins have been shown to efficiently inhibit tyrosinase [1-3]. In this study, new substitution patterns were explored, and the biological evaluation was extended to include other key enzymes involved in skin aging, the antioxidant profile of the compounds, and an assessment of their sun protection factor. Of the first nine compounds tested, six demonstrated inhibitory activity against tyrosinase, along with DPPH and ABTS radical scavenging capacity, being all non-cytotoxic to human skin keratinocytes. 6,7Dihydroxy-3-(4-nitrophenyl)coumarin exhibited the highest tyrosinase inhibitory activity, with an

IC^{50} of $^{0.99}$ µM, along with an ABTS EC^{50} of ^{14} µM and a DPPH EC^{50} of ^{15} µM. This compound also displayed photo-protective effects. Furthermore, based on the overall biological activities, it emerged as the most promising anti-aging candidate. To further understand their interactions with target enzyme, computational studies were performed to predict the binding sites.



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P - 05

DESIGN, SYNTHESIS AND EVALUATION SULFONAMIDES AS ANTITUMOR AND ANTIPARISITIC AGENTS

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Tubulin-binding drugs are one of the most successful chemotherapy approaches. Tubulin is responsible for the formation of microtubules, which are part of the cytoskeleton, transport organelles and vesicles and are responsible for the mitotic spindle. Tubulin has α and β subunits and a wide variety of drug binding sites. The colchicine site is one of them located at the interface between the α and β tubulin subunits. Combrestastatin A-4 (CA-4) inhibit tubulin polymerization by binding at that site, but have several limitation such as low solubility, toxicity, drug resistance etc.

Here, we proposed a new family of tubulin inhibitors with potential antitumor and/or antiparasitic activity by binding to the colchicine site on tubulin (Figure 1). The synthetic methodology developed allows to obtain a huge number of compounds in quantities and high purity.

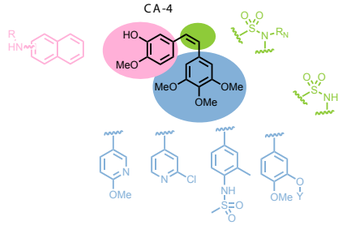

Figure 1: New antimitotic and antiparistisc compunds

These compounds were evaluated in vitro against human tumour cell lines and agains four parasites: Strongyloides spp., Trichinella spp., Schistosoma spp., and Leishmania spp. The results suggest that these compounds on tumor cells inhibit tubling polymerizatio. On the other hand, molecules with antiparasitic effects have been reported especially against Strongyloides venezuelensis and Trichinella spiralis

In conclusion, the improved of pharmacokinetics problems and high potency make these compounds promising as new antitumor agents acting on tubulin and antiparasitic.

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Keywords: Sulfonamides, tubulin, antimitotic, combrestastatin A-4, ABT-751, antitumor, antiparasitic

BACK TO MAIN INDEX

P - 06

VALORIZATION OF DOMESTIC PLANT RESIDUES AS ANTIFUNGAL AGENTS

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In European countries, vegetable waste generation ranged from 35 to 78 kg per capita in 2022 [1], posing both an opportunity for the valorization of agro-industrial byproducts and an environmental challenge. Numerous studies have revealed that these byproducts can contain secondary metabolites with antifungal properties. Fungal infections pose a serious problem, as they can cause significant health issues such as skin infections or gastrointestinal disturbances. Some strains of the fungus *Penicillium griseofulvum* produce mycotoxins such as patulin and griseofulvin, which can contaminate human foods leading to gastrointestinal issues, immunotoxicity and even carcinogenic effects when consumed. Thus, the objective of this study was to characterize the phytochemical profiles of some vegetable byproducts and to evaluate their potential antifungal activity against a patulin-producing strain of *P. griseofulvum*. The findings revealed that two extracts derived from fruit peels inhibited the fungal growth. Additionally, it was observed that hydroxycinnamic acids, terpenes and flavonoids could be the responsible compounds for this antifungal activity. These results suggest that vegetable byproducts could help reduce mycotoxin contamination in food, offering a sustainable solution within the framework of a circular economy.

Figure 1. Growth of P. griseofulvum over eight days in the presence of different plant residue extracts.

Acknowledgements

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P - 09

ANTIDEPRESSANT-LIKE EFFECTS OF A NOVEL IMIDAZOLINE I_2 RECEPTOR LIGAND

Fernando Romero [1,2], Maria-Eleni Kouridaki [1,2], Sandra Codony [1,2], Paula Romero-Peña [1,2], Rebeca Diez-Alarcia [3,4], Luis F. Callado [3,4], Fernando Yáñez-Gómez [5], Rubén García-Cabrerizo [5], M. Julia Garcia-Fuster [5], Eddy Sotelo,[6,7], Christian Griñán,[8], Mercè Pallàs,[8], and Carmen Escolano.[1]

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Imidazoline I_2 receptors (I_2-IRs) are non-adrenergic binding sites for imidazolines that emerged as relevant biological targets.[1] The dysregulation of the levels of I_2-IRs is a hallmark in human brain disorders encompassing depression, Alzheimer's disease, and Parkinson's disease, among others.[2] Due to the absence of structural data on I_2-IRs, their pharmacological characterization relies on the discovery of selective I_2-IRs ligands endowed with high affinity. Unfortunately, the known I_2-IRs ligands are restricted to 2-heterocyclic-2-imidazolines, such as standard non-selective idazoxan. Being aware of the importance of discovering new ligands, we took the challenge of developing structurally original ligands.[3,4] A family of 2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2,5-dihydro-1*H*-imidazole derivatives (Figure 1) were synthesized to avoid the stereocenter of idazoxan. LSL60129, was selected for performing *in vivo* studies in rats, showing dose-dependent antidepressant-like effects.

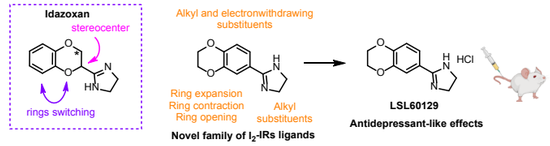

Figure 1. Idazoxan and the new family of I_2-IRs ligands of this work.

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BACK TO MAIN INDEX

P - 10

TAILORIGN THE TRIANGULENIUM SCAFFOLD TO FIND NOVEL TOOLS FOR BIOIMAGING TECHNIQUES

Carmen Viedma-Barba[1], Esther Ortega-Naranjo[2], Carmen Salto[2], M. Dolores Giron[3], Rafael Salto[3], Juan A. González-Vera[2], Ángel Orte[2] and Marta Gutiérrez-Rodríguez[1]

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Fluorescent small molecules have shown a wide range of applications such as cellular staining, detection of specific bioanalytes, and tracking biomolecules of interest. The photophysical properties of the fluorophore define the particular applications in which they are most beneficial, considering the sensitivity, efficiency, and operative fluorescence lifetime of the detection process. Long fluorescence lifetime fluorophores offer many advantages in time-resolved imaging.[1] However, only a few dyes with fluorescence times greater than 5 ns emit in the visible region.

Over the last decade, triangulenes have received more attention. These dyes are essentially ultrabright and more stable versions of fluorescein and rhodamine. Triangulenes present the unique combination of having long fluorescence lifetimes (10-20 ns) and high quantum yields, making them useful tools for many applications. In this regard, novel triangulenium dyes constitute useful tools for bioimaging techniques such as FLIM or polarization assays.

In our research group, we are developing new triangulenos dyes to use in FLIM imaging. In fact, all of the tested dyes exhibit rich behavior for FLIM, because they present different fluorescence lifetimes depending on which part of the cell are located. Furthermore, some triangulenium dyes are known to act as efficient DNA binders. The planarity of the DAOTA moiety helps them to insert into DNA strands as intercalators. Interestingly, they have been shown to differentially bind Gquadruplex strands,[2] making them useful tools for the identification of different types of DNA.

In this communication, we will describe the design, synthesis and photophysical properties of novel triangulenium dyes with long fluorescence lifetimes useful for bioimaging techniques and DNA visualization.

Acknowledgements

The study was funded by: grant PID2022-137214OB-C22 funded by MCIN/AEI/10.13039/501100011033 and by "ERDF A way of making Europe"; grant PID2020-114256RB-I00 funded by MCIN/AEI/10.13039/501100011033; CSIC grant 202180E073 and grants P21_00212 and A-FQM-386UGR20 funded by FEDER/Junta de Andalucía-Consejería de Transformación Económica, Industria, Conocimiento y Universidades. C. Viedma Barba holds a FPI Predoctoral contracts subsidized by Spanish

Minister of Science and Innovation (PRE2020-093542) granted by MCIN/AEI/10.13039/501100011033 and "ESF Investing in your future"

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P - 12

HARNESSING ACETYLCHOLINESTERASE TEMPLATE EFFECTS FOR THE DEVELOPMENT OF A NEW CLASS OF MULTITARGET ANTI-ALZHEIMER AGENTS

Anna Sampietro[1, 2], Wawrzyniec Haberek[1], Aina Bellver[3, 4], Christian Griñán-Ferré[3, 4], Belén Pérez[5], Carmen Pérez de la Lastra Aranda[6], Valle Palomo[6, 7, 8], Marina Naldi[9], Rosaria Spagnuolo[9], Manuela Bartolini,[9] María Isabel Loza[10] José Brea[10], Clara Bartra[11], Coral Sanfeliu[11], Christophe Morisseau[12], Raimon Sabate[13, 14], Jordi Juárez-Jiménez[13, 15], Bruce D. Hammock[12] Mercè Pallàs[3, 4], Santiago Vázquez[1, 2] and **Diego Muñoz-Torrero**[1, 2]

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The particular architecture and composition of the catalytic gorge of acetylcholinesterase (AChE) make that multisite inhibitors, designed to hit both the active and peripheral aromatic sites of the enzyme, are structurally well suited to hit other biological targets of interest for Alzheimer's disease (AD) treatment[1]. They include soluble epoxide hydrolase (sEH), another enzyme with a large active site cavity, involved in neuroinflammation, and the aggregation of amyloidogenic proteins with key pathogenic roles. Here we show a new class of multisite inhibitors of AChE and sEH that additionally inhibit the aggregation of Aβ42, tau and TDP-43 in different experimental settings (*E. coli*, SH-SY5Y cells, *C. elegans*). A lead compound (ASP45) with a very interesting activity profile, brain permeability, favorable aqueous solubility and microsomal stability, and devoid of neurotoxicity, has been selected for further preclinical studies.

Acknowledgements

This work was funded by grants PID2020-118127RB-I00 and PID2023-147004OB-I00 from MICIU/AEI/10.13039/501100011033 and FEDER, EU, and 2021SGR00357 from AGAUR.

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BACK TO MAIN INDEX

P - 13

FINE-TUNING GLYCOSIDASE INHIBITION THROUGH A FOCUSED LIBRARY OF sp²-IMINOSUGAR GLYCOPEPTIDES

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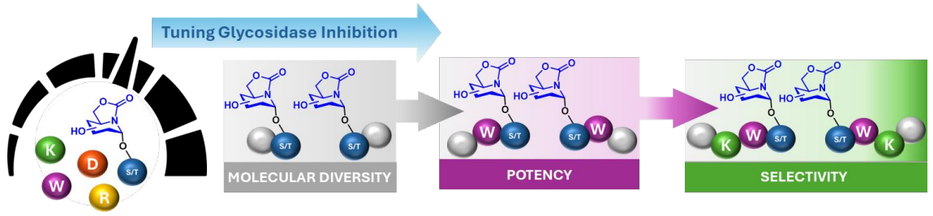
Iminosugars, nitrogen-containing analogues of monosaccharides, are among the most extensively studied glycomimetics, with several compounds already approved for clinical use.[1] Despite their potent glycosidase inhibition activity, their therapeutic utility is often limited by poor selectivity. To overcome this limitation, sp²-iminosugars have been developed, in which the endocyclic nitrogen is incorporated into a pseudoamide moiety.[2] These molecules mimic both the hydroxylation pattern and electronic features of native monosaccharides, while forming chemically stable α-glycosides. This unique profile enables the rational design of ligands that engage both glycone and aglycone binding pockets of the target glycosidase. In this context, we propose sp²-iminosugar–based glycopeptides as a promising platform to enhance enzyme binding affinity and selectivity.[3] By combining the structural versatility of peptide chemistry with the distinctive reactivity of sp²-iminosugars, we aim to develop a modular, diversity-oriented approach for the generation of a focused library of these novel glycomimetics. This strategy is intended to provide fine control over molecular recognition and expand the chemical toolbox for selective glycosidase inhibition.



Acknowledgements

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ERDF A way of making Europe" (Grants number PID2022-141034OB-C21), MCIN/AEI/10.13039/501100011033 (Grant RYC2021-034263-I, and EU "Next Generation EU/Recovery, Transformation and Resilience Plan".

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P - 14

NOVEL OPTOGLYCOMIC STRATEGIES FOR MODULATING GLYCOSIDASE INHIBITION SELECTIVITY

Gonzalo Rivero-Barbarroja [1], Stéphane Maisonneuve [2], Juan Xie [2], José Manuel García Fernández[3] and Carmen Ortiz Mellet.[1]

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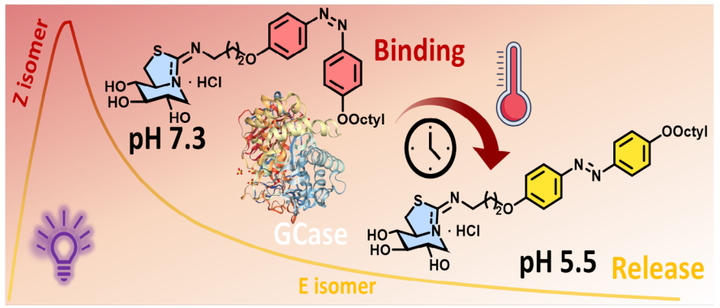
Photopharmacology harnesses light-responsive drugs to achieve precise spatiotemporal control of biological interactions, which is crucial for therapies requiring dynamic drug-target binding.[1] Pharmacological chaperone (PC) therapy for lysosomal storage disorders (LSDs) is a paradigmatic example: PCs must stabilize the corresponding disease-associated misfolded glycosidase in the endoplasmic reticulum (ER) while releasing in the lysosome to restore function. Azobenzene-equipped photoswitchable sp²-iminosugars can meet these requirements by exploiting differential *E*-/*Z*-isomer interactions with the aglycone-accommodating regions of the enzyme.[2] In this research, we finely-tuned glycomimetic, linker, and azobenzene structure to optimize light-promoted *E*→*Z* conversion and temperature-dependent *Z*→*E* reversion using a diversity-driven approach. This strategy yielded derivatives capable of selectively toggling between α- and β-glucosidase inhibition with remarkable switching factors. Moreover, conjugates exhibiting nanomolar inhibition of human β-glucocerebrosidase—the dysfunctional enzyme in Gaucher disease—upon photoactivation and delayed deactivation under physiological conditions mimicking ER-to lysosome trafficking were optimized. These findings advance the field of optoglycomics, providing a blueprint for next-generation of photoresponsive glycosidase inhibitors with therapeutic potential for LSDs and broader biomedical applications.



Acknowledgements

We acknowledge funding by MCIU, the Agencia Estatal de Investigación (AEI/10.13039/501100011033) and "ERDF A way of making Europe" (PID2021-124247OB-C21 and PID2022-141034OB-C21) and the Booster program of ENS Paris-Saclay.

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BACK TO MAIN INDEX

P - 16

LEVERAGING KEAP1 E3 LIGASE ACTIVITY FOR THE DEVELOPMENT OF DUAL-ACTING PROTACS

Anna Sampietro [1,2,3], Roger Castaño-Muñiz [2,3], Álvaro Serrano-Morrás [2,3], Ana Buj [1,2], Alejandra Rodríguez-Gimeno [2,3], Diego Muñoz-Torrero [1,2], Carles Galdeano [2,3]

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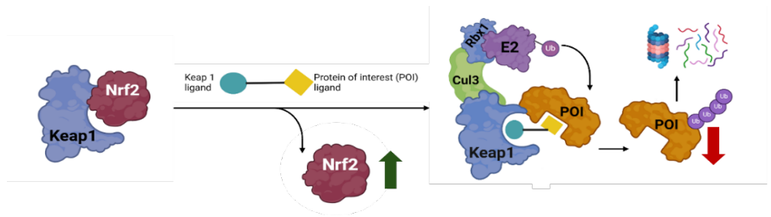
Targeted Protein Degradation (TPD) has emerged as a strategy to target undruggable proteins, however only few E3 ligases have been exploited for PROTAC development.[1] KEAP1, an underutilized E3 ligase, naturally ubiquitinates and degrades Nrf2, a transcription factor with antioxidant properties.[2] This work aims to identify novel, non-covalent KEAP1 ligands that serve a dual purpose: disrupting KEAP1-Nrf2 interaction to enhance the antioxidant effects and acting as PROTAC warheads. This approach holds promise for treating neurodegenerative diseases and KEAP1-overexpressing cancers, where oxidative stress is a hallmark.



To identify novel ligands, we have performed a computational approach developed in our Lab. MDMix[3] calculations were performed to determine key interactions and define a new pharmacophore. A virtual screening campaign, followed by undocking simulations,[4] allowed us to select 20 ligands. Biophysical techniques such as Surface Plasmon Resonance (SPR) and Fluorescence Polarization (FP) assays validated eight ligands. Further SAR studies using the EnamineREAL space library led to the discovery of three high-quality hits with favorable drug-like properties. From these three hits, we selected the one that showed better conditions to be developed as a PROTACs (vector exit). Ultimately, five novel PROTACs have been synthesized. These PROTACs can retain their binding affinity and successfully form ternary complexes, as confirmed by SPR. Degradation studies are on-going in our Lab.

Acknowledgements

This work was supported by grant PID2023-147004OB-I00 funded by MICIU/AEI/10.13039/501100011033 and FEDER, EU, 2021SGR00357 funded by AGAUR, and FPU21/00810 by MICIU.

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P - 17

DE NOVO MULTICOMPONENT SYNTHESIS OF PYRIDINE AND PYRIMIDINE SCAFFOLDS ENABLES THE DISCOVERY OF NOVEL ANTICANCER AGENTS

Iván Rodríguez-Pampín [1], David Reza [1], Vicente Yaziji-Lorenzo [1], Rubén Prieto-Díaz [1], José M-Brea [2], María I. Loza [2], M. Jesús Núñez [3], Silvia Novio [3], and Eddy Sotelo.[1]

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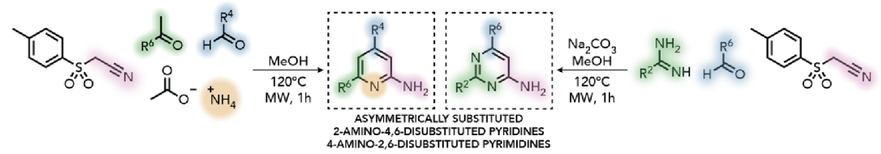
Pyridines and pyrimidines are prototypical privileged heterocyclic scaffolds frequently found in approved drugs, owing to their favorable pharmacodynamic and pharmacokinetic properties. Their incorporation into drug candidates often improves bioactivity, selectivity, and overall developability, facilitating progression through optimization and clinical evaluation. This has sustained considerable interest in the development of efficient and modular synthetic strategies to access structurally diverse analogues. Although various methods exist for assembling these scaffolds, there remains a pressing need for novel, innovative, and environmentally friendly approaches that enable the rapid and cost-effective synthesis of diversely substituted pyridine and pyrimidine derivatives.

Adenosine receptors are compelling therapeutic targets[1] for the treatment of serious conditions such as cancer, glaucoma, and neurodegenerative diseases. Owing to their structural similarity to the purine core, pyridine and pyrimidine derivatives have been widely explored as adenosine receptor ligands, with several candidates progressing into clinical trials. Nonetheless, the rapid generation of structurally diverse ligands with high ligand efficiency remains a major synthetic challenge. Herein, we describe a previously unreported multicomponent synthetic methodology that enables the efficient one-pot assembly of 2-amino-4,6-disubstituted pyridines and 4-amino2,6-disubstituted pyrimidines. This operationally simple and modular approach provides rapid access to unexplored chemical space and has led to the discovery of potent and selective adenosine receptor antagonists with promising anticancer activity.



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P - 18

FROM PEPTIDES TO PEPTIDOMIMETICS: THE JOURNEY TOWARDS TRIAZOLE-PHENYL-THIAZOLE SCAFFOLDS AS LITRYR DIMERIZATION DISRUPTORS

Miguel Maldonado [1], Sonia de Castro [1], Héctor de Lucio [2], Mercedes Alcón-Calderón [2], Antonio Jiménez [2], Federico Gago[3] and María José Camarasa[1]

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Leishmaniasis is the second most lethal parasitic disease, yet the therapeutic arsenal remains limited and outdated. The urgent need for new, less toxic drugs and novel mechanism of action is widely recognized. Leishmania infantum Trypanothione Reductase (*Li*TryR) is a key enzyme in the parasite's antioxidant defense system and a well-established target for rational drug design. Our research group has developed an alternative inhibition strategy focused on disrupting the homodimeric interface of LiTryR.[1] This approach was initially validated using peptides and peptidomimetics that mimic the α-helix that interact with the 'hot spots' at the dimerization interface. [2,3]

In pursuit of more effective dimerization inhibitors with an improved activity/toxicity profile, we previously reported a symmetrical peptidomimetic based on a 1,2,3-triazole-phenyl-thiazole scaffold.[4] Molecular modeling studies revealed an underexplored hydrophobic region at the enzyme's central interfacial domain as a potential binding site for this inhibitor. To assess their leishmanicidal potential and conduct structure-activity relationship (SAR) studies, we now present the design and synthesis of novel symmetrical triazole-phenyl-thiazole derivatives featuring structural modifications at the R_1, R_2 and R_3 positions (Figure 1).

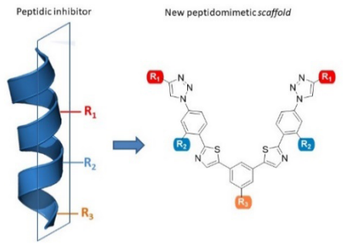

Figure 1. *Target symmetrical triazole compounds* **I**.

Acknowledgements
We would like to acknowledge the funding support to MICINN (project Nº PID2022-136307OB-C21).

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P - 20

(3-PHENYLCARBAMOYL-3,4-DIHYDRO-2*H*-PYRROL-2-YL) PHOSPHONATES WITH ANTI-ALZHEIMER AND ANALGESIC PROPERTIES

Carmen Escolano[1 2], Alba López-Ruiz [1, 2], M. Carmen Ruiz-Cantero [1], Christian Griñán-Ferré [3, 4], Mercè Pallàs [3, 4], José M. Entrena,[5, 6], Enrique J. Cobos.[5,6]

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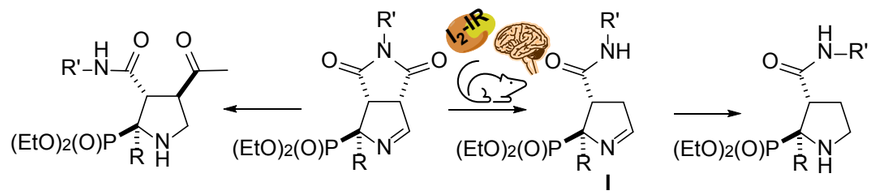
The dysregulation of the levels of imidazoline I_2 receptors (I_2-IRs) is a common hallmark in a plethora of illness such as Alzheimer's disease (AD) and their modulation have an analgesic effect. I_2-IRs are not structurally described, and their pharmacological characterization relies on their modulation by selective ligands. In this context, we have provided several structurally new families of ligands with outstanding affinity and selectivity upon I_2-IRs [1]. More recently, we identified diethyl (2*RS*,3*RS*)-3-((3-chloro-4-fluorophenyl)carbamoyl)-2-phenyl-3,4-dihydro-2*H*-pyrrol-2-yl) phosphonate, with an optimal ADME and pharmacokinetic profile that secured it *in vivo* exploration in an AD murine model revealing improvement in the cognitive impairment. The treatment of a capsaicin-induced mechanical hypersensitivity murine model with this compound reveals analgesic properties devoid of motor coordination issues [2].

In the same framework, we synthetised unprecedented diversely substituted (pyrrolidine-2-yl)phosphonates that were also pharmacologically evaluated.

Overall, the selected compound (general structure I R=Ph, R'=3Cl4FPh) is a putative candidate for advancing preclinical phases and supports the modulation of I_2-IRs as an innovative approach for therapeutics.



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Acknowledgements
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BACK TO MAIN INDEX

P - 21

NOVEL BIODEGRADABLE POLYMER COATINGS FOR POROUS TITANIUM: A HOLISTIC APPROACH TO ENHANCE IMPLANT PERFORMANCE

Guillermo Martínez [1], Ernesto Delgado-Pujol [2], David Casado [1], [3], Manuel Merinero[3], Mario Balbuena[2], David Rodríguez-Lucena [1], Manuel de Miguel [3], Maikel CastellanoPozo [4], Eloisa Pajuelo[5], Belén Begines[1], Yadir Torres[2], Ana Alcudia [1].

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This study explores innovative strategies in biomedical engineering to improve titanium implants by integrating porous substrates with biodegradable polymeric coatings. Porous titanium substrates, fabricated using space-holder techniques, enhance tribomechanical properties and minimize modulus mismatch with cortical bone, addressing a critical challenge in implant design. Additionally, biodegradable hydrogels synthesized from polyacrylamide and poly(acrylic acid) with reduction-sensitive crosslinkers exhibit strong antibacterial activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Comprehensive in vitro and in vivo studies confirm the biocompatibility, low toxicity, and safety of these coatings, demonstrating their potential for clinical applications. This work offers a synergistic approach to next-generation implants, advancing mechanical, antibacterial, and bioactive properties for innovative solutions in bone tumor replacement and biomaterials development.

Acknowledgements

This work is part of the project PID2022-137911OB-I00, funded by MICIU/AEI/ 10.13039/501100011033 and by ERDF/EU. Also, we would like to mention previous projects which laid the foundation for these investigations from Ministerio de Ciencia e Innovación Programa Estatal de I+D+i Retos de la Sociedad: Pruebas de Concepto (PDC2022-133369-I00) and Unión Europea: Proyectos I+D+i FEDER Andalucía 2014-2020 (US-1380878). D.C., G.M., E.J.D.-P. and M.B. would like to thank Ministerio de Educación y Formación Profesional, Plan Propio de Investigación Universidad de Sevilla and Ministerio de Universidades for their respective Beca de Colaboración, University of Seville (VII_PPITUS) and FPU21/06762 and FPU23/01664 grants.

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P - 22

sp²-IMINOSUGAR-BASED TRIMANNOSYL GLYCOLIPID CONJUGATES AS TLR4 ANTAGONISTS

M. Carmen Padilla-Pérez [1], Alan Chuan-Ying Lai [2], Elena M. Sánchez-Fernández [1], Chieh-Hsin Ho [2], Po-Yu Chi [2], Ko-Chien Wu [2], Ya-Jen Chang [2], José M. García Fernández [3], Carmen Ortiz Mellet [1]

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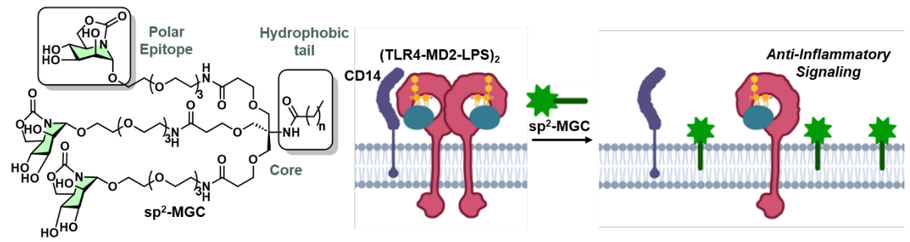
Toll-Like Receptor 4 (TLR4) is a key mediator in inflammatory pathways implicated in various pathological conditions, including ischemia, neuropathic pain, neurodegeneration, and cancer. Traditional glycolipid-based TLR4 antagonists exert their effects by binding within the $(TLR4)_2(MD2)_2$ complex, thereby preventing interactions with natural ligands. However, trimannosyl glycolipid conjugates (MGCs), act via a distinct mechanism. These molecules possess a branched core functionalized with three mannose units and a hydrophobic tail.[1] MGCs selectively inhibit TLR4-driven immune activation in LPS-stimulated human monocytes and dendritic cells by altering lipid rafts at the plasma membrane, thereby disrupting the colocalization of the CD14 cofactor and TLR4. Here, we explore the impact of replacing the α-D-mannopyranosyl units with sp²-iminosugar motifs, generating novel conjugates with enhanced chemical and enzymatic stability. The intrinsic structural versatility of sp²-iminosugars facilitates the rational design of molecularly diverse derivatives,[2] enabling systematic modifications in the sp²-iminosugar core, glycosidic bond type, spacer composition, and lipid chain characteristics. Preliminary immunological assays reveal that sp²-MGCs preserve the antagonistic properties observed in MGCs.



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BACK TO MAIN INDEX

P - 23

DOCKTOX: TARGETING MOLECULAR INITIATING EVENTS IN ORGAN TOXICITY THROUGH MOLECULAR DOCKING

Rita Ortega-Vallbona [1], David Talavera-Cortés [1], Laureano E. Carpio 1, 2, Jessica Coto Palacio [1], Alessandra Roncaglioni [3], Marina Garcia De Lomana [4], Domenico Gadaleta [3], Emilio Benfenati 3, Rafael Gozalbes [1, 2], Eva Serrano-Candelas [1]

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The prediction of chemical toxicity remains a critical challenge in drug development and safety assessment. The ONTOX project leverages Adverse Outcome Pathways (AOPs) to anticipate toxic effects by focusing on Molecular Initiating Events (MIEs), where small molecules interact with key proteins [1]. To support this approach, we have developed DockTox

(https://chemopredictionsuite.com/DockTox), an online docking tool that facilitates the virtual screening of compounds against a curated set of MIE-associated proteins.

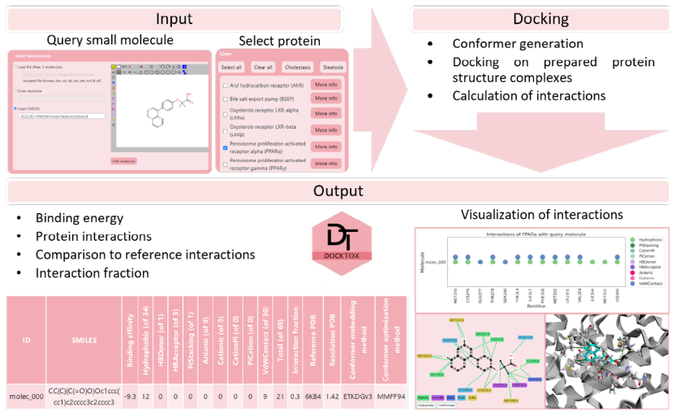
DockTox automates molecular docking workflows, generating ligand conformers, calculating binding energies, and mapping interactions. A key feature is the interaction fraction, which compares query compounds to reference ligands, providing enhanced discrimination between binders and non-binders. For validation, we conducted a case study on Peroxisome ProliferatorActivated Receptor α (PPARα) using known PPARα ligands from the ChEMBL subset of the NURA database [2]. Results demonstrated that interaction fraction values outperform binding energy alone in distinguishing active compounds.

With its user-friendly interface and a collection of 23 pre-processed proteins, DockTox enables researchers to efficiently assess protein-ligand interactions. By offering mechanistic insights into binding behavior, the tool enhances predictive toxicology strategies and supports safer drug design, contributing to the advancement of medicinal chemistry while reducing reliance on animal testing.

Acknowledgements

This work was performed in the context of the ONTOX project (https://ontox-project.eu/), which has received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement No 963845. ONTOX is part of the ASPIS project cluster

(https://aspis-cluster.eu/). We gratefully acknowledge the financial support of the Agencia Valenciana de la Investigación (AVI, https://innoavi.es/en/) by its program Innodocto (Reference number INNTA3/2022/13). This action has been financed by the European Union through the European Regional Development Fund (ERDF) of the Valencian Community 2021-2027.



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P - 26

ENHANCING ANTIOXIDANT EFFICIENCY OF ENZYME MIMETICS THROUGH PYRIDINE ELECTRON MODULATION

Navarro-Madramany Pablo [1], Martínez-Camarena Alvaro [2], Bonastre-Sabater Irene [1], Blasco Salvador [1], Delgado-Pinar Estefanía [1], García-España Enrique [1]

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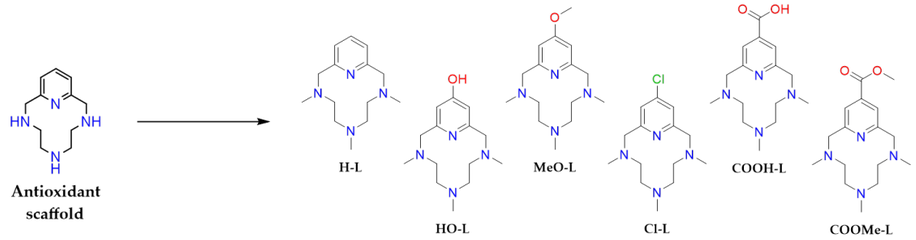
In 2023, the World Health Organization reported that over 55 million people worldwide were living with dementia, with associated healthcare costs exceeding $1 trillion. These numbers are projected to double every two decades, underscoring a growing global health challenge. As populations continue to age, advances in the life sciences are expected to be crucial in addressing this challenge. [1]

Neurodegenerative diseases are closely linked to disruptions in metal ion homeostasis and oxidative stress. In conditions such as Alzheimer's disease, elevated copper and iron concentrations within beta-amyloid plaques are thought to exacerbate oxidative damage in vulnerable brain regions. Current research seeks to counteract these effects by chelating transition metals to prevent protein aggregation and by leveraging their redox activity to promote antioxidant defense mechanisms. [2]

A series of tetraaza-pyridinophane macrocycles capable of binding Fe(II) and Cu(II) has been synthesized to explore their potential as antioxidant agents. Their superoxide dismutase and catalase/peroxidase activities have been modulated by modifying the pyridine electron density with various substituents, ranging from hydroxyl to ester groups. [3, 4]



Acknowledgements

We would like to acknowledge the funding support from European Social Fund, Univ. de València and Generalitat Valenciana (ACIF/2021/302, APOSTD/2020/065, CIPROM/2021/030, PID2019110751RB-I00).

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BACK TO MAIN INDEX

P - 27

UNRAVELING THE ANTIPLASMODIAL POTENTIAL OF NOVEL ANALOGUES OF THE AGGREGATED PROTEIN DYE YAT2150: BIOLOGICAL INSIGHTS

Antonino Nicolò Fallica [1, 2], Inés Bouzón-Arnáiz [1, 2], Ana Mallo-Abreu [3, 4], Elsa M. Arce [3], Pau Reolid [3], Miriam Ramírez [2], Lucía Román-Álamo [1, 2], Claudia Camarero-Hoyos [1, 2], Daniela Currea-Ayala [1, 2], Diego Muñoz-Torrero [3, 4], Yunuen Avalos-Padilla [1, 2], Xavier Fernàndez-Busquets [1, 2]

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The aggregated protein dye YAT2150 has been recently characterized by our research group as a potent antiplasmodial agent with a fast-acting activity, but relatively high cytotoxicity and low selectivity index (SI = CC_{50}/IC_{50}) that would prevent its clinical development [1]. With the aim of identifying more potent and less toxic derivatives, a hit-to-lead optimization allowed us to identify three compounds, namely EMA377, PRC72, and AMB82, as better performing YAT2150 analogues. In this contribution we will focus on their detailed biological characterization in terms of inhibition of gametocyte development and antiplasmodial activity towards multidrug resistant *P. falciparum* strains. The inhibition of protein aggregation was confirmed as the mode of action of these compounds in live *P. falciparum* asexual blood stages according to thioflavin T (ThT) fluorescence assays. Photochemical studies performed with two highly aggregative peptides of different morphology derived from *P. falciparum* coupled with confocal microscopy studies have shown that the novel analogues increase their fluorescence intensity upon binding to the parasite's protein aggregates. The preliminary in vivo toxicity evaluation performed in the *Caenorhabditis elegans* model and the calculated maximum tolerated doses in vivo confirmed a favorable safety profile, paving the way for in vivo studies in a murine malaria model. Overall, these results are highly relevant in a scenario where drug resistance currently represents one of the biggest challenges in eliminating malaria worldwide.

Acknowledgements

The project that gave rise to these results has received funding from the "la Caixa" Foundation under the grant agreement LCF/PR/HR24/52440003. We would like to acknowledge for the funding support grants PID2021-128325OB-I00, PID2020-118127RB-I00, and PDC2022-133085-I00, funded by Ministerio de Ciencia, Innovación y Universidades/Agencia Estatal de Investigación (MCIU/AEI/10.13039/501100011033), which included FEDER funds.

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P - 28

CHALCOGEN-BASED DERIVATIVES AS POTENTIAL THERAPEUTICS AGAINST T.CRUZI AND T.BRUCEI INFECTION

Nuria Martínez Sáez [1], Mercedes Rubio-Hernández [1], Jair L. Siqueira-Neto [2], Conor R. Caffrey and [2], Silvia Pérez-Silanes [1]

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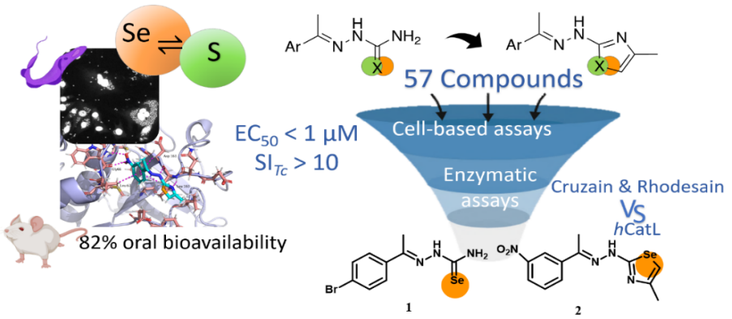
Trypanosoma cruzi (*T. cruzi*) and *Trypanosoma brucei* (*T. brucei*) are the etiological agents responsible for Chagas disease and African trypanosomiasis, respectively. Both diseases represent significant challenges for global public health, making the search for novel therapeutic strategies imperative due to the inherent limitations of current treatments.[1] Within this context, selenium emerges as a promising therapeutic candidate due to its efficacy in various pathologies, being superior compared to sulfur derivatives.[2] Using an isosteric substitution strategy, new thiosemicarbazones and thiazoles, along with their selenium analogs (selenosemicarbazones and selenazoles), have been developed.



In this study, 57 novel chalcogen-containing molecules were synthesized. The compounds were evaluated for their antiparasitic activity, complemented by specific inhibition studies on cruzain and rhodesain proteases, key enzymes in *T. cruzi* and *T. brucei*, respectively. Among the tested compounds, selenosemicarbazone **1** exhibited the highest activity against *T. cruzi*, [3] while compound **2**, a selenazole derivative, demonstrated superior potency against *T. brucei*. The compounds showed improvements in EC_{50} values compared to the currently used reference drugs. Of note, derivative **1** displayed a favorable profile at subsequent *in vivo* assays.[3] Molecular dynamics simulations revealed distinct modes of interaction for linear and cyclic derivatives. These findings highlight the enhanced therapeutic potential of selenium-based derivatives against both parasites, underscoring their value as promising drug candidates for the treatment of these types of trypanosomiases.

Acknowledgements

We would like to acknowledge for the funding support to the Ministry of Science, Innovation and Universities (MICIU) of Spain and the Government of Navarra

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BACK TO MAIN INDEX

P - 29

NEXT-GENERATION ANTICANCER THERAPEUTICS: EXPLORING RU(III) NAMI-TYPE COMPLEXES FOR IMPROVED TUMOR SELECTIVITY

Manel Estruch-Blasco [1], Jose M. Calderón-Montaño [2], Miguel López-Lázaro [2], Eleuterio Alvarez [3] and Manuel Pernía Leal.[1]

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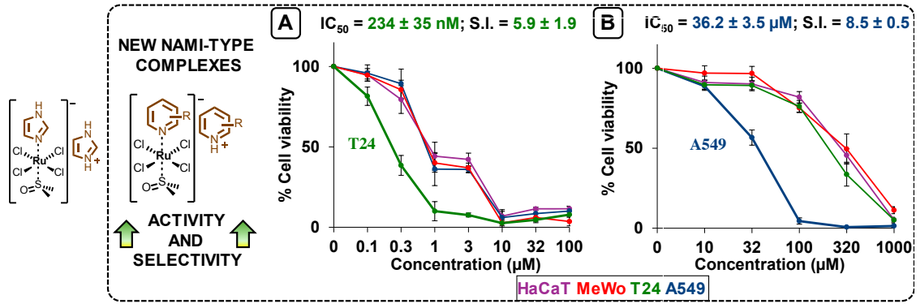
Ruthenium-based complexes are emerging as promising alternatives to traditional anticancer Pt(II) chemotherapeutics such as cisplatin. Especially NAMI-A, the first Ru(III) anticancer compound to be tested in humans [1]. It demonstrated high antimetastatic activity with low toxicity. But it only reached phase II clinical trials because it was considered not active enough against primary tumors [2]. It is known that the properties of the NAMI-A analogues strongly depend on the axial heterocyclic ligand [3]. And, consequently, cytotoxicity could also vary with this ligand.

Therefore, in order to increase the activity against the primary tumor, we synthetized and characterized a variety of Ru(III) NAMI-type complexes. Their anticancer activity was tested against three cancer cell lines: Lung adenocarcinoma A549, Melanoma MeWo and Bladder cancer T24, and compared with the non-malignant keratinocyte HaCaT cells. The different functional groups in the axial ligand of the complexes play a crucial role in the selectivity towards cancer cells. In fact, two lead compounds were obtained: **A** with an IC_{50} of 234 ± 35 nM and SI of 5.9 against the T24 cell line, and **B** with IC_{50} of 36.2 ± 3.5 μM and SI of 8.0 against the A549 cell line. These results represent remarkable promising results for this chemotherapeutic anticancer family, and are already under review for their publication.



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We would like to acknowledge the financial support provided by grant PID2020-118448RBC22 funded by MICIU/AEI/ 10.13039/501100011033. and la Ju nta de Andalucía (P18-RT-1663 PAIDI 2020).

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P - 30

THE FUTURE OF TITANIUM IMPLANTS: SAFER, SMARTER, AND ENHANCED

David Casado-Jurado [1, 7], Ana Castillejo [1], Guillermo Martínez [1], Ernesto J. Delgado-Pujol [2], Eduardo Villalobo [3], Francisco Carrillo [4], Juan Luis Pérez-Bernal [5], Juan Vázquez [6], Luisa M. Rodríguez Albelo [2], David Rodríguez-Lucena [1], Mario Balbuena [2], Belén Begines [1], Yadir Torres [2] and Ana Alcudia [1]

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Titanium faces limitations such as infection risk, stress shielding, and poor osseointegration. To address these challenges, a novel approach was proposed, combining the fabrication of porous titanium substrates, to reduce implant stiffness and minimize bone resorption, with the application of bioactive polymer coatings. A composite coating of chitosan, silver nanoparticles, and nanohydroxyapatite (nHA) was optimized to enhance antibacterial properties and promote osseointegration. Chitosan with an ^{80,5}% degree of deacetylation was used to prepare composites with diverse compositions, exploring different methodologies for incorporating silver nanoparticles, while maintaining Ag concentrations below toxic levels. Antibacterial activity was evaluated against three different bacterial strains, including Gram+ and Gram-, demonstrating excellent inhibition after ^{21} days. The induction of nHA formation was investigated. The optimal porous metallic substrate, exhibiting a stiffness of ^{29} GPa (like cortical bone tissue), was selected for infiltration with the chosen composites. In conclusion, this synergistic approach, based on the combination of porous titanium substrates with ^{60} vol% porosity and a $^{355\text{-}500}$ μm pore size distribution, coated with the ^{3}%CS-nHA-AgNPs-TPP-AgNPsbath composite, offers a potential solution for developing implants with improved biomechanical balance and biofunctionality.

Acknowledgements

This work is part of the project PID2022-137911OB-I00, funded by MICIU/AEI/ 10.13039/501100011033 and by ERDF/EU. Also we would like to mention previous to Ministerio de Ciencia e Innovación Programa Estatal de I+D+i Retos de la Sociedad: Pruebas de Concepto (PDC2022-133369-I00) and Unión Europea: Proyectos I+D+i FEDER Andalucía 2014-2020 (US1380878) and FPU21/06762 and FPU23/01664 grants.

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BACK TO MAIN INDEX

P - 31

HEMAGGLUTININ-TARGETED STRATEGIES FOR INFLUENZA: TOWARDS BROAD-SPECTRUM ANTIVIRALS

Álvaro de la Cruz [1], Marina Serrano [1], Francisco J. Hermoso [2], Lieve Naesens [3], Francisco J. Luque [2], María José Camarasa [1], Sonia de Castro [1]

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The emergence of resistant Influenza strains undermines the efficacy of existing antiviral therapies, leaving few reliable treatment options. As a result, Influenza remains a leading cause of morbidity and mortality, imposing a substantial economic burden due to increased hospitalizations and healthcare costs. This urgent scenario demands novel antiviral strategies capable of delivering broad-spectrum efficacy.

One of the most promising strategies is the design of drugs targeting highly conserved viral regions, a strategy that could eventually overcome viral resistance. With this in mind, our research group has identified a novel class of **N-benzyl-4,4-disubstituted-piperidines**, as the first molecules known to specifically inhibit the fusion process of **H1N1 Influenza A virus** by directly interacting with the fusion peptide of hemagglutinin (HA). These fusion inhibitors represent a revolutionary advance, since no other compounds have been reported to bind to this critical viral component.

Mechanistic and computational studies, on the peptidomimetic prototype **DICAM180,** revealed that its antiviral activity is driven by interaction in a previously unexplored pocket in the HA2 subunit. This unique binding mechanism is mediated by a **direct π-stacking interaction with the Phe9 residue of the HA2 fusion peptide**, a key structural feature required for viral entry. By exploiting this weak spot of Influenza, our approach opens the door to a new class of broad-spectrum antivirals with the potential to overcome resistance.

Taking advantage of the **trimeric structure of hemagglutinin (HA)**, we have conducted structure-activity relationship (SAR) studies, complemented by molecular dynamic simulations, to optimize interactions and to improve the inhibitory potency. Our strategy aims to simultaneously target a second fusion peptide, an innovative approach designed to amplify antiviral efficacy and broaden the anti-influenza activity.

To further assess the drug-like potential of the most promising candidates, we have conducted **stability, aggregation and ADME-Tox studies**, ensuring their suitability for pharmaceutical formulation. Additionally, we have explored **alternative delivery strategies** to optimize bioavailability and therapeutic efficacy. These efforts are essential to advancing our fusion inhibitors towards clinical application, reinforcing their potential as next-generation broad-spectrum anti-Influenza agents.

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P - 32

CANNABINOID-BASED CHEMICAL PROBES FOR THE IDENTIFICATION OF RELEVANT THERAPEUTIC TARGET IN THE IMMUNE SYSTEM

Verónica Muñoz-Canales [1] Patricia García-López [1], Ángel Maldonado [2], Óscar Palomares [2], Bellinda Benhamú [1] and Mar Martín-Fontecha [1]

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The endogenous cannabinoid system is a complex molecular network involved in a large number of physiological processes that has been extensively studied because of its wide therapeutic potential.[1] In particular, the synthetic cannabinoid ligand WIN55,212-2 (WIN) is receiving a great interest due to its immunomodulatory capacity.[2] However, the molecular mechanism by which WIN regulates the immune system, beyond the cannabinoid receptors, remains poorly understood.

In this regard, we are involved in a project aimed at the development of chemical probes based on WIN for the identification of relevant therapeutic targets in the immune system. We have synthesised a series of WIN-based compounds functionalized with a tag containing a diazirine group as a photocrosslinker and a terminal alkyne as a handle. Those probes that mimic the *in vitro* profile of WIN, inhibiting the NF-κB signalling pathway in THP-1 cells and the production of pro-inflammatory markers in dendritic cells (DCs) from human donors, have been used in our chemical proteomic platform[3] for profiling WIN-binding proteins. Identified proteins involved in important biological pathways are currently being validated in DCs. The discovery of relevant therapeutic targets will open new avenues for the development of effective drug treatments for immune-related diseases.

BACK TO MAIN INDEX

P - 33

FIRST-IN-CLASS DUAL QC / SEH INHIBITORS: FROM RATIONAL DESIGN TO PRECLINICAL DEVELOPMENT

Noemi Martinez-Conde [1, 2], Eugènia Pujol 1, Tina Löffler [3], Daniela Brunner [3], Julia Jarne-Ferrer [4, 5], Christian Griñán-Ferré [4, 5], Mercè Pallàs [4, 5], María Isabel Loza [6], José Brea [6], Belén Pérez,7, Christophe Morisseau [8], Bruce D. Hammock [8], Manuela Prokesch [3], Roland Rabl [3], Birgit Hutter-Paier [3], Santiago Vázquez [1, 2], Diego Muñoz-Torrero [1, 2]

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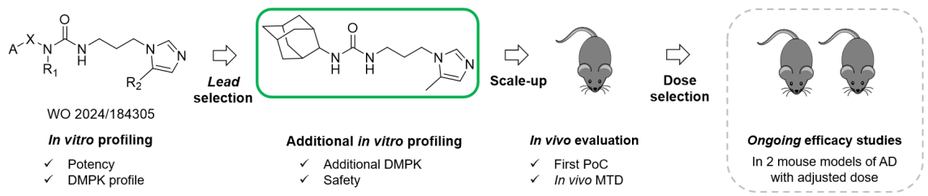
After decades of research, Alzheimer's disease (AD) remains an unmet medical need, in part due to the lack of effective and safe disease-modifying treatments, possibly due to its multifactorial origin. In this context, we identified common structural motifs in inhibitors of two underexplored targets for AD: glutaminyl cyclase (QC), involved in amyloid pathology and neuroinflammation, and soluble epoxide hydrolase (sEH), modulating neuroinflammation. Considering the potential synergistic effects of the simultaneous inhibition of QC and sEH addressing early disease mechanisms, we have rationally designed a first-in-class family of small-molecule dual QC / sEH inhibitors.[1] The *in vitro* profiling of the novel dual inhibitors led to the identification of a lead compound with inhibitory activity in the nanomolar range for both targets, good aqueous solubility, brain permeability, metabolic stability and an adequate safety profile. The selected compound also exhibited favorable biodistribution and safety profiles in mice, with demonstrated brain exposure and a relatively high maximum tolerated dose (MTD), as well as promising effects in a first proof of concept (PoC) in a mouse model of AD (hQC x hAPP mice). The lead compound is currently undergoing additional *in vivo* efficacy studies in two different AD mouse models (5xFAD and SAMP8) with an adjusted higher dose aiming to robustly prove its efficacy and advance its preclinical development, as a promising treatment for AD.



Acknowledgements

This work was supported by grants PID2020-118127RB-I00 and PID2023-147004OB-I00 funded by MICIU/AEI/10.13039/501100011033 and FEDER, UE, 2021SGR00357, 2021LLAV00082, and 2023PROD00079 funded by AGAUR, and FPU20/03463 by MICIU.

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P - 34

MULTI-TARGETING ANTICANCER AGENTS: EXPLORING THE CD44 PATHWAY IN LUNG CANCER

Soledad Romero-Tamudo [1, 2, 3], M. Dora Carrión [1, 3], Jose Manuel Espejo-Román [1, 2, 3], Meriem Chayah [1, 2, 3], Ana Conejo-García [1, 3], Olga Cruz-López [1, 3]

[1] Department of Medicinal and Organic Chemistry and Excellence Research Unit of Chemistry Applied to Biomedicine and the Environment, Faculty of Pharmacy, Campus Cartuja s/n, 18071, University of Granada, Granada, Spain, [2] GENYO, Centre for Genomics and Oncological Research, Pfizer/University of Granada/Andalusian Regional Government, PTS Granada, Avda. Ilustración 114, 18016 Granada, Spain [3] Biosanitary Institute of Granada (ibs.GRANADA), SASUniversity of Granada, Avenida de Madrid, 15, 18012, Granada, Spain

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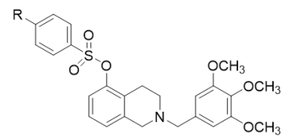
In 2022, nearly 20 million new cancer cases were reported worldwide, with 9.7 million cancerrelated deaths. Lung cancer was the most commonly diagnosed cancer, representing one in eight cancers worldwide [(1)].

Molecular interactions at the cell surface, in particular between hyaluronic acid (HA) and the cluster of differentiation 44 (CD44) receptor, are crucial in several biological processes and diseases such as cancer. [(2)] Thus, inhibition of the HA-CD44 interaction has become a promising therapeutic strategy. Etoposide was the only antitumor compound known to inhibit the binding of CD44 to HA, thereby disrupting key functions that drive malignancy.[(3)] However, our recent research led to the development of *N*-aryl and *N*-alkyl THIQ derivatives, which represented a significant advancement in this field [(4,5,6)].

In this study, we present a novel series of THIQ derivatives exhibiting low-micromolar antiproliferative activity in A-549 and NCI-H23 lung cancer cell lines (Figure 1). To assess whether their activity is mediated via the CD44 pathway, we first evaluated CD44 expression in both cells lines by flow cytometry. Then, cytotoxicity was determined by IC_{50} values using a resazurin-based assay. Furthermore, apoptosis induction in NCI-H23 cells was analyzed through Annexin V/Propidium Iodide (PI) staining and flow cytometry. Lastly, selectivity profiling of compounds **SRT7** and **SRT8** against a panel of 31 protein kinases and 2 lipid kinases suggested that their antiproliferative effects may be mediated via SRC kinase inhibition, a key regulator of CD44 signaling.

Therefore, our findings highlight the therapeutic potential of THIQ-based HA-CD44 inhibitors in lung cancer and support further investigation into their mechanism of action.



Compounds	R	EC_{50} (µM) A549	EC_{50} (µM) NCI-H23
SRT-7	CH_3	4,05 ± 1,36	3,11 ± 1,83
SRT-8	NO_2	5,00 ± 0,83	1,37 ± 0,52

Figure 1. *Antiproliferative activities of* **SRT7** *and* **SRT8** *against A549 and NCI-H23 cells.*

Acknowledgements:

This work was funded by the project PID2021.128109OB.I00 financed by MICIU AEI/10.13039/501100011033.

BACK TO MAIN INDEX

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https://doi.org/10.3390/pharmaceutics14040788

P - 35

OPEN-CHAIN sp²-IMINOSUGARS: TARGETING GLYCOSIDASES VIA NON-GLYCONE INTERACTIONS

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sp²-Iminosugars have demonstrated notable advantages over classical iminosugars in various medicinal chemistry and drug discovery applications.[1,2] However, their synthesis typically involves multistep procedures and purification steps that hinder scalability. Building on prior findings highlighting the critical role of nonglycone-type interactions in the potency and selectivity of glycosidase inhibition by *N*-thiocarbamoyl sp²-iminosugars,[3] we hypothesized that strategic substituents could guide glycone-site binding using structurally simplified surrogates accessible via more practical synthetic routes. Here, we report the design and synthesis of a novel library of open-chain analogs in which the piperidine ring is replaced by an acyclic iminopolyol motif. These compounds are readily obtained from inexpensive commercial starting materials through scalable procedures. We propose that recognition via the nonglycone motif enables the acyclic polyol chain to adopt conformations that complement the enzyme active site, thereby enhancing inhibitory potency and selectivity. Our synthetic approach centers on a reductive amination between aminoalcohols and aldehyde or ketone derivatives to generate the iminopolyol core, followed by a click-like reaction with isothiocyanates (Figure 1). This modular, diversity-oriented protocol is well-suited for library development and structure–activity relationship (SAR) studies.

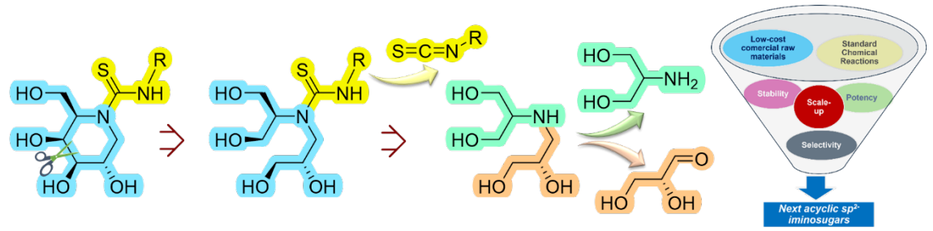

Figure 1. *Retrosynthetic scheme for the novel open-chain sp²-iminosugars.*

Acknowledgements

We acknowledge the funding support by MCIN/AEI/10.13039/501100011033 and ERDF A way of making Europe" (Grant numbers PID2022-141034OB-C21 and PID2021-124247OB-C21).

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BACK TO MAIN INDEX

P - 36

TOWARDS THE DESIGN OF MULTIVALENT FUSION PEPTIDE INHIBITORS OF HEMAGGLUTININ

F. J. Hermoso-Pinilla [1], A. de la Cruz Potenciano [2], S. de Castro [2], S. Velázquez [2], M. J.Camarasa [2], T. Ginex [3] and F. J. Luque.[1]

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Influenza remains a persistent global health threat due to its high mutation rate and recurring pandemics. Despite extensive research, the development of effective antiviral therapies remains still challenging. This project focuses on hemagglutinin (HA), a homotrimeric glycoprotein crucial for host-cell recognition and membrane fusion in influenza A virus (IAV).[1] The lead compound is the fusion peptide inhibitor DICAM180, which was discovered by Profs. M. J. Camarasa, S. Velázquez and S. de Castro (IQM-CSIC), Remarkably, the binding mode involves a new pocket at the bottom of the HA stem that enables a direct stacking interaction with Phe9, present in the fusion peptide (FP).[2,3]

This study explores structural modifications introduced in DICAM180 to improve HA binding and antiviral activity through multivalency. To this end, several chemical modifications have been explored to gain an additional stacking with the Phe9 residue of the neighboring protomer in the trimeric structure of HA. The success of this strategy is highly dependent on the balance between polar/apolar nature of the substituents introduced in the chemical core of DICAM180, peptide, as suggested by experimental assays performed to check the formation of aggregates in solution. This problem can, nevertheless, be alleviated by the introduction of a positively charge amine group, which afforded stabilizing electrostatic Glu120. The results obtained from experimental assays support the molecular design of the new antiviral compounds.

These findings underscore the relevance of the introduction of an additional charge that potentially improves the solubility as well as the pharmacokinetic profile of these compounds, while enabling a dual interaction with distinct fusion peptides in HA.

Acknowledgements

We would like to acknowledge for the funding support of Grant PRE2021-100418 funded by MICIU/AEI/10.13039/501 10001 1033 and by ESF+ .

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P - 37

HARNESSING LIGHT AND TEMPERATURE RESPONSIVENESS FOR NONVIRAL NUCLEIC ACID VECTOR DESIGN

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Light-responsive, self-assembling systems offer distinct advantages for drug and gene delivery, including spatio-temporal precision, relative safety, and minimal disruption of cellular signaling pathways. Building on prior work with carbohydrate-based nucleic acid carriers[1] and photoresponsive bioactive compounds,[2] we introduce a new class of materials centered on an azobenzene core. Light irradiation triggers the *E*-to-*Z* isomerization, while thermal relaxation in the dark restores the *E*-form. We propose that this reversible isomerization modulates the co-assembly behavior of cationic azobenzene Janus amphiphiles (CAJAs; Figure 1) and dendrimers (CADs), thereby altering the nanocomplexes' stability, structure, and transfection efficiency. This enables precise control over nucleic acid encapsulation and release. To demonstrate this approach, we synthesized a series of candidates via a convergent route and characterized their photophysical and self-assembly properties in the presence of pDNA.

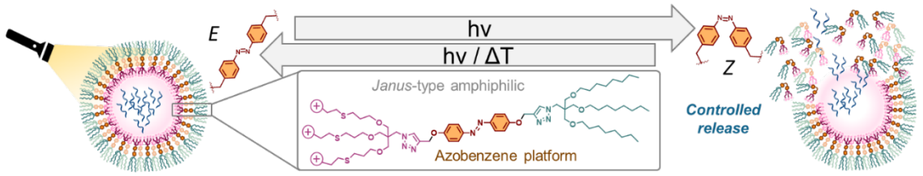

Figure 1. *Schematic structure of a Janus-type azobenzene-based vector and illustration of the co-assembled nanocomplexes with nucleic acid and the release of the cargo upon isomerization.*

Acknowledgements

The authors acknowledge the grants PID2021-124247OB-C21 and PID2022-141034OB-C21 funded by MICIU/AEI/10.13039/501100011033 and FEDER/UE, University of Paris-Saclay and the EU's Horizon Europe MSCA-Staff Exchanges program (grant agreement 101130235–Bicyclos).

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BACK TO MAIN INDEX

P - 39

DESIGN AND SYNTHESIS OF ETHIDIUM-BASE G-QUADRUPLEX LIGANDS AS POTENTIAL ANTIPARASITE AND ANTITUMORAL AGENTS

Juan Camilo Cardozo-Muñoz [1, 2], Christophe Dardonville [1]

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G-quadruplexes (G4s) are unusual nucleic acid structures formed by guanine-rich sequences that fold into non-canonical secondary structures and can be recognized by specific G4 ligands. G4s are considered potential targets for antiparasitic and antitumoral drugs.

In protozoa, G4s are present in the promoter region of parasite genomes[1], are involved in immune evasion and virulence, and participate in the regulation of gene expression[1-3]. Most of these mechanisms are essential for parasite survival and thus represent a good target for parasite chemotherapy. In cancer cells, G4 formation at telomeres can be used to block telomerase and hence prevent uncontrolled DNA replication by blocking cellular replication or expression of oncogenes[5].

The DNA intercalating drug ethidium bromide (ETB) is an interesting scaffold for the design and synthesis of G4 ligands because it has intrinsic fluorescence, G4 binding properties, and it shows antitumor and antitrypanosomal activity. In this work, we have performed molecular docking studies of a small collection of newly designed ETB-based ligands to observe binding modes, interaction energies and the residues involved in the interaction with G4. We found that some ETB derivatives have optimal outcomes and key modes and interactions to achieve the inhibition of these targets.

The ligands were synthesised and biophysical studies were performed to confirm the interaction with G-quadruplexes from the parasites *T. brucei*, *L. major*, and *T. cruzi*. The new compounds were also tested in vitro against trypanosomes and *Leishmania* parasites, and cancer line cells.

Acknowledgements

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P - 40

OPTIMIZING pDNA DELIVERY BY FINE-TUNING TREHALOSE-BASED VECTOR STRUCTURES AND FORMULATIONS

S. Adorna-Sánchez [1], I. Juárez-Gonzálvez [2], C. Di Giorgio [3], I. Vélaz [4], M. J. Garrido [2], J. M. Benito [1], C. Tros de Ilarduya [2], and J. M. García Fernández[1]

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In recent years, nucleic acid therapeutics have made a remarkable clinical impact, most notably exemplified by the mRNA-based vaccines developed against SARS-CoV-2. Much of this success is attributed to the development of suitable delivery carriers that help nucleic acids overcoming physiological barriers en route to their targets. Although viruses have traditionally served as a blueprint for delivery systems, non-viral platforms such as lipid nanoparticles (LNPs) are gaining prominence due to their greater potential for functional customization through synthetic and pharmaceutical technologies. Conformationally locked carbohydrates like cyclodextrins or α,α′-trehalose have emerged as versatile molecular scaffolds for designing such carriers.[1,2] Their bifacial architecture enables the diversity-oriented construction of Janus amphiphiles that combine functional modules capable of (i) electrostatic interaction with nucleic acids and (ii) hydrophobic interactions to drive condensation. In this work, we present a novel family of α,α′-trehalose-based vectors bearing cationic heads and lipophilic tails at the secondary and primary position, respectively (Figure 1). Their pDNA delivery properties are strongly dependent on formulation conditions and correlate with key structural features of the amphiphiles, including the pK_a of their cationic groups, and the density and length of their hydrophobic domains.

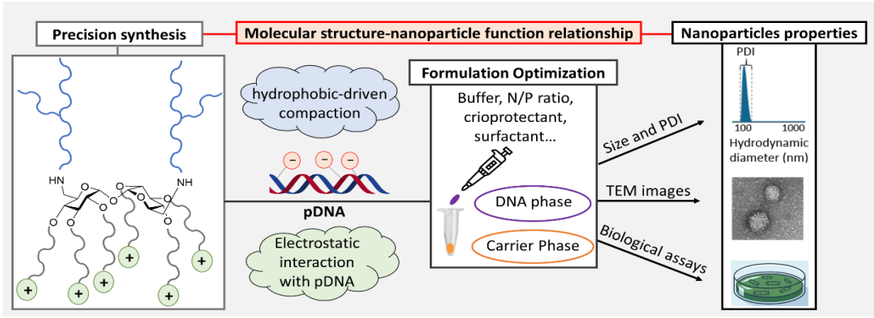

Figure 1. *Structure of the novel trehalose-based vectors and their use for pDNA complexation.*

Acknowledgements

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BACK TO MAIN INDEX

P - 41

TOWARDS SMARTER PEPTIDE THERAPEUTICS: INTEGRATING QSAR AND MOLECULAR MODELING FOR PEPTIDE DRUG DESIGN

Laureano E. Carpio [1, 2], Debora Iaculli [3], Eva Serrano-Candelas [1], Brenda R. Kwak [4], Mathieu Vinken [5], Steven Ballet [4] and Rafael Gozalbes [1, 2]

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Therapeutic peptides, normally composed of 2 to 50 amino acids, are emerging relevant biomolecules in modern drug discovery due to their high target specificity, strong biological activity, low immunogenicity, and favorable biodegradability. These advantages, together with their capacity to interact with challenging targets such as protein–protein interfaces, have positioned peptides as promising candidates in diverse therapeutic areas, including inflammation, metabolic disorders, and neurological diseases, among others[1].

Recent breakthroughs in computational techniques, especially those based on machine learning, have contributed to improve and accelerate the early stages of drug development[2]. Among these, Quantitative Structure–Activity Relationship (QSAR) modeling has proven particularly valuable for predicting a wide array of physicochemical, pharmacokinetic, and pharmacological properties of peptide-based drug candidates[3]. Through the use of curated peptide datasets and advanced algorithmic strategies, peptide-specific QSAR models enable the *in silico* prediction of key descriptors such as aqueous solubility, plasma half-life, hemolytic potential, and even target-specific bioactivity. These tools greatly facilitate the prioritization and optimization of lead peptides while reducing experimental cost and time.

In this work, we present an integrated computational pipeline tailored to the development and application of QSAR models for therapeutic peptides. This workflow incorporates chemoinformatic approaches for ADMET and pharmacological predictions alongside molecular modeling techniques, including molecular docking and molecular dynamics simulations, to explore peptide–protein interactions in depth. We demonstrate its utility in identifying and optimizing peptides targeting diverse proteins of therapeutic interest, including membrane channels and disease-related enzymes. Furthermore, we discuss how this combined approach can elucidate binding mechanisms, reveal interaction hotspots, and support the rational design of more effective and safer peptide therapeutics.

Altogether, our strategy highlights the growing potential of computational methodologies to enhance peptide-based drug discovery and underscores the importance of specialized QSAR models in harnessing the therapeutic promise of therapeutic peptides.

Acknowledgements

We would like to acknowledge for the funding support of European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie grant agreement No 893810 (PEPTIMOL) and from the European Union's Horizon 2020 Future and Emerging Technologies program under grant agreement number 858014 (project PANACHE). Moreover, we would like to acknowledge the financial support of the Agencia Valenciana de la Innovació (AVI) by its program Innodocto (Reference numbers INNTAL32/19/002, INNTA3/2021/16 and INNTA3/2022/20). This action has been financed by the European Union through the European Regional Development Fund (ERDF) of the Valencian Community.

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P - 43

A MULTICOMPONENT REACTION PLATFORM OPENS NEW AVENUES IN ARYL HYDROCARBON RECEPTOR MODULATION

P. Nadal Rodríguez [1, 2], F. Hartung [3], M. Pedrola [1, 2], S. Coomar [4], A. Diaz-Moreno [1, 2], A. M. Hätälä,[3], K. M. Rolfes [3], I. Sánchez-Vera [5], J. Gil [5], E. Molins [6], A. Viayna [2, 7], A. Hanzl [4], N. H. Thomä [4], T. Haarmann-Stemmann [3], F. J. Luque [2, 7], R. Lavilla [1, 2], and O. Ghashghaei [1, 2]

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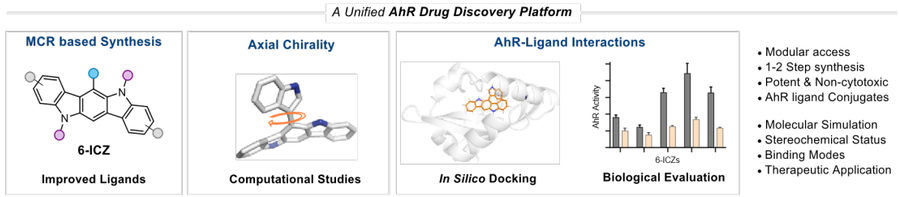
The Aryl hydrocarbon Receptor (AhR) is a transcription factor with pivotal roles in xenobiotic metabolism and immunity.[1] It is a promising target against cancer and autoimmune inflammatory diseases. However, AhR drug discovery (DD) faces various challenges, mainly related to the lack of reliable synthetic access to safe ligands. The 6-indolo[3,2-b]carbazole (6-ICZ) scaffold is an attractive target, underexplored in DD due to synthetic issues and poor understanding of its AhR interaction.

We developed novel indolocarbazole-based high-affinity ligands of the AhR by charting the reactivity space of indole-2-CHO in multicomponent reactions (MCRs).[2] Based on earlier results,[3] a new MCR was designed to obtain a set of 6-ICZs. This straightforward, one step approach allows the modular synthesis of a wide array of derivatives, ideal for a drug discovery campaign. Direct linking of distinct moieties leads to relevant constructs (dimers, probes, PROTACS). Experimental and computational studies address the conformational behavior of the 6-ICZ, rationalizing their axial chirality. Docking studies show the binding trends to the adaptative pocket of AhR. Subsequent reporter gene expression analyses, and cytotoxicity assays revealed that these novel structures are highly potent and safe activating ligands of the human AhR. Several compounds show anti-inflammatory activity, competing with tapinarof®, the only FDA-approved AhR drug. Our approach enables the modulation of this target through a designed, new chemistry, opening novel avenues in AhR DD.



Acknowledgements

Funding from Ministerio de Ciencia e Innovación-Spain (PID2022-139180OB-I00), Generalitat de Catalunya (SGR-DGR00357). PNR thanks Ministerio de Ciencia e Innovación for a predoctoral grant.

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BACK TO MAIN INDEX

P - 44

N-[(THIOPHEN-3-YL)METHYL]BENZAMIDES AS INFLUENZA VIRUS FUSION INHIBITORS ACTING ON H1 AND H5 HEMAGGLUTININS

Celia Escriche [1, 2], Silke Rimaux [3], Aitor Valdivia [2, 4, 5] Juan Martín-López [1, 2] Valeria Francesconi [1] Cato Mestdagh [3] Ria Van Berwaer [3] Kaat Verleye [3] Samuel Noppen [3] Manon Laporte [3] Óscar Lozano [1,2] Annelies Stevaert [3] F. Javier Luque [2,4,5] Lieve Naesens [3] Santiago Vázquez [1, 2]

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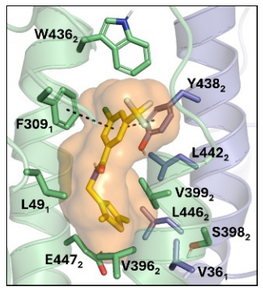
Influenza A and B viruses are highly contagious respiratory pathogens and the cause of annual epidemics with a high medical and economic burden. Although a few anti-influenza drugs are in clinical use, there is an increasing number of drug-resistant variants. Therefore, the development of newer anti-influenza drugs, preferably endowed with innovative mechanisms of action, is of the greatest relevance.



Hemagglutinin (HA), a homotrimer located on the viral envelope that is crucial for viral infectivity, has gained interest as a potential target for anti-influenza treatment[1]. In this work[2], we disclose a series of benzamides endowed with potent anti-influenza activity able to inhibit both H1 and H5 HAs. Antiviral assays have revealed that they act as fusion inhibitors. In conjunction with the analysis of resistance-associated mutations, computational studies have provided a structural model to rationalize the structure-activity relationships and selectivity.

Acknowledgements

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P - 45

DEVELOPMENT OF HYDROGEN SULFIDE-ACTIVATED THERANOSTIC PRODRUGS FOR SELECTIVE CANCER TREATMENT THROUGH TETRAZINE DYNAMIC CHEMISTRY

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A novel approach using the dynamic nucleophilic aromatic substitution of tetrazines (SNTz) constructs theranostic prodrugs activated by hydrogen sulfide (H_2S). Targeted delivery in cancer therapy aims to mitigate adverse effects and enhance drug efficiency. The dynamic covalent chemistry (DCC) of tetrazines provides a reversible and environment-responsive system, ideal for the selective release of therapeutics.[1] The overexpression of H_2S in cancer cells, such as colon cancer, triggers the release of the therapeutic agent camptothecin (CPT), a topoisomerase inhibitor known for its instability, which this approach aims to stabilize, alongside a fluorescent marker.[2] This dual-release mechanism not only promises enhanced selectivity towards malignant cells but also enables simultaneous imaging capabilities, marking a significant step forward in theranostic applications.[3] The potential of tetrazine-based systems in developing sensitive and selective therapeutic solutions is underscored, particularly for conditions marked by elevated H_2S levels. The modularity of this strategy opens avenues for incorporating a range of cytotoxic agents and luminescent probes, broadening the scope for innovative sensing and treatment modalities in cancer and other H_2S related diseases.

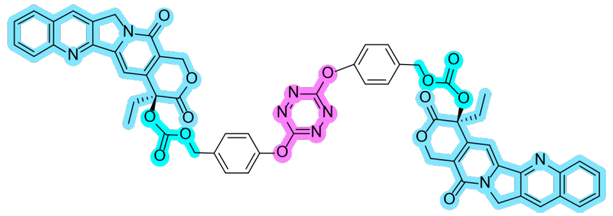

Figure 1. Chemical structure of a self-immolative system based on tetrazine.

Acknowledgements

We would like to acknowledge for the funding support from Grants PID2021-122558OB-I00 funded by MICIU/AEI/10.13039/501100011033 and by the "European Union Next Generation EU/PRTR", GV-IT1701-22 funded by the Basque Government and EHU-N23/36 funded by the University of de Basque Country (EHU/UPV) is gratefully acknowledged.

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BACK TO MAIN INDEX

P - 46

FAST CHARACTERIZATION OF PROTEIN-LIGAND INTERACTIONS IN FBDD BY NOVEL ADDVANCED STD NMR METHODS: REDDAT AND REDMAT

Gabriel Rocha [1], Jonathan Ramírez-Cárdenas [1], M. Carmen Padilla Perez [2], Elena Sánchez-Fernández [2], Samuel Walpole [3], Ridvan Nepravishta [3], Thomas Hicks [3], Serena Monaco [3], Carmen Ortiz Mellet [2], Juan Carlos Muñoz García [1], Jesus Angulo [1, 3]

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Saturation transfer difference (STD) NMR spectroscopy is a powerful tool for screening small molecules and low molecular weight fragments for interactions with a given macromolecule, based on spectroscopic observation of ligand signals, and has become the spectroscopic technique of choice for the study of medium/weak affinity protein-ligand interactions. The relative distribution of STD intensities on the ligand protons allows mapping the ligand binding epitope, revealing structural details of the interaction and thus providing insight into the molecular basis of biomolecular recognition processes, which is fundamental for drug discovery [1].

However, to obtain quantitative structural or affinity information from STD NMR experiments, long series of experiments must be run to perform a complete analysis of the so-called STD build-up curves ("initial slope approach"). This typically results in extremely long measurement times, which can become the bottleneck of the study. To solve this problem, we have developed the *RedDat* approach, which allows to obtain both initial slopes and accurate dissociation constants (K_D) with very few saturation time data points, and even to obtain a very good approximation to quantitative data with only two saturation times [2].

On the other hand, the structural characterization of these complexes is also critical for the development of new drugs through the process of fragment-based drug discovery (FBDD). To that aim, we have developed the *RedMat* software, which allows the comparison of relaxation and exchange matrix calculations with experimental ^{1}H STD NMR data for the validation of 3D models of protein-ligand complexes [3].

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P - 47

A COMBINED COMPUTATIONAL/NMR PROTOCOL FOR VALIDATING 3D MODELS OF CHALLENGING PROTEIN-LIGAND COMPLEXES

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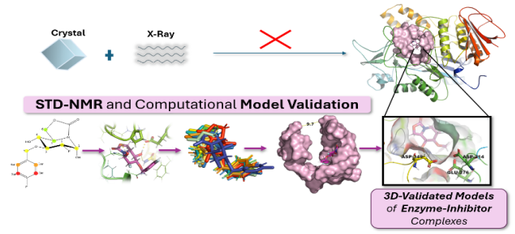
Enzyme-ligand interactions are essential in biological processes and diseases, making their molecular characterization crucial for drug development. However, some protein-ligand systems present severe challenges for structural investigation, such as the absence of crystallographic data. This study aims to generate validated 3D models of sp²-fluoroiminosugars[1] bound to α-Glucosidase using an AlphaFold[2]-predicted structure of the enzyme and an in-house protocol based on docking calculations, MD simulations, and quantitative validation against experimental STD NMR[3] binding epitopes with our RedMat[4] software. The resulting 3D molecular model aligns with experimental data, as demonstrated by RedMat validation, and reveals the opening of a cryptic pocket, a feature often overlooked but with significant potential for drug design. This finding suggests new opportunities for developing more effective inhibitors by targeting previously inaccessible binding sites. Additionally, the most probable active site correlates with the catalytic site predicted by similarity to other glycoside hydrolases.



This advanced protocol provides structural and dynamic insights into biomolecular interactions that are challenging to study experimentally, contributing to medicinal chemistry by enhancing drug design strategies and improving therapeutic efficacy.

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BACK TO MAIN INDEX

P - 48

UNDERSTANDING SIGLEC-15 LIGAND SELECTIVITY FOR THE EFFICIENT DESIGN OF HIGH-AFFINITY SUGAR MIMETICS

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Siglecs (Sialic acid-binding immunoglobulin-type lectins) constitute a large family of membrane receptors present on most of white blood cells. They allow immune cells to distinguish between self and non-self antigens by interacting with the sialic acid moieties that commonly decorate complex glycans.

Over the last decade, siglecs have become important therapeutic targets for treatment of several diseases, especially cancer, asthma, allergies and autoimmune diseases. In particular, Siglec-15 upregulation has been described in TAMs (Tumor Associated Macrophages)[1] and it might have a signalling role in osteoclastogenesis as well.[2] So far, research efforts have been focused on antibody-based therapies and on the development of high affinity ligands. Both approaches aim to disrupt the sialic acid-siglec axis and modulate the immune outcome. However, while the sialic acid-lectin interaction has been well characterized at a molecular level for other human and murine siglecs, the selectivity of siglec-15 for sialic-acid containing glycans still remain elusive. Indeed, the few data reported so far are not fully consistent. Some of us have recently described the X-Ray crystallographic 3D structure of Siglec-15 bound to an antibody and disclose the basic recognition features required for its binding to natural sialoglycans.[3] Herein, we have employed a ligand-based NMR approach to establish a first molecular basis that allows understanding glycan selectivity and opening new avenues to find improved, high affinity sialic acid mimetics.

Acknowledgements

This project has been supported by an MSCA grant (European Commission) awarded to PV (Grant Ref. 101028477-CD28). PV also acknowledges JCP, JJB and JEO for additional support.

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P - 50

TOPOISOMERASE I INHIBITORS AND ANTIPROLIFERATIVE AGENTS WITH INDENO[2,1-C]QUINOLINYLPHOSPHINE OXIDE SCAFFOLD

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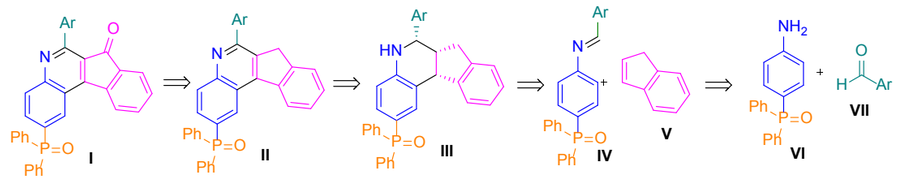
Among the antiproliferative compounds studied for cancer therapy, it is worth highlighting the enzyme inhibitors of topoisomerase I (TopI), an overexpressed target in tumor cells.[1] Fused nitrogen heterocycles seem to have relevant importance in the antiproliferative activity of this enzyme.[2] On the other hand, in the last years some compounds with phosphine oxide function in their structure have been described in medicinal chemistry as anticancer drugs.[3]

With all this in mind, in this work we decided to pre pare newly indenoquinoline derivatives **III** (Scheme 1) with phosphine oxide substituent. A Povarov type reaction between the corresponding phosphorated aldiminas **IV**, obtained in situ by the reaction of phosphorated aniline **VI** and aromatic aldehydes **VII**, with indene **V** allows the formation of these heterocycles. In addition, oxidation of indenoquinoline derivatives **III** would afford compounds **II** and carbonylic derivatives **I** with more planar structure. Following the synthetic preparation, the biological evaluation as Topoisomerase I inhibitors and as antiproliferative agents against different cancerous cell lines was studied.



Scheme 1. *Retrosynthetic pathway.*

Acknowledgements

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BACK TO MAIN INDEX

P - 51

MULTIFACETED ACTIVITY OF CARBOHYDRATE-DERIVED IBERIN ANALOGS: ANTICANCER EFFECT, ANTIOXIDANT PROPERTIES, AND MOLECULAR DYNAMICS INSIGHTS.

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In this work, carbohydrate-based analogs of iberin, a sulforaphane homolog, were synthesized and evaluated for anticancer and antioxidant activities.[1] Resazurin assays showed significant cytotoxicity against cancer cell lines, particularly bladder cancer, with sulfonyl carbohydrate derivatives exhibiting IC50 values comparable to those of natural isothiocyanates (ITCs) (10-20 μM). Molecular docking studies suggest that these analogs interact with the STAT3 SH2 domain, indicating their potential as STAT3-targeted anticancer agents. Additionally, they exhibited antioxidant activity through Nrf2 activation (CD values ranging from 1.55 to 10.36 μM), with the phenylsulfone **1β** (Figure 1) showing comparable or superior activity to natural isothiocyanates. This phenylsulfone analog was identified as the *lead* compound due to its dual efficacy, and its solid form which simplifies handling.[2]

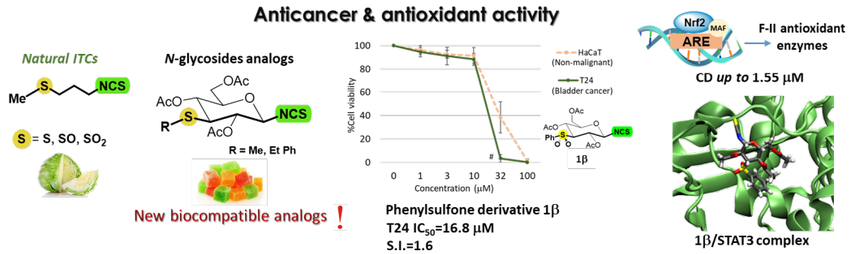

Figure 1

Acknowledgements

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P - 52

NEW SUBSTITUTED BENZOXAZINE DERIVATIVES AS POTENT INDUCERS OF MEMBRANE PERMEABILITY AND CELL DEATH

Ana Conejo-García[1,2], Yaiza Jiménez-Martínez[3,4], Rubén Cámara[1], Francisco Franco - Montalbán[1], Jesús Peña-Martín[3,4], Houria Boulaiz[3,4], M. Dora Carrión[1,2]

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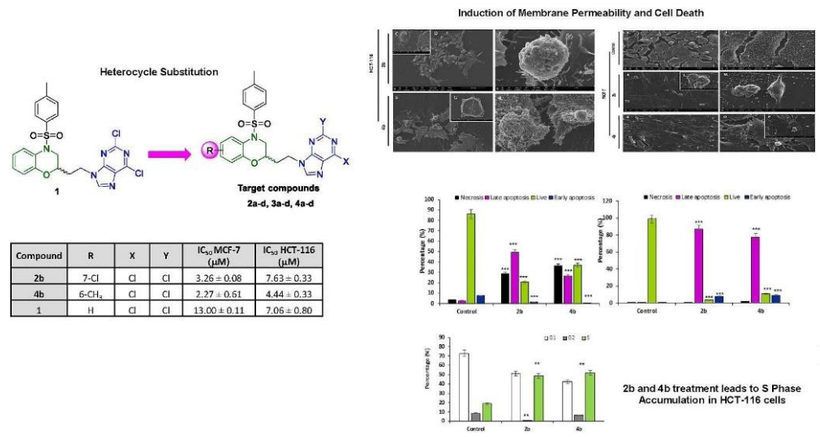
The search for new agents targeting different forms of cell death is an important research focus for developing new and potent antitumor therapies. As a contribution to this endeavor, we have designed and synthesized a series of new substituted 3,4-dihydro-2*H*-1,4-benzoxazine derivatives. These compounds have been evaluated for their efficacy against MCF-7 breast cancer and HCT-116 colon cancer cell lines. Overall, substituting this heterocycle led to improved antiproliferative activity compared to the unsubstituted derivative **1** (Figure 1).[1,2] The most active compounds, **2b** and **4b**, showed IC_{50} values of 2.27 and 3.26 μM against MCF-7 cells and 4.44 and 7.63 μM against HCT-116 cells, respectively. To investigate the mechanism of action of the target compounds, the inhibition profile of 8 kinases involved in cell signaling was studied highlighting residual activity on HER2 and JNK1 kinases. **2b** and **4b** showed a consistent binding mode to both receptor kinases, establishing significant interactions with known and catalytically important domains and residues. Compounds **2b** and **4b** exhibit potent cytotoxic activity by disrupting cell membrane permeability, likely triggering both inflammatory and noninflammatory cell death mechanisms (Figure 1).[2] This dual capability increases their versatility in the treatment of different stages or types of tumors, providing greater flexibility in clinical applications.



Compound	R	X	Y	IC_{50} MCF-7 (μM)	IC_{50} HCT-116 (μM)
2b	7-Cl	Cl	Cl	3.26 ± 0.08	7.63 ± 0.33
4b	6-CH_3	Cl	Cl	2.27 ± 0.61	4.44 ± 0.33
1	H	Cl	Cl	13.00 ± 0.11	7.06 ± 0.80

Figure 1. *New substituted benzoxazine derivatives as anticancer agents*

BACK TO MAIN INDEX

Acknowledgements:

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P - 53

PEPTIDE–PLATINUM(IV) CONJUGATE MITIGATE CHEMOTHERAPY SIDE EFFECTS BY MINIMIZING TUMOR MICROENVIRONMENT ACCUMULATION

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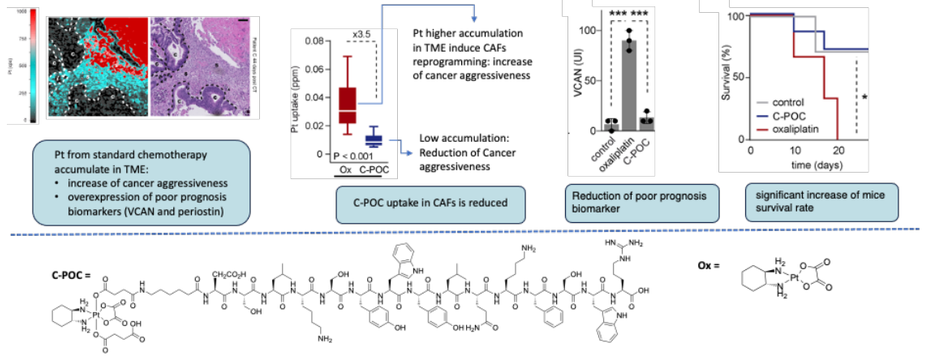
Cancer cells do not exist as isolated entities but are embedded within a dynamic tumor microenvironment (TME) composed of non-malignant cells that play a crucial role in cancer progression. Increasing evidence suggests that platinum-based therapy influences non-malignant cells within the TME. [2,3] Notably, oxaliplatin is predominantly retained by CAFs, leading to heightened TGF-beta activity and the secretion of various factors that enhance cancer aggressiveness.[4] We conjugated oxaliplatin with a cell-penetrating peptide (C-POC) designed to selectively target colorectal cancer cells over TME. C-POC retains the anticancer activity of oxaliplatin while exhibiting reduced accumulation in cancer-associated fibroblasts (CAFs) leading to a decrease in periostin expression, a bio marker of poor prognosis, and shows reduced accumulation in healthy organs, thereby minimizing off-target effects.[5]



These findings indicate that CAFs-Pt mediated protumoral program could be reverted using Pt(IV) leading to a new generation of Pt based drugs.

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BACK TO MAIN INDEX

P - 54

POTENTIATING SULFORAPHANE ANTIOXIDANT ACTIVITY: A DESIGN APPROACH BASED ON MULTIVALENCY

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Sulforaphane (SFN), [(*R*)-1-Isothiocyanato-4-(methylsulfinyl)butane] (Figure 1) is a structurally simple chiral sulfoxide first isolated in 1992 from broccoli extract. To date, the therapeutic potential of sulforaphane has been explored in various applications, with one of the most developed being its antioxidant activity as an Nrf2 activator through covalent binding to Keap1. The activation of Nrf2 results in the production of a variety of proteins (phase II detoxification enzymes) with antioxidative, anti-inflammatory and cytoprotective qualities.[1] We have applied the principle of pharmacomodulation based on molecular multivalency by incorporating several identical structural elements within the same molecule,[2] with the aim of obtaining new compounds that exhibit common pharmacological properties with those of sulforaphane, with an increased affinity of the multivalent analogues for their therapeutic target, the Nrf2 factor. A series of polyisothiocyanates derived from S and P have been prepared, where the incorporated polyvalent groups are intended to facilitate favorable statistical rebinding, thanks to the flexible carbon chains that enable a better fit of the isothiocyanate groups into the binding site of the protein (with minimal entropic cost).

The determination of antioxidant activity has been carried out using the "luciferase assay," which allows for the assessment of the Nrf2 transcription factor induction potential and, consequently, the cytoprotective capacity against oxidative agents in cellular models.[3]

The results obtained confirm our hypothesis, yielding compounds that demonstrate an activation capacity for the Nrf2 factor far superior to that of sulforaphane.

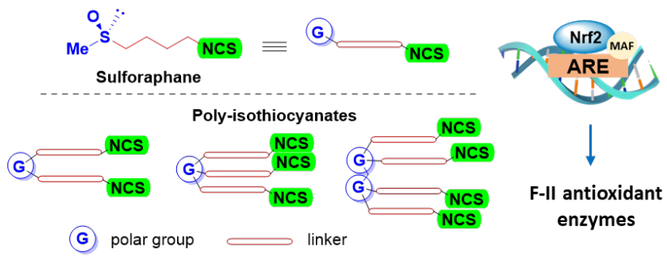

Figure 1

Acknowledgements:

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P - 56

CONJUGATION WITH DEXTRANS AS A MEANS OF IMPROVING THE ANTITUMOR PROPERTIES OF PODOPHYLLOTOXIN

Houssem E. Ghoul, Enol de Prado, Ángela. P. Hernández, Pablo A. García, Pilar García-García and **Mª Ángeles Castro**

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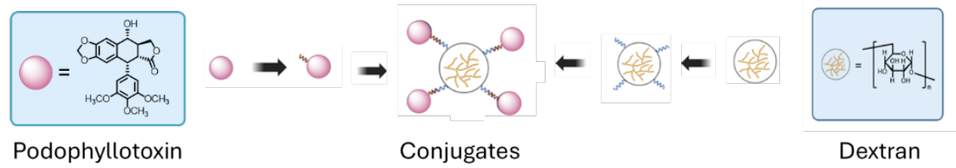
Podophyllotoxin is a natural product belonging to the cyclolignan family of natural products, extracted mainly from the rhizomes of *Podophyllum* sp. It is used as antiviral for the treatment of venereal warts and, because of its interesting cytotoxic activity, it is also used as the starting material for the anticancer drugs etoposide or teniposide[1]. Despite their importance in chemotherapy, several secondary effects are associated with their clinical use, such as drug resistance, lack of selectivity and poor bioavailability. The use of drug delivery systems could be a solution to overcome some of these limitations[2]. A wide range of drug delivery systems have been developed, like liposomes, polymer-based drug carriers or micelles. Among them, we focused on natural polysaccharides, specifically on dextran. Dextran is a non-toxic, biodegradable, water soluble polysaccharide that can be modified chemically and can be used to improve drug bioavailability and selectivity into cancer tissues[3].

In light of the benefits of using dextran as a drug carrier, it was envisioned that conjugation of podophyllotoxin and derivates, with dextran may increase its bioavailability and decrease its toxicity. Thus, we planned to obtain podophyllotoxin-dextran conjugates by attaching the drug to the dextran through different bonds. Dextran has been functionalized to introduce various alkyne linkers, while podophyllotoxin has been chemically modified to introduce azide groups. Ultimately, click-chemistry reactions have been carried out to achieve the desired conjugation. Other linkers are also explored to join both components of the hybrid by ester or amide bonds. Several podophyllotoxin-dextran conjugates were synthesized and characterized by means of NMR spectroscopy and their biological evaluation is in progress. A schematic representation of the objective is illustrated below.



Acknowledgements

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BACK TO MAIN INDEX

P - 57

SYNTHESIS AND ANTITUMORAL EVALUATION OF NEW HYBRIDS OF NAPHTHOHYDROQUINONES AND INDOLIZIDINES/ TETRAHYDROPYRROLOAZOCINES

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Hybridation is a current strategy in rational drug design to generate new multifunctional compounds by connecting diverse structures. It provides a wide number of combinations, which increase greatly the natural variability[1]. The combination of different chemical entities with expected synergistic or dual effects also constitutes a promising strategy to avoid resistances or to discover new treatments in cancer therapy. Thus, different natural products with diverse structures, origins, and mechanisms of action have been combined to create new bioactive entities. Our group has been involved for many years in the synthesis of generally named lignohydroquinones by linking cyclolignans and mono- and di-terpenylnaphtohydroquinones trough aliphatic and aromatic linkers[2]. Recently have appeared many studies on Pyrrolizine/Indolizine-NSAID Hybrids as potential anticancer candidates[3]. For this reason, we decided to synthesize several Indolizidines/Pyrroloazepines-terpenylquinone hybrids in order to study their biological activities. In figure 1, it can be seen the Indolizines/pyrroloazepines. and a terpene hybrid with diacetylated naphthohydroquinone derivative synthesized and tested as cytotoxics.

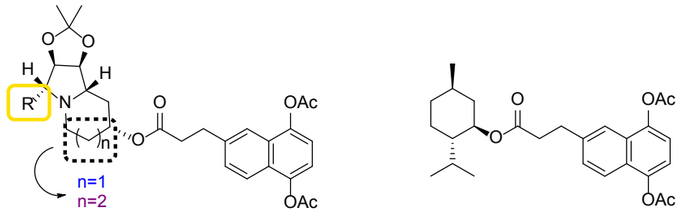

Figure 1. New Hybrids synthetized and biologically evaluated

Acknowledgements

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P - 58

DISCOVERY OF NEW NIK LIGANDS AS NON-CANONICAL NF-KB INHIBITORS FOR THE TREATMENT OF KIDNEY-RELATED DISEASES

Francisco Maqueda-Zelaya [1], Lara Valiño-Rivas [2], José Luis Aceña [1, 3], **Javier Garcia-Marin** [1, 3], Mª Dolores Sánchez-Niño [2, 3, 4], Juan J. Vaquero [1, 3], Alberto Ortiz [2, 4]

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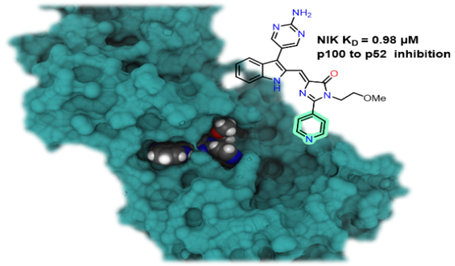
Chronic Kidney Disease (CKD) is a growing health concern with a projected high mortality rate in high-income countries over the next decade. It also represents a significant economic burden on healthcare systems due to its only available therapy, the kidney replacement via dialysis or transplantation. Furthermore, CKD can progress to Acute Kidney Injury (AKI), and conversely, AKI can also be a cause of CKD. Given the paramount importance and the thread of these disorders, there is a critical need to develop effective pharmacological treatments. A promising new approach to improve patient outcomes involves addressing kidney inflammation through the inhibition of the master regulator of inflammation Nuclear Factor κB. In this communication, we will present our initial results on a new family of imidazolone derivatives that bind to the Nuclear Factor κB-inducing Kinase (NIK) and inhibit the non-canonical NF-κB activation pathway in phenotypic assays.[1] Bioisosteric replacement of the aromatic ring at position 4 yielded a derivative with a 4-pyridyl ring that effectively inhibited the NIK-dependent processing of NF-κB p100 to NF-κB2 p52 in cultured renal tubular cells. Molecular modeling studies revealed that the aminopyridine motif is key to binding the hinge region of NIK. These results provide the foundation for the development of drugs targeting NIK in the context of chronic kidney disease.



Acknowledgements

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BACK TO MAIN INDEX

P - 59

TOWARDS BETTER ANTIMITOTIC AGENTS: PYRAZOLE DERIVATIVES AS KINESIN-5 INHIBITORS

Gabriel Rodríguez-Santos [1, 2], Irene Herrera-González [1, 3], Jaime Font de Mora [3], Concepción Pérez-Melero [1, 2, 4]

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Kinesin-5 is a mitotic protein that, through the hydrolysis of ATP, generates the mechanical force which drives the formation of the bipolar mitotic spindle and the positioning of the chromosome in the metaphasic plate[1]. When this protein is inhibited, the mitotic cell collapses into a characteristic monopolar spindle that leads to apoptosis. Due to its only role in cell division and overexpression in cancer cells, kinesin-5 inhibition is considered a promising strategy to overcome the adverse effects of the antimitotic drugs that are currently used in clinic, such as paclitaxel o vincristine. There are two main families of inhibitors which each target a different allosteric site in the motor domain of kinesin 5. The most important one includes several compounds that have reached clinical trials and bind to a site formed by helices α2, α3 and loop 5[2]. This site is formed by 3 pockets that can be occupied by ligands bearing fragments properly orientated on a central core. In this work, we propose a family of pyrazole derivatives, bearing hydrophobic moieties at positions 1, 3 and 5 of the ring, as kinesin 5 inhibitors. To this purpose, we have designed a set of structures which were ranked using the software AutoDock Vina (Fig. 1). The top scoring compounds were synthesized by means of a cyclocondensation reaction between chalconoids and phenylhydrazine derivatives. Further oxidation of the formed dihydropyrazole ring yielded the expected pyrazole derivatives. The complete synthetic route was optimized to match greener criteria, with special emphasis in solvent selection and heating method. The obtained compounds have been assayed as antiproliferative agents on neuroblastoma tumor cells.

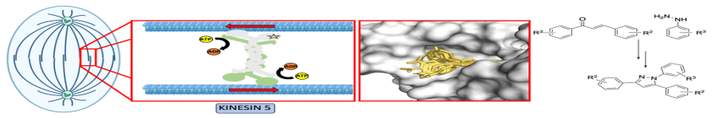

Figure 1. *Schematic mechanism of inhibition of the proposed inhibitors*

Acknowledgements

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P - 61

STRUCTURE–ACTIVITY RELATIONSHIPS OF 2-DEOXY SP²-IMINOGLYCOLIPIDS AS ANTICANCER, ANTILEISHMANIAL, AND ANTI-INFLAMMATORY AGENTS

Rocío Rodríguez-Marín [a], M. Carmen Padilla-Pérez [a], Raquel García-Hernández [b] José M. Pérez-Victoria [b], Francisco Martín-Loro [c], Ana I. Arroba [c], Aday González-Bakker [d], José M. Padrón [d], Elena M. Sánchez-Fernández [a], José M. García Fernández [e], Carmen Ortiz Mellet [a]

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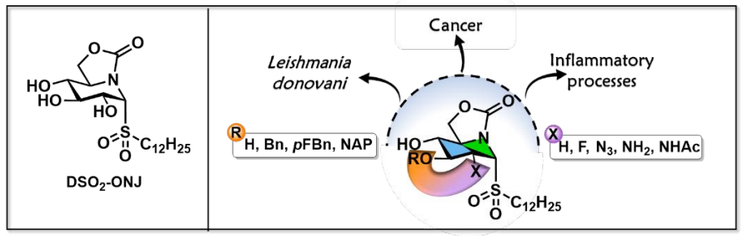
(1*R*)-1-Dodecylsulfonyl-5*N*,6*O*-oxomethylidenenojirimycin (DSO_2-ONJ) is a representative member of the sp²-iminoglycolipids (sp²-IGLs) family with outstanding pharmacological activity against cancer, parasitic infections and inflammatory disorders[1]. Structure-activity relationship studies have been focused on the pharmacological relevance of structural modifications in the aglycone moiety of these glycolipid mimetics. However, the impact of structural changes within the glycone region on therapeutic performance remains largely unexplored. Building on recent findings showing that the incorporation of lipophilic substituents into the glycomimetic unit, such as a fluorine atom at C2 or a benzyl (Bn) group at O3, can significantly enhance biological activity,[2] we now report the stereoselective synthesis of a novel series of 2-deoxy-sp²-IGLs. These analogues feature substitution of the C2 hydroxyl group with hydrogen or nitrogen-based groups (azide, amine, acetamide), and are prepared in both D-*gluco* and D-*manno* configurations. Additionally, our synthetic strategy enables the selective introduction of aromatic moieties at the O3 position, including Bn, *p*-fluorobenzyl (pFBn), and 2-naphthylmethyl (NAP). The antiproliferative, antileishmanial, and anti-inflammatory activities of this new collection of sp²-IGLs will be presented and discussed, highlighting their potential as multi-target therapeutic agents.



Acknowledgements

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BACK TO MAIN INDEX

P - 62

THERMAL STABLE GELATIN-BASED HYDROGELS FOR TISSUE ENGINEERING

Fátima Díaz-Carrasco [1], Roberto G rosso [1], **Elena Benito** [1], Elena Vidal-Nogales [1], Manuel J. Díaz-Blanco [2], M.ª de Gracia García-Martín and M.ª Violante de Paz [1]

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Tissue engineering aims to develop biomaterial-based substitutes for repairing or regenerating damaged tissues. Gelatin, a collagen-derived natural polymer, is valued for its biocompatibility and biodegradability but is limited in biomedical use due to its low melting point near physiological temperatures, leading to instability and loss of mechanical properties.[1] This study addresses these limitations by creating interpenetrating polymer networks (IPN) from gelatin and a synthetic polymer via Diels-Alder (DA) chemistry, which enables orthogonal crosslinking without toxic catalysts, resulting in improved mechanical and thermal properties.[2]

IPN systems with varying polymer concentrations and crosslinking degrees were prepared using two polymers in a 1:1 relative ratio. Polymer 1 was synthesized by Diels Alder reaction from a monosaccharide-based difurfuryl monomer), a bismaleimide monomer[3] and a crosslinking agent with three furfuryl groups, while Polymer 2 was gelatin from bovine skin (G). Thermal stability of the synthesized IPN were analyzed by rheology at heating/cooling ramps from 25 °C to 65 °C and vice versa.

Compared to gelatin-only hydrogels, the IPNs demonstrated significantly enhanced thermal and rheological stability, maintaining or improving their elastic modulus at room to physiological temperatures (25–37.3 °C) and remaining stable up to 51 °C. This improvement is attributed to the additional crosslinked polymer network, which mitigates the gelatin's inherent thermal instability. The findings indicate that these DA-crosslinked gelatin IPNs are promising candidates for tissue engineering scaffolds, as they combine biocompatibility with mechanical robustness suitable for biomedical applications.

Acknowledgements

We would like to acknowledge for the funding support to the Ministerio de Ciencia e Innovación-Agencia Estatal de Investigación (MCIN/AEI/10.13039/501100011033), grant number PID2020-115916GB-I00

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P - 63

RATIONAL DESIGN OF POTENT P2X7 RECEPTOR ANTAGONISTS: A NEW APPROACH FOR ALZHEIMER'S DISEASE TREATMENT

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The P2X7 receptor (P2X7R) is an ATP-gated ion channel involved in regulating inflammation. Furthermore, P2X7R has been implicated in the pathogenesis of Alzheimer's disease (AD), making it an attractive therapeutic target.[1] However, despite its clinical relevance, no P2X7R antagonists have been approved to date, possibly due to species-specific pharmacological differences and lack of human structural data. Very recently, we reported the first high-resolution cryo-EM structures of the human P2X7R (*h*P2X7R) and used structural and functional data to develop UB-MBX-46, a potent and selective antagonist with a unique polycyclic scaffold.[2] In this study, we present a drug discovery program based on UB-MBX-46 aimed at identifying a new candidate for the treatment of AD. We first conducted structure-activity relationship studies and synthesized several derivatives of UB-MBX-46. All the compounds underwent a screening cascade to assess their activity at *h*P2X7R and their selectivity over other P2X subtypes. The most promising compounds were further evaluated for potency at rodent P2X7R and subjected to *in vitro* DMPK profiling. Finally, a proof-of-concept *in vivo* study in the 5xFAD murine model of AD demonstrated that the compound selected reversed cognitive deficits to levels comparable to those of control mice and reduced both amyloid and tau pathology.

Acknowledgements

We would like to acknowledge for the funding support to Spanish *Ministerio de Ciencia, Innovación y Universidades*, MICIU/AEI/10.13039/501100011033: grant PID2023-147004OB730 I00.

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BACK TO MAIN INDEX

P - 65

GIVING A SECOND LIFE TO CHEMICAL COMPOUNDS: THE SPANISH PUBLIC CHEMICAL LIBRARY

Antonio Gómez [1], Inés Ardao [1], Ismael Bermejo-Álvarez [1], Jose Brea [2], Geert Daudey [2], Jose Manuel Santamaría [2], Ana Martínez [3], Carmen Gil [3], Olga Genilloud [4], Mar Orzáez [5], María J. Vicent [5], Susana Torrente [2], Jordi Quintana [6] and Mabel Loza [1, 2]

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The goal of the Spanish Public Chemical Library project is to create a common framework which provides value to the compounds that have been synthesized or isolated by the Spanish academic groups. These compounds will be screened for novel targets, thus providing them with the opportunity to have a second life as probes in Biological Chemistry or to emerge as hits in programs of Medicinal Chemistry targeted at the development of novel drugs.

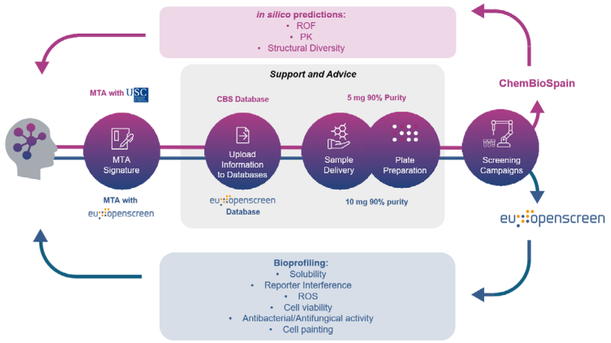
This program seeks to build synergy among three important capabilities now available in Spain: the chemical diversity in the compounds that have been prepared or isolated by the Chemistry groups, the novelty in targets identified by the groups in Pharmacology and the skills and expertise of the screening nodes partnering in this initiative.

The Spanish Public Chemical Library is a joint venture between the ES-OpenScreen Strategic Network and the Complementary Plan for Biotechnology Applied to Health (PCBAS) of the PERTE de Salud de Vanguardia. It is coordinated with different complementary national programs, and mainly with the European chemical library EU-Openscreen within the European Research Infrastructure Consortium for early drug Discovery, which counts Spain among its six founder countries. The goal is the creation of a shared platform which ultimately results in the generation of new solutions for unmet medical needs.

The compounds are submitted following a simple and proven process. They are provided as a deposit, so that the chemical group always keeps ownership over their compounds with the possibility of claiming them back at any moment in time. The groups providing the compounds will receive data from screening campaigns, in silico predictions, and a series of bioprofiling tests. The goal is that the chemists get valuable data which can enrich their publications or become the starting point for novel collaborations, while retaining full control of their products throughout the process.

Acknowledgements

We would like to acknowledge for the funding support from the State Research Agency (MICIU/AEI /10.13039/501100011033) in the framework of the Strategic Research Network 'Synergies in drug discovery in Spain' (RED 2022-134659-E) and by the Spanish Ministry of Science, Innovation and Universities with funds from the European Union NextGenerationEU, from the Recovery, Transformation and Resilience Plan (PRTR-C17.I1) and from the Autonomous Community of Galicia, within the framework of the Biotechnology Plan Applied to Health, integrated into the framework of PERTE for Vanguard Health.



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P - 66

MACROCYCLIC PHAGE DISPLAY FOR IDENTIFICATION OF SELECTIVE PROTEASE SUBSTRATE PROBES

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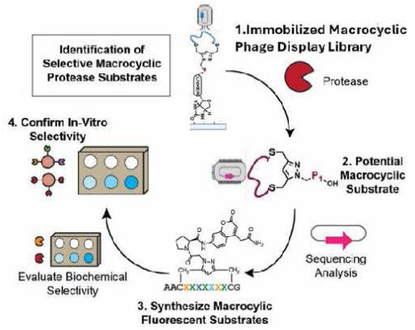
Proteases are enzymes that hydrolyze peptide bonds of specific peptide and protein substrates. These enzymes are involved in a number of key physiological processes and their dysregulation plays an important role in a number of disease states such as cancer or diabetes. A key tool to study and understand protease function are fluorogenic substrates, which allow monitoring of protease activity and can be used to develop inhibitors or covalent chemical probes. One of the greatest challenges when designing fluorogenic substrates is to achieve selectivity towards only one enzyme. This is especially difficult among proteases of the same family since they often present a conserved active site and similar catalytic mechanism. The cross-reactivity of substrates can prevent investigations of a target protease.

Traditional methods for identifying selective protease substrates have primarily relied on synthetic libraries of linear peptides, which offer limited sequence and structural diversity. Here, we present an approach that leverages phage display technology to screen large libraries of chemically modified cyclic peptides, enabling the identification of highly selective substrates for a protease of interest. We demonstrate the utility of this approach using Fibroblast Activation Protein alpha (FAPa) and the related proline-specific protease, dipeptidyl peptidase-4 (DPP4), as targets. Phage selection and subsequent optimization identified substrates with selectivity for each target that have the potential to serve as valuable tools for applications in basic biology and fluorescence image-guided surgery (FIGS). Overall, our strategy provides a rapid and unbiased platform for effectively discovering highly selective, non-natural protease substrates, overcoming key limitations of existing methods.



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BACK TO MAIN INDEX

P - 67

A NEW FAMILY OF PENTAFLUOROSULFANYL-CONTAINING ACETAMIDES AS SOLUBLE EPOXIDE HYDROLASE INHIBITORS

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Soluble epoxide hydrolase (sEH) catalyzes the degradation of epoxyeicosatrienoic acids, which exhibit anti-inflammatory and analgesic activities. The inhibition of sEH is a promising therapeutic strategy for treating pain, which is still an unmet medical need. Indeed, the sEH inhibitor (sEHI) **EC5026** has reached clinical trials for neuropathic pain,[1] and our group has developed novel sEHIs with activity in a murine model of visceral pain.[2]

The family of compounds of the present work was designed based on **TPPU**, a well-known sEHI, by replacing the urea pharmacophore by an amide group and the propionyl substituent by a benzyl group. With the favourable physicochemical properties of amides and by introducing a protonable basic centre, we aimed to overcome one of the limitations of ureas: their poor solubility. Initially, these modifications were detrimental to the inhibitory activity. However, replacing the trifluoromethoxy substituent by the pentafluorosulfanyl group (SF_5) led to increased inhibition in human sEH but not in the murine enzyme. Then, the Topliss approach was used on the right aromatic ring to optimize the potency in both species. As a result, we obtained several compounds with nanomolar activity against both human and murine sEH.

With this work we intended to reinforce the importance of finding a potent compound in both species, which is essential for preclinical and clinical success. We have proved that the incorporation of SF_5 in these candidates is an effective strategy for potency optimization. This group presents higher lipophilicity, volume and electronegativity compared to the trifluoromethyl substituent, a fact that could increase drug-like properties of the compounds.

Acknowledgements

This work was funded by the Grants PID2020-118127RB-I00, to S.V., by MICIU/AEI/10.13039/501100011033 and by "European Union NextGenerationEU/PRTR", and the Xunta de Galicia (ED431G 2019/02 and ED431C 2018/21) (to M.I.L.). A.L.R. thanks the Spanish MICIU for a PhD Grant (PRE2022-105091, FPI program).

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P - 68

FLUORESCENT PYRAZOLE DERIVATIVES AS DUAL-FUNCTION AGENTS: MOLECULAR PROBES AND POTENTIAL KINESIN Eg-5 INHIBITORS

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Kinesin Eg5 is a molecular motor protein essential for mitotic spindle assembly during cell division, playing a crucial role in separating spindle poles by crosslinking and sliding apart microtubules, ensuring proper chromosome segregation. Given its vital function in mitosis, Eg5 has attracted significant interest as a potential anticancer or antifungal therapy target. Several small-molecule Eg5 inhibitors entered clinical trials as antitumor agents. However, except for filanesib, they exhibited limited efficacy. One group of inhibitors targets a specific allosteric site in the Eg5 motor domain covered by loop-5 (L5), which presents a hydrophobic pocket in which its main interactions with the inhibitors involve hydrogen-bonding interactions and van der Waals interactions, including hydrophobic contacts.[1]

In this context, 1,3,5-trisubstituted pyrazole derivatives have emerged as promising candidates for inhibiting kinesin Eg5 binding allosteric L5 site. The pyrazole ring provides a core scaffold that can be functionalized to enhance binding affinity and specificity (Fig. 1). Furthermore, these derivatives can exhibit tunable fluorescence through appropriate functionalization.[2] The introduction of conjugated π-systems, such as aromatic or heteroaromatic substituents, along with electron-donating or withdrawing groups, can influence the fluorescence properties. This structural modulation enables the design of fluorescent inhibitors that facilitate real-time monitoring of their interactions with Eg5 and intracellular distribution.

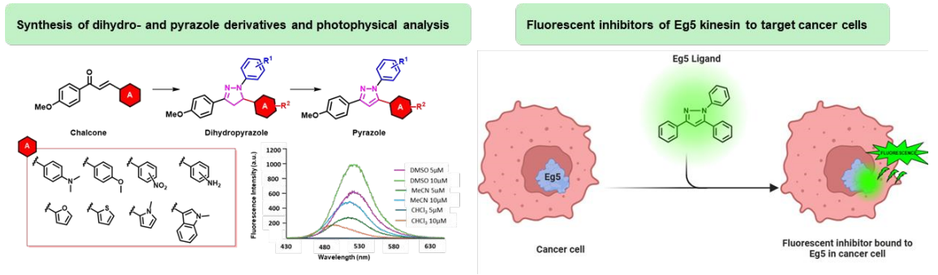

Fig. 1.- Synthesis of pyrazole derivatives as molecular probes and potential kinesin Eg-5 inhibitors

Acknowledgements

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BACK TO MAIN INDEX

P - 69

NEW MULTITARGET NEUROPROTECTANTS ABLE TO ACTIVATE PROTEIN PHOSPHATASE 2A AND BLOCK P2X7 RECEPTORS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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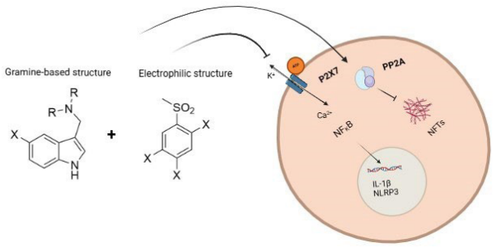
Aging has increased the occurrence of neurodegenerative diseases such as Alzheimer's disease (AD), for which current treatments are not effective. Among several reasons for this fail, there is a poor validation of therapeutic targets implicated in the pathological mechanisms entailing to neurodegeneration. In this regard, the use of strategies based on multi-target-directed ligands (MTDL), which can interact with various biological targets within the pathological framework of a single disease, represents a significant advance in drug R&D for the treatment of multifactorial diseases such as AD[1]. The most studied pathological mechanisms responsible for neuronal damage in AD are closely related to neuroinflammation triggered by the overexpression and activation of pro-inflammatory mediators, where the purinergic receptor P2X7 plays a key role[2]. Considering that one of the hallmarks of AD is the generation of neurofibrillary tangles (NFTs) formed mainly by hyperphosphorylated tau protein, protein phosphatase 2A (PP2A), the main phosphatase of tau, is found depressed in several models of AD, what could favor the formation of NFTs[3]. Supported by this evidence, this work focuses on the development of MTDLs capable of restoring the enzymatic capacity of PP2A and blocking the purinergic receptor P2X7. Thus, most of the designed compounds have shown an excellent neuroprotective profile in different neurodegeneration models related to PP2A impairment, demonstrating the restoration of PP2A activity, measured with the *p*-nitrophenyl phosphate method. These compounds have been preliminarily tested in YO-PRO-1 uptake assays in a HEK293 cell line expressing human P2X7, proving some P2X7 antagonist profile. Further experiments will probe their capability to prevent interleukin 1β release and the formation of the NLRP3 inflammasome.



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We thank Agencia Estatal de Investigación for funding to Dr. Cristobal de los Ríos (Consolidación Investigadora Program, ref: CNS2022-135290).

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P - 71

SYNTHESIS OF A 6-O-BENZYLATED, SULFATED TETRASACCHARIDE SHOWING MICROMOLAR AFFINITY FOR MIDKINE

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Midkine is a heparin-binding growth factor that plays an important role in cancer cell proliferation and is also involved in several diseases of the central nervous system, such as glioblastoma and multiple sclerosis. There is a great interest in the discovery of high-affinity midkine ligands that could modulate the activity of this protein. In this context, we previously demonstrated that synthetic oligosaccharides following the sequence GlcN(4,6-di-OSO_3)-β(1→4)-Glc-β(1→3), closely related to the structure of biologically active chondroitin sulfate E, bound to midkine and were able to block midkine stimulating effect on cell proliferation.[1] Our data indicated that increasing the overall hydrophobicity of the oligosaccharide by the introduction of additional phenyl rings enhanced the binding affinity.[1,2]

Here, we present the synthesis of tetrasaccharide **1** displaying additional benzyl groups at position 6 of the glucose units (Figure 1). For this purpose, we carried out iterative 1 + 1 glycosylations with building blocks **2** and **3**. The use of the *N*-phenyltrifluoroacetimidate donor **2**, instead of the analogous tricloroacetimidate, was key to obtain **1** in high yield. The presence of the fluorous tag at the reducing end allowed purification of the reaction intermediates by simple fluorous solid-phase extraction. Once the fully protected compound was generated, the deprotection-sulfation steps afforded the desired tetrasaccharide. Finally, the relative binding affinity between **1** and midkine was estimated by fluorescence polarization competition experiments.

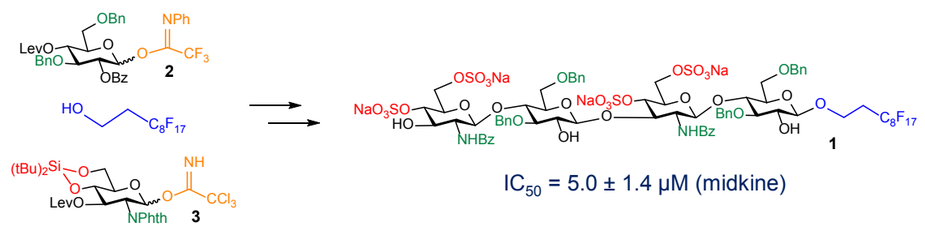

Figure 1 Lev = levulinoyl, N-Phth = N-phthaloyl

Acknowledgements

The authors acknowledge MCIN/AEI/10.13039/501100011033 and ERDF A way of making Europe, EU (Grant PID2021-125094NB-100) for financial support.

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BACK TO MAIN INDEX

P - 72

DESIGN, SYNTHESIS, AND BIOLOGICAL EVALUATION OF HYDROXYTYROSYL PUNICATE, A NOVEL PHENOLIPID WITH ANTIPROLIFERATIVE AND ANTITRYPANOSOMAL ACTIVITIES

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Hydroxytyrosol (HT) is a potent natural antioxidant with recognized health benefits[1] and demonstrated antiproliferative effects[2]. Lipophilic derivatives of HT, especially those conjugated with polyunsaturated fatty acids, have shown enhanced antioxidant, antiproliferative, and antiparasitic activities[3]. However, little is known about their conjugation with omega-5 fatty acids. Punicic acid (PA), the major fatty acid in pomegranate seed oil[4], has shown neuroprotective, metabolic, antiproliferative, and antiparasitic properties[5].The aim of this study was to prepare the novel phenolipid hydroxytyrosyl punicate (HT-PA) and evaluate its antiproliferative and antiparasitic properties.

HT-PA was synthesized from HT and PA in a two-step chemical synthesis. The compounds showed a similar antiproliferative activity against the breast cancer MDA-MB-231 cells with EC_{50} values ranging from 24.42 µM to 39.30 µM. These results indicate that the combination of HT and PA in the phenolipid HT-PA does not increase the cytotoxic effect. In contrast, the compounds showed different activities against the lung A549 cancer cells. HT-PA had an EC_{50} of 8.93 µM against cell lung carcinoma A549 cells and was 13-fold and 7-fold more active than PA and HT, respectively. It achieved a selectivity index of 11.20 for tumor cell line A549 over non-tumor cell line MCR-5. HT-PA displayed 80-fold and 60-fold greater activity against Trypanosoma brucei parasites (EC_{50} of 0.95 µM) compared with HT and PA, respectively, and > 100-fold selectivity for *T. brucei* over healthy MRC-5 cells (Figure 1).

Further studies will be carried out to identify the biological targets of HT-PA and to elucidate the mechanisms underlying its anticancer and antiparasitic effects. Efforts will also focus on developing a sustainable synthesis of HT-PA from Mediterranean fruit by-products, such as olive leaves and pomegranate seeds, and on comparing chemical and enzymatic approaches.

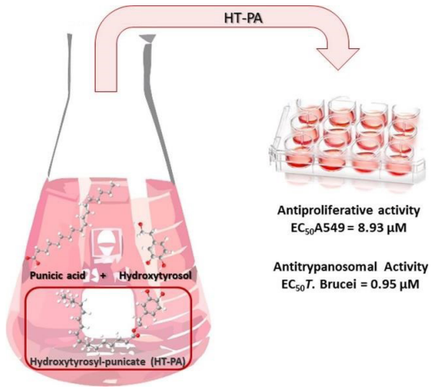

Figure 1. *Synthesis and biological evaluation of HT-PA*

Acknowledgements

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P - 73

NOVEL SOLUBLE EPOXIDE HYDROLASE INHIBITORS: N-SUBSTITUTED PIPERIDINES IN BENZOHOMOADAMANTANE UREAS WITH POTENT ANTI-INFLAMMATORY ACTIVITY

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The soluble epoxide hydrolase (sEH) enzyme has been suggested as a pharmacological target for the treatment of several diseases including inflammation and pain-related disorders.[1] In spite of efforts made to procure drug candidates, none has reached the market yet, mainly because of poor drug-like properties.

We have recently observed that the lipophilic cavity of the enzyme is flexible enough to accommodate polycycles larger than adamantane,[2] that inspired us for to the discovery of a new family of benzohomoadamantane-based ureas endowed with low nanomolar activity.[3] In order to improve the solubility and the DMPK properties of these compounds, we designed and synthesized a new series of piperidine derivatives retaining the urea group as the main pharmacophore. Gratifyingly, we obtained compounds with improved DMPKs properties which showed a robust analgesic effect in a murine model of cystitis.[4]

In this work, we synthesized a new series of benzohomoadamantane-based ureas to further explore the *N*-substitution of the piperidine moiety. These compounds were fully characterized and evaluated as sEH inhibitors. A subnanomolar inhibitor endowed with excellent DMPK properties was further evaluated in *in vitro* experiments for testing its anti-inflammatory properties. This compound showed high efficacy as inhibitor of the nitric oxide pro-inflammatory pathway in activated BV2 microglial cells. Overall, the results emphasize the significance of sEH as a druggable target in therapies involving inflammatory processes.

Acknowledgements

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P - 74

NEW BENZOHOMOADAMANTANE-BASED SOLUBLE EPOXIDE HYDROLASE INHIBITORS FOR THE TREATMENT OF CHEMOTHERAPHY-INDUCED NEUROPATHIC PAIN

Santiago Vázquez [1, 2] Miriam Santos-Caballero [3], Beatrice Jora [1, 2], Sandra Codony [1, 2], Celia Escriche [1, 2], Andreea L. Turcu [1, 2], Carla Calvó-Tussell [4], Christophe Morisseau [5], M. Isabel Loza [6], Clara Bartra [7], Coral Sanfeliu [7], Belén Pérez [8], Christian Griñán-Ferré [9], Mercè Pallàs [9], José Brea [6], Bruce D. Hammock [5], Silvia Osuna [4, 10], Ferran Feixes [4] and Enrique J. Cobos [3]

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Current treatments for neuropathic pain (NP), anti-inflammatory drugs (NSAIDs), antidepressants and opiates, present serious side effects and moderate efficacy. Inhibition of soluble epoxide hydrolase (sEH) has recently emerged as a promising target for the treatment of NP.[1] We have recently found that urea-containing benzohomoadamantane compounds are low nanomolar inhibitors of sEH.[2] So far, our work has revolved around benzohomoadamantanes unsubstituted in the aromatic ring. The challenge of improving the metabolic stability and increasing the solubility while keeping a high inhibitory potency led us to study the effect of introducing substituents in the aromatic group leading to a new family of sEH inhibitors. *In vitro* evaluation of the drug-like properties through an extensive screening cascade led to the selection of one compound for the *in vivo* studies. This compound displayed excellent drug-like properties and good pharmacokinetic characteristics in terms of exposure, distribution and elimination. The subcutaneous administration of the selected compound in a mice model of paclitaxel-induced neuropathic pain was able to prevent and to treat this pain-related disorder. The findings herein disclosed can pave the way for the discovery of novel efficacious and safer analgesic compounds.

Acknowledgements

Grant PID2023-147004OB-I00 funded by MCIN/AEI/10.13039/501100011033, by "ERDF/UE". Xunta de Galicia. Partial support was provided by NIH-NIEHS River Award R35 ES03443, NIH-NIEHS Superfund Program P42 ES004699, NINDS R01 DK107767, and NIDDK R01 DK10361.

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BACK TO MAIN INDEX

P - 75

TARGETING NEUROPILIN-1 FOR AORTIC VALVE CALCIFICATION: A NOVEL LYSOSOMAL DEGRADATION APPROACH TO HALT DISEASE PROGRESSION

Pablo Rodríguez García [1, 2], Macarena Fernández Chacón [2], Antonio Ordóñez Fernández [1, 2, 3], Encarnación Gutiérrez Carretero [1, 3] and Valeria Pingitore [2].

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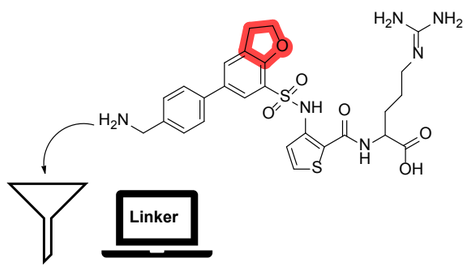
Aortic Valve Calcification (AVC) is a pathological process characterized by the progressive deposition of calcium phosphate minerals within the valve leaflets, leading to their stiffening and subsequent impairment of valvular function. To date, there are no pharmacological treatments available to halt or reverse AVC.

Neuropilin-1 (NRP-1) is a transmembrane protein key to angiogenesis, cellular signaling, inflammation, and osteogenic differentiation. Recent studies have shown its upregulation in the calcification aortic valve disease[1].-

LYTACs are a class of engineered molecules that exploit the induced proximity strategy to selectively degrade extracellular and membrane proteins through the lysosomal degradation pathway. Based on a known antagonist of NRP-1[2], we present a novel molecular modeling approach involving the virtual screening of a chemical library of new NRP-1 degraders with various linkers. The development of LYTAC against NRP-1 presents a novel and promising strategy to address an urgent medical need.



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P - 76

SYNTHETIC STRATEGIES TOWARDS ARYLPURINE DERIVATIVES AS SINEFUFIN ANALOGUES

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S-Adenosyl-L-methionine (SAM) (1, Figure 1) serves as a universal substrate for enzymes involved in methyltransferase activities. During this process, it is converted into S-adenosyl-Lhomocysteine (SAH) (2, Figure 1), which functions as an endogenous competitive inhibitor. Methyltransferases play a crucial role in epigenetics by regulating gene expression through the covalent modification of histones or nucleic acids (DNA or RNA). Among the various methyltransferases being explored as potential therapeutic targets, those associated with singlestranded positive-sense (+ss) RNA viruses stand out as particularly promising.[1] This is the case for the methyltransferase of orthoflavirus such as dengue or Zika virus. The methyltransferase activity is located in the N-terminal subdomain of the viral NS5 protein, which also contains the polymerase activity in its C-terminal subdomain.[2] Due to the important roles of the methyltransferase activity in translation and immune evasion, inhibition of the methyltransferase activity is an attractive target for direct antivirals.[1] Sinefungin (3, Figure 1), a naturally occurring nucleoside, has been identified as a potent methyltransferase inhibitor interacting at the SAM/SAH binding site. Moreover, its complex with ZIKV methyltransferase has also been reported (PDB ID: 5MRK).[3] Using these coordinates we have designed new derivatives meant to interact at the SAM/SAH binding site where the ribose has been replaced by a disubstituted aryl ring keeping a purine on one side mimicking adenine in nucleosides 1-3 while on the other side an amino acid chain is incorporated. The synthetic approaches employed to obtain these compounds, along with the challenges encountered during the process, will be discussed in detail. Additionally, the results of docking studies conducted to evaluate their interaction with ZIKV methyltransferase will also be presented.

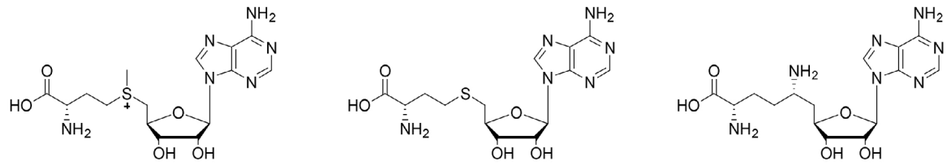

Figure 1. Structural formulae of SAM, SAH and sinefungin

Acknowledgements:

Financed by the Spanish Ministry of Science and Innovation AEI / 10.13039/501100011033 grant PID2022137372OR-C22, by AECSIC grant number PIE-202380E090 and by PANVIPREP funded by European Union's Horizon Europe research and innovation program under Grant Agreement no. 101137229.

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BACK TO MAIN INDEX

P - 77

TARGETING TRPM8 CHANNELS WITH REDUCED HYP DERIVATIVES: SYNTHESIS AND PRELIMINARY INSIGHTS

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TRPM8 channels, or transient receptor potential cation channel subfamily M member 8, are primarily located in sensory neurons. They play a crucial role in detecting cold temperatures and initiating responses to cold stimuli. These channels are involved in various physiological processes, such as pain perception and thermoregulation, and have been associated with pathological conditions, including inflammatory and neuropathic pain, as well as different types of cancer[1].

In previous researches, we identified 4-trans-hydroxiproline (Hyp) ring as an effective and interesting central scaffold for modulating TRPM8 channels. During the hit-to-lead optimization process, we investigated the combination of the most effective groups at the *N*- and *C*-terminal positions to discover promising leads. However, the low solubility of these compounds compels us to explore an alternative strategy by reducing the carbonyl group of the ring. This study focuses on the synthetic approaches and preliminary biological evaluation of novel reduced Hyp derivatives **1** as TRPM8 modulators

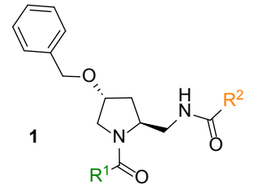

Figure 1. General structure of reduced 4-trans-hydroxyproline derivatives

Acknowledgements

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P - 78

APPLICATION OF DRUG PENETRATION CHEMICAL RULES TO THE SEARCH FOR SELECTIVE DRUGS AGAINST *STRONGYLOIDES*

Rafael Peláez [1, 2, 3], Miguel Marín [1, 2, 3], Noelia Fernández-Ceballos [1, 2, 3], Laura Gallego [1, 2, 3], Javier Sánchez-Montejo [1, 2, 4], Alejandra Villamizar-Monsalve [1, 2, 4] and Julio López-Abán [1, 2, 4]

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Strongyloidiasis, a soil-transmitted parasitic helminth (STH) infection, is a significant public health challenge in tropical regions due to the limited repertoire of effective treatments. Strongyloidiasis treatment in humans relies mainly on the macrocyclic lactones ivermectin (IV) and the benzimidazoles albendazole and mebendazole. Few new drugs, such as emodepside, monepantel, and derquantel have received approval to target parasitic nematodes, but only for veterinary purposes. Screening of chemical libraries against the therapeutically relevant third-stage larvae (L3) of the model parasite *Strongyloides venezuelensis* has yielded meager success rates.

Recently, we have shown that drug penetration into *Strongyloides* L3s is particularly difficult and we have established chemical rules for drug penetration[2]. We applied these drug penetration rules to modify drugs designed against the tubulin of the parasite. We synthesized and assayed against *Strongyloides* the new drugs and showed that the structural modifications in fact improved the success rate of the assayed families.

This work shows that designing new antiparasitic drugs must take into account the complex pharmacokinetic requirements associated with the parasitic life cycles, and provides a strong justification of studying drug penetration in the evaluation of new anti-parasitic drugs.

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BACK TO MAIN INDEX

P - 79

AMPHIPHILE-ASSISTED SYNTHESIS OF RUTHENIUM NANOPARTICLES FOR CONTROLLED RELEASE AND ENHANCED ANTIBACTERIAL ACTIVITY.

Manuel Pernía Leal [1], Raúl Gimeno Ferrero [1], Eloísa Pajuelo [2], and Inmaculada Fernandez [1]

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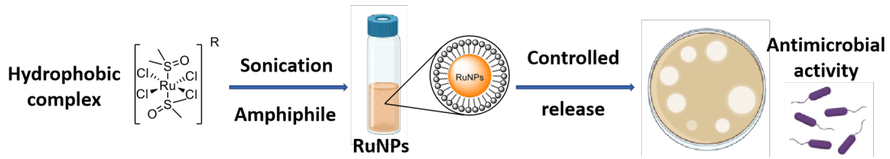
According to recent studies, by 2050, around 10 million people could die from bacterial infections.[1] While subsequent studies have revised these estimates, antimicrobial resistance remains a public health problem, in particular *S. aureus*, *E. coli* and *M.* tuberculosis. Among various strategies, transition metal-based ions are gaining significant attention in biomedical research as promising antimicrobial agents.[2] Despite the extensive research into these metallodrugs, there are still other issues about the bacterial resistance and the degradation of the complexes. A potential solution to tackle these issues is the use of nanotechnology, encapsulating the complexes in organic nanomaterials such as micelles, vesicles and hydrogels.[3] In this study, a novel procedure for preparing of Ruthenium nanoparticles based on low-molecular-weight amphiphilic molecules and Ru(III) complexes as antibacterial agents with controlled release properties has been developed. Two hydrophobic Ru(III) complexes are encapsulated within the core of the micelles formed through the self-assembly of the amphiphiles. Compared to Ru(III) complexes, these RuNPs offer several advantages, including protection from aqueous degradation and enhanced bacterial uptake. Moreover, post-synthesis modification of the RuNPs with molecular staples based on polyethylene glycol chains of varying lengths enables controlled Ru release, reducing the burst effect. Interestingly, these RuNPs demonstrated excellent antibacterial activity, with minimum inhibitory concentration (MIC) values of 16 $mg \cdot L^{-1}$ and minimum bactericidal concentration (MBC) values of 32 $mg \cdot L^{-1}$ against a broad range of Gram-positive bacteria, including *S. aureus*, *S. pseudintermedius* and *E. faecalis*, highlighting their potential efficacy against clinically relevant bacteria strain.



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P - 80

DEVELOPMENT OF KEAP1-NRF2 INTERACTION INHIBITORS: A POTENTIAL THERAPEUTIC APPROACH FOR ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is a neurodegenerative disorder characterized by oxidative stress, neuroinflammation, and progressive neuronal loss. The NRF2-KEAP1 pathway is a key cellular defense mechanism against oxidative damage[1]. Under homeostatic conditions, KEAP1 (Kelchlike ECH-associated protein 1) binds to NRF2 (nuclear factor erythroid 2-related factor 2), facilitating its ubiquitination and subsequent proteasomal degradation. This tight regulation ensures NRF2 is only activated in response to cellular stress. However, in AD, excessive KEAP1 activity leads to sustained NRF2 suppression[2], impairing the expression of antioxidant and cytoprotective genes and exacerbating neuronal vulnerability to oxidative damage.

A promising therapeutic strategy is to disrupt the KEAP1-NRF2 interaction, thereby stabilizing NRF2 and restoring its transcriptional activity[3]. This study focuses on the structure-based design and synthesis of small-molecule inhibitors targeting the KEAP1 Kelch domain. Using molecular docking and molecular dynamics simulations, we have identified lead compounds with high affinity for KEAP1. These computational studies guided the rational design of synthetic routes, allowing us to obtain candidate inhibitors with favorable physicochemical properties.

Future research will focus on evaluating these inhibitors in cellular models to assess their ability to activate NRF2 and induce the expression of antioxidant response element (ARE)-driven genes. By targeting this regulatory pathway, our work aims to develop novel neuroprotective strategies to mitigate oxidative stress and slow AD progression.

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BACK TO MAIN INDEX

P - 81

EXPLORING UGI ADDUCTS AS INHIBITORS OF INFLUENZA A VIRUS OR HUMAN CORONAVIRUSES

Marina Serrano [1], Álvaro de la Cruz [1], Lieve Naesens [2], María José Camarasa [1], Sonia de Castro [1]

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Annually, Influenza A virus causes epidemics, which are controlled by vaccination and antiviral medicines.[1] On the other hand, the outbreak of COVID19 in 2020, caused around 6 million deaths worldwide and encouraged the development of novel antivirals to control SARS-CoV-2 infection SAR-CoV-2.[2] Due to the ability of both viruses to mutate and the lack of activity of actual antiviral drugs new small molecule antivirals urgently need to be designed.

In our research group we have previously identified a unique class of N-benzyl-4,4-diubstituted- piperidines as specific H1N1 influenza A virus fusion inhibitors[3] or SAR-CoV-2 depending on the substitution of R_2 (Figure 1): amide or ester group in this position result in compounds that present activity against influenza virus while aromatic groups lead derivatives with activity against coronavirus. In the case of influenza virus, these compounds have as a target the fusion peptide in hemagglutinin (HA), that allowed the virus entry into the host cell.[4] In the case of SAR-CoV-2, the target of our compound is the main protease (Mpro) which has a pivotal role in mediating viral replication and transcription.[5] Both, fusion peptide and Mpro, present only minor variations between strains and represent attractive drug target for each virus.

In this project we synthesized analogues of the N-benzyl-4,4-disubstituted-piperidines that were recognized[3] as anti-influenza H1N1 fusion inhibitors or showed micromolar activity for SAR-CoV- 2. For the synthesis of these molecules, the four-component Ugi reaction (Ugi-4C) is used, in which different amines are used and amino acids to direct the compounds to the target of the influenza or coronavirus, while maintaining the same isocyanide and piperidone.

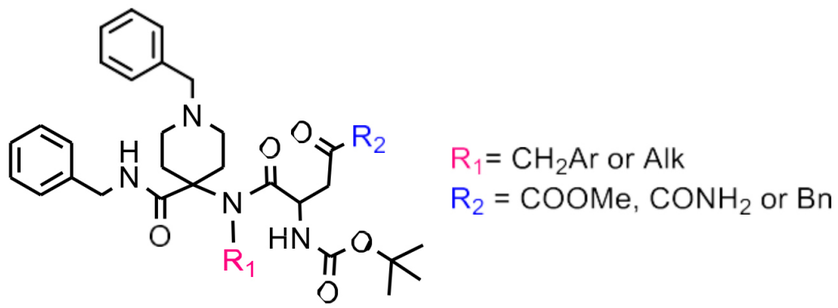

Figure 1. *General structure of N-benzyl-4,4-disubtituted piperidines*

Acknowledgements

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P - 82

DIRECTING THE POWER OF CARBOHYDRATE-DERIVED ISOTHIOCYANATES: EXPLORING NRF2 ACTIVATION AND NEUROPROTECTION BEYOND SULFORAPHANE

Nora Khiar [1], Luis Alberto Prieto [2], Rafael León [3], Victoria Valdivia [2], Rocío Recio [2] and Inmaculada Fernández [2]

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Neurodegenerative diseases like Alzheimer's and Parkinson's cause progressive neuronal degeneration, leading to motor and cognitive impairments. Current treatments are limited, creating a need for new therapies. Activating Nrf2, a key regulator of antioxidant responses, shows promise for neuroprotection. [1] While natural isothiocyanates (ITCs) like sulforaphane and iberin (Figure 1) can activate Nrf2, their low bioavailability and inability to cross the blood-brain barrier limit their effectiveness.[2]

This project focuses on developing a new family of carbohydrate-based isothiocyanates,[3] structurally analogous to sulforaphane, to improve bioavailability and target the central nervous system. We explore their capacity to protect neuronal cells from oxidative stress-induced damage, assessing both their efficacy and underlying mechanisms. Our findings suggest that these isothiocyanates may offer promising therapeutic avenues for neurodegenerative diseases by modulating Nrf2 activity and enhancing cellular resilience against oxidative injury.

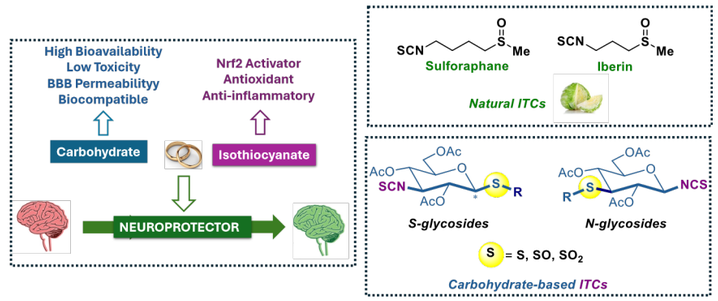

Figure 1

Acknowledgements:

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BACK TO MAIN INDEX

P - 83

POLYCATIONIC AMPHIPHILIC GLYCOPHANES AS NUCLEIC ACID DELIVERY VECTORS

Alejandro Méndez-Ardoy [1,2], Fernando Ortega-Caballero [1], Carmen Ortiz Mellet [1], José M. García Fernández [2], José Luís Jiménez-Blanco [1]

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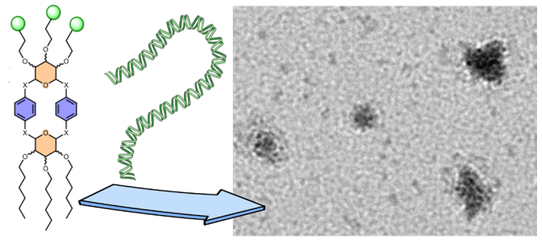
Nucleic acid-based therapeutics represents a groundbreaking approach towards the treatment and prevention of a wide range of diseases. These therapies rely on the complexation of therapeutic nucleic acids with delivery vectors that protect against enzymatic degradation (e.g. nucleases) and facilitate cellular uptake. The biodistribution of these complexes, particularly tissue tropism, critically depends on their physicochemical properties. For example, nanoparticle sizes below 200 nm prevent sequestration by the liver and spleen.[1] Although cationic lipid nanoparticles are currently the gold standard, their limitations have prompted the development of alternative non-viral vectors. We have previously demonstrated that carbohydrate-based macrocycles such as polycationic amphiphilic cyclotrehalans with topological segregation of hydrophobic and protonable domains can efficiently generate small pDNA nanoparticles, that facilitate gene transfection both *in vitro* and *in vivo*. The vector architecture significantly influenced nanoparticle morphology, and consequently, cellular and tissue selectivity.[2] Here we present a new class of carbohydrate-based macrocyclic vectors: *polycationic amphiphilic glycophanes,* characterized by alternating carbohydrate and aromatic units. We show that these novel structures can efficiently complex pDNA into nanoparticles with size and surface charges suitable for systemic delivery.



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P - 84

CHITOSAN INTERPENETRATING POLYMER NETWORKS: BOOSTING IMMUNE RESPONSE AND REDUCING INFLAMMATION IN WOUND AND BURN HEALING

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Chitosan (CTS) is a natural biopolymer widely used in biomedical applications for its biocompatibility, non-toxicity, antimicrobial activity, bioadhesion, and ability to promote healing and cell permeability. These properties make CTS an ideal base for wound and burn dressings, as it supports tissue regeneration, has a hemostatic effect and demonstrates strong cellular affinity.[1] However, the mechanical and physicochemical limitations of CTS-based hydrogels, due to internal matrix interactions, restrict their application in advanced therapies.

This study aimed to develop improved, biocompatible hydrogel systems based on CTS for applications in skin and mucous membrane therapies. To enhance mechanical stability, 1st generation of interpenetrating polymer networks (IPN) with complex 3D structures were synthesized via orthogonal click thiol-ene reactions between diamines and bis- or tris(cyclic carbonates).[2] Furthermore, the concentrations of crosslinker and CTS, and the ratio of AcOH-H_2O (used as solvents) were systematically varied to optimize the properties of the resulting hydrogels.

The prepared IPN exhibited good mucoadhesive properties and improved rheological properties compared to hydrogels that only contain CTS, with a predominance of the elastic character as the CTS concentration increased. Furthermore, the obtained hydrogels demonstrate high porosity (17-23% pore area) and excellent fluid absorption (swelling indices of 2200%-20000% in two hours).

All these characteristics make these systems good candidates to be loaded with anti-inflammatory and local anesthetic drugs, increasing therapeutic efficacy for wound and burn care[3].

Acknowledgements

We would like to acknowledge for the funding support to the Ministerio de Ciencia e Innovación-Agencia Estatal de Investigación (MCIN/AEI/10.13039/501100011033), grant number PID2020-115916GB-I00

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BACK TO MAIN INDEX

P - 85

DISCOVERY OF A LDH DEGRADER FOR PH1 TREATMENT

Pilar María Luque Navarro [1], Fabio Arias [2], Sumati Rohilla [2], Yudibeth Sixto-López [1], Samanta Villanueva [1], Sandeep Das [2], Francisco Franco [1], José Antonio Gómez-Vidal [1], Oren Rom [2] and Mónica Díaz-Gavilán [1].

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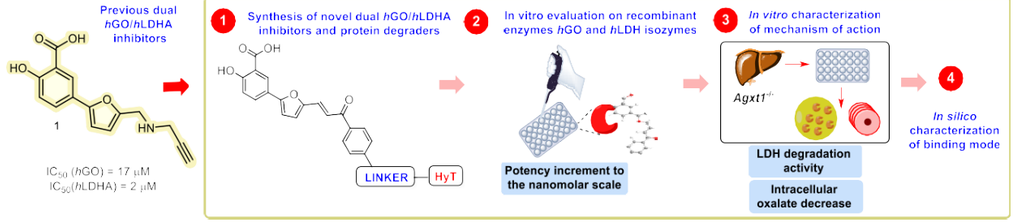
Oxalate is a toxic end-product of glyoxylate metabolism. Its endogenous overproduction is related to the group of rare diseases known as primary hyperoxalurias (PHs).[1,2] In PHs, the overproduction of endogenous oxalate is due to impairment of key enzymes of hepatic and extra- hepatic glyoxylate metabolism. Clinical manifestations of PHs involve oxalate urolithiasis, impairment of the renal function until end-stage renal disease (ESRD) and organ malfunctioning. Enzymes glycolate oxidase (GO) and lactate dehydrogenase (LDH) catalyze consecutive steps in the biosynthesis of oxalate and both enzymes are validated targets for the treatment of PHs.[1,2] Furyl salicylic acids (FSAs) (*Figure 1*) are dual inhibitors of the human enzymes *h*GO and *h*LDHA.[4] Compound **1** can improve the phenotype of PH1, the most severe type of PH, after oral administration in mice,[3] producing notable reductions in urinary oxalate. Despite its good therapeutic profile, the inhibitory potency of **1** against *h*GO and *h*LDHA remains in the micromolar range.[3] Encouraged by the promising expectations raised by a nanomolar dual inhibitor of these enzymes, we prepared the first dual inhibitor, salicylic acid derivative, which is also capable of activating LDH proteolysis *in vitro* and *in vivo.* We characterized its binding mode using *in silico* methodologies and we demonstrated its efficiency in decreasing urine oxalate concentration in a mouse model of PH1 (*Figure 1*).



Acknowledgements

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P - 86

BIOORTHOGONAL HYDROGEL NETWORKS FOR ADVANCED GASTRORETENTIVE DELIVERY: MUCOADHESIVE AND FLOATING SYSTEMS FOR CONTROLLED AMOXICILLIN RELEASE

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Gastroretentive drug delivery systems (GRDDS) have emerged as a pivotal strategy to enhance the pharmacokinetics and therapeutic efficacy of orally administered drugs. In this study, novel GRDDS were developed by synthesising interpenetrating polymer networks (IPN) using Ltartramidederived building blocks, via an optimised DielsAlder bioorthogonal reaction within a guar gum matrix[1–3]

The resulting hydrogels exhibited mucoadhesive and floating properties, rendering them suitable for prolonged gastric retention. Porosogens such as sucrose and polyethylene glycol (PEG) were incorporated to modulate the microstructure (Figure 1) and the release profile of the drugs. Rheological analysis confirmed the colloidal stability and favourable mechanical properties of the biomaterial suspensions.

Amoxicillin (AMOX), a first-line antibiotic for the treatment of *Helicobacter pylori* infection, was loaded into the IPN and its release profile was evaluated at pH 2.0 and pH 5.0 to simulate gastric conditions[4].These systems achieved high drug loading and demonstrated sustained release, with cumulative AMOX release reaching 65100% over eight hours, particularly at an acidic pH. These findings highlight the potential of tartramide-based IPN prepared via efficient bioorthogonal chemistry as robust platforms for the controlled oral delivery of antibiotics and other therapeutics.

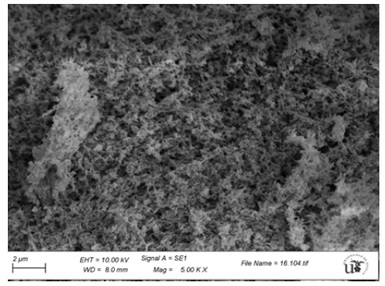

Figure. 1. *SEM images from superporous IPN hydrogel at 5000X.*

Acknowledgements

We would like to acknowledge the funding support from the Ministerio de Ciencia e Innovación–Agencia Estatal de Investigación (MCIN/AEI/10.13039/501100011033), grant number PID2020-115916GB-I00.

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BACK TO MAIN INDEX

P - 87

MECHANISMS AND MULTITARGETING STRATEGIES IN THE TREATMENT OF NEURODEGENERATIVE DISORDERS: THE ROLE OF NRF2 PATHWAY

Irene Jiménez [1], Aida Pinacho [1], Francisco José Sánchez-Porro [1] and Rafael León [1]

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Alzheimer's disease (AD) is the most common neurodegenerative disorder. The lack of effective treatments to halt its progression highlights the urgent need for new therapeutic approaches. Key pathological features, such as the accumulation of beta-amyloid plaques and tau protein tangles, are central to AD. Notably, oxidative stress plays a crucial role in the disease's progression, leading to the disruption of protein processing, mitochondrial dysfunction, and neuroinflammation. These factors further increase oxidative stress, creating a cycle that accelerates neurodegeneration[1].

The wide range of physiological roles regulated by the transcription factor NF-E2-related factor 2 (NRF2) makes it an attractive target for novel drugs towards chronic diseases characterized by complex pathological networks. In that sense, we are currently in the process of developing a novel family of NRF2 inducers with complementary activities for the treatment of AD. Additionally, the compounds are being optimized to selectively target and modulate key pathways involved in neurodegeneration, offering a promising approach for Alzheimer's treatment[2].

This work will present a synthetic process for the preparation of multitarget electrophilic compounds of indole-type derivatives, which are highly reactive Nrf2 inducers. These compounds covalently modify critical cysteine residues (Cys) of Kelch-like ECH-associated protein 1 (KEAP1), such as Cys-151, Cys-273, and Cys-288, thereby activating the Nrf2 pathway to promote the expression of antioxidant response element (ARE)-driven genes.

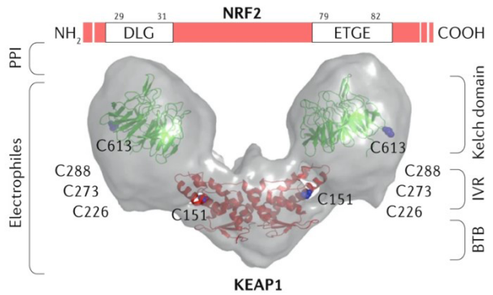

Figure 1. *Representation of a single-particle electron microscopy image of the KEAP1 dimer with the crystal structures of the BTB domain*[2].

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P - 88

NOVEL 3D TRPM8 STRUCTURES UNLOCK OPPORTUNITIES FOR HIT OPTIMIZATION

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The Transient Receptor Potential Melastatin 8, TRPM8, is a non-selective calcium channel, also known as the cold and menthol receptor. It has gained interest as therapeutic target for several diseases, including neuropathic pain, chronic migraine, cold allodynia and cancer.[1] TRPM8 consists of a domain-swapped tetramer, in which each protomer has a transmembrane (TM) and a cytosolic domain. The TM region contains the voltage-sensor-like domain (VSLD) and the pore domain.[2] Recent structural studies have revealed multiple ligand binding pockets.[3]

A structure-based virtual screening of in-house compound collections using induced fit docking (IFD) identified a family featuring a nitrogen six-membered heterocyclic core, with micromolar IC_{50}. Initially, IFD studies were based on a homology model of human TRPM8 (hTRPM8) generated from the *parus major* structure in complex with the ligand TCI-2014 (PDB: 6O72),[2] selecting its binding site at the VSLD (Fig. 1). However, structure-guided optimization failed to improve affinity. The reason became evident when recent cryo-EM studies revealed a different TCI-2014 binding pocket (Fig. 1) at the interface of two protomers (PDB code 9B6H)[3]. Further IFD studies were carried out based on an updated hTRPM8 homology model generated from 9B6H using the newly identify cavity as the binding pocket. These studies have generated novel hypotheses and several designed compounds are currently being synthesized. In conclusion, a nitrogen six-membered heterocyclic core was identified which, together with the revised binding site, appears promising for the development or potent TRPM8 inhibitors.

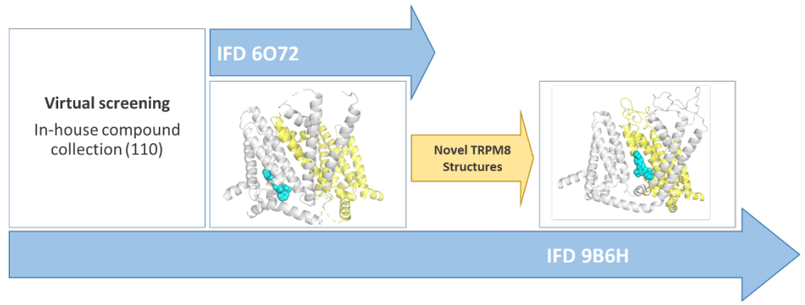

Figure 1. *Workflow of IFD studies. TM of two protomers (white and yellow) and TCI-2014 (cyan).*

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BACK TO MAIN INDEX

P - 89

ANTIPROLIFERATIVE ACTIVITY EVALUATION OF NEW 3,7-DISUBSTITUTED 6-AZAINDOLES

Nicole Pouli [1], Panagiota Lampiri [1], Athanasios Pousias [1], Panagiotis Marakos [1], Nikolaos Lougiakis [1], Eleni Mavrogonatou [2], Harris Pratsinis [2] and Dimitris Kletsas [2]

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Fused pyridine and pyrimidine derivatives constitute an interesting medicinal chemistry scaffold, since their structural resemble to purines results in their involvement in crucial biological processes. Numerous purine or purine-like compounds have already reported as cytotoxic agents, through a variety of investigated mechanisms. As part of a program aiming to discover novel derivatives with potential cytotoxic activity, our research group has previously synthesized a number of nitrogen containing heterocyclic compounds, that exhibited promising in vitro and/or in vivo anticancer activity. In this work, we have designed and synthesized a number of new, suitably substituted pyrrolo[2,3-c] pyridines, using as lead compound a hit, recently identified by our group. For the synthesis of the target derivatives 2-amino-3-nitro-4-methylpyridine was used as the starting material, which was initially converted to the key intermediate 7-chloropyrrolo[2,3-c]pyridine, followed by the introduction of appropriate substituents to this scaffold. The new derivatives were subsequently evaluated for their potential to inhibit the proliferation of human origin cancer cell lines. The evaluation of the cytotoxicity results revealed interesting SARs since certain compounds possessed strong antiproliferative activity, that could assist to the design of the next generation of derivatives. Interestingly, the new compounds proved to be more effective against the A431 cancer cell line, which expresses abnormally high levels of the epidermal growth factor receptor (EGFR) and contains no functional p53, a potent tumor suppressor gene.

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P - 90

SYNTHESIS AND CYTOTOXIC ACTIVITY EVALUATION OF NEW 3,7-DIARYLOSUBSTITUTED PYRROLO[2,3-C]PYRIDINES

Panagiotis Marakos [1], Maria Georgiou [1], Nikolaos Sakalis 1, Nikolaos Lougiakis [1], Nicole Pouli [1], Eleni Mavrogonatou [2], Harris Pratsinis [2] and Dimitris Kletsas [2]

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Purine analogues are important therapeutic tools due to their affinity to enzymes or receptors that are involved in critical biological processes. With the aim to discover novel derivatives with potential cytotoxic activity, our research group is actively involved in the synthesis of numerous purine isosters and the subsequent evaluation of their cytotoxic activity. We have thus discovered compounds possessing IC_{50} values in the nM, or low μM concentration, against a variety of cancer cell lines of human origin. As a continuation of this project, we present here the design and synthesis of some new 6-azaindole derivatives, substituted with aryl groups at positions -3 and -7 of the scaffold. Commercially available 2-amino-3-nitro-4-methylpyridine was used as the starting material for the preparation of the target compounds. In total, 20 novel derivatives were synthesized and were evaluated for their potential to inhibit the proliferation of four cancer cell lines (A431, HT-1080, MCF-7, MDA-MB-231). Additionally, their effect on the proliferation of normal, non-cancer cells was examined. The cytotoxicity results revealed interesting SARs concerning the effect of the substitution pattern of the novel compounds on the antiproliferative activity. The analogues bearing the 2,4-dimethoxyphenyl group at position -7 of the 6-azaindole core proved to be the most potent, with IC_{50} values in the range 12-18 nM against the HT-1080 and MDA-MB-231 cancer cell lines. Notably, all analogues showed insignificant effect on the normal cell line AG01523, thus possessing great selectivity indices. In order to investigate the possible mechanism of action of the novel derivatives, a cell cycle analysis was performed for the most active compounds. The novel derivatives proved to cause a significant cycle arrest at phase G2/M when tested at the breast cancer cell line MDA-MB-231.

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BACK TO MAIN INDEX

SELECTIVE DIARYLSULFONAMIDES TARGETING TRYPANOSOMATID TUBULIN: SYNTHESIS AND PRELIMINARY EVALUATION

Cristina Sanz [1, 2], Raquel Álvarez [1, 2], Laura Gallego-Yerga 1, 2, Nuno Santarem [3, 4], Rafael Peláez [1, 2], Anabela Cordeiro da Silva [3, 4]

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Neglected tropical diseases (NTDs) present a major public health challenge, particularly in developing regions, with trypanosomatid infections such as Leishmaniasis and Sleeping sickness disease causing significant health and socioeconomic burdens. This requires innovative treatments with more effectiveness necessary to mitigate this impact.

Microtubules are essential for key cellular processes, including division and motility, making tubulin a validated therapeutic target in various diseases, including cancer and parasitic infections[1]. Of the seven known tubulin binding sites targeted by antimitotic agents, the colchicine site stands out due to the small and synthetically accessible nature of its ligands[2]. Despite the high sequence conservation of tubulin across species, structural differences in the colchicine binding site between trypanosomatid and mammalian tubulin offer an opportunity for selective drug design[3]. Notably, while colchicine effec tively inhibits microtubule polymerization in human cells, it exhibits limited antiparasitic activity (Luis et al., 2013).

In this study, we synthesized a series of diarylsulfonamides designed to selectively target the colchicine binding site of trypanosomatid tubulin by interacting with parasite-specific amino acids absent in the host. Their biological activity was evaluated in *Leishmania infantum* promastigotes and *Trypanosoma brucei* bloodstream forms, alongside cytotoxicity assays in HeLa and THP-1 cells, in order to test selectivity. Preliminary results indicate that several sulfonamides display antiparasitic activity without being cytotoxic against human cancer cell lines, which can be considered a new scaffold to find novel antiparasitic therapeutics.

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- "ERDF A way of making Europe" by the "European Union"
- EMBO Scientific Exchange Grant

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P - 92

DEVELOPMENT OF TET2 PROTACS TO IMPROVE THE EFFICACY OF CAR-BASED CELL THERAPIES

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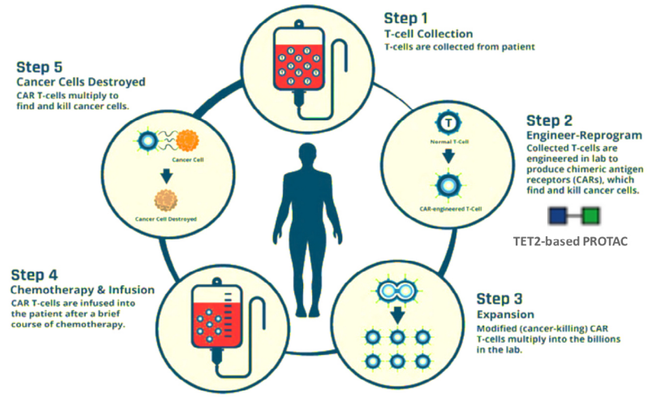
Genetically engineered CD8⁺ T-cells (CAR-T cells) have been progressively used as cancer immunotherapy to treat blood cancers, such as B cell malignancies and multiple myeloma. However, apart from the common side effects associated with CAR-T cell treatments, the efficacy of CAR-T cells is still insufficient. A high percentage of patients relapse some years after CAR-T cell infusion; mainly owing to deficient expansion and persistence of CAR-T cells. [1,2]

In this context, there are some recent studies demonstrating that TET2 might function as a governor of CD8⁺ T-cells differentiation by altering the epigenetic regulation of gene expression. The absence of TET2 results in hypermethylated regions of DNA that diverge the regulation of gene expression. Given this circumstance, the downregulation of TET2 terminates in a remodelled CD8⁺ T-cells memory phenotype, which is distinguished to persist longer in the body and respond faster upon re-exposure to antigens. [3,4] These results suggested us that a PROTAC-based molecule redirecting TET2 to proteasomal degradation could mimic the demonstrated effect provoked by TET2 downregulation. [5]

In this scenario, we aim to design, synthesize and evaluate TET2-based PROTACs that could be beneficial for CAR-based therapies using some of allosteric TET2 ligands that was previously identified by our group.



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BACK TO MAIN INDEX

P - 93

OXIDATIVE STRESS, CHRONIC NEUROINFLAMMATION, AND NEUROTRANSMISSION AS TARGETS FOR ALZHEIMER'S DISEASE TREATMENT: DESIGN, SYNTHESIS, AND PHARMACOLOGICAL EVALUATION OF NEW TRIFUNCTIONAL HYBRIDS

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Alzheimer's Disease (AD) represents a neurodegenerative disorder that progresses chronically and progressively, linked to the natural aging process, and is the most prevalent cause of dementia globally. AD presents high complexity and is considered a multifactorial disease. From a pathophysiological perspective, it is characterized by the accumulation of β-amyloid deposits, neurofibrillary tangles, dysregulation of calcium homeostasis, mitochondrial dysfunction, oxidative stress, and chronic neuroinflammation, among others. Currently, most treatments are symptomatic or do not control the majority of processes involved in the pathophysiology. This has led to the creation of a new therapeutic strategy based on multitarget ligands.

In this framework, a series of compounds have been developed with the aim of acting on different therapeutic targets, intervening in complementary pathways of the neurodegenerative process to prevent or slow down the neurodegenerative progression associated with AD. The expected pharmacological profile includes Nrf2 transcription factor induction activity, modulation of the α7 nicotinic receptor (α7-nAChR), and inhibition of the inflammasome, acting at oxidative, cholinergic, and inflammatory levels.

Based on previously developed structures with Nrf2 induction and α7 nAChR modulation activities, hybrids have been designed with the compound MCC950, a well-known inflammasome inhibitor.

A family of 21 compounds has been synthesized, which have been pharmacologically evaluated to study their in vitro activity on different targets, as well as their ability to scavenge free radicals and their neuroprotective effect in models of oxidative stress and tau protein hyperphosphorylation, events closely related to the pathophysiology of AD.therapeutic effectiveness for various conditions. (Abstract text in arial font: size 10, justified)

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P - 94

PYRIMIDINE-2-ONE DERIVATIVES: A NOVEL FAMILY OF POSITIVE ALLOSTERIC MODULATORS OF THE CB2R WITH ANTI-INFLAMMATORY ACTIVITY

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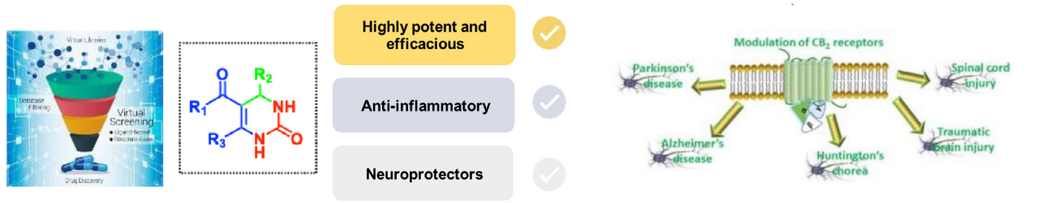
CB2R, one of the two subtypes of Cannabinoid receptors (along with CB1R), is predominantly expressed in immune cells and peripheral tissues. This receptor plays a key role in immunomodulatory and anti-inflammatory processes.

Allosteric modulators of CB2R provide a unique strategy for selectively regulating receptor activity, enabling more precise control of cellular responses while minimizing unwanted side effects. Their ability to fine-tune CB2R function has sparked significant interest in the development of new therapies for inflammatory disorders, neurodegenerative conditions, and autoimmune diseases. To date, only one synthetic positive allosteric modulator of CB2R had been previously identified. In this context, CB2R allosteric modulators have demonstrated promising antiinflammatory effects by modulating immune responses and reducing the release of proinflammatory mediators. Additionally, these compounds have shown neuroprotective properties in preclinical models of neurodegenerative diseases, suggesting potential therapeutic applications for conditions such as Alzheimer's disease and multiple sclerosis.

As part of a project aimed at identifying new scaffolds for cannabinoid receptor allosteric modulators using MCR-based approaches, we report here the discovery and optimization of a novel family of CB2R PAM ligands synthesized via the Biginelli reaction. These compounds exhibit high activity and excellent efficacy.



Acknowledgements

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ED431B 2023/023 and ED431B 2020/43 is gratefully acknowledged.

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BACK TO MAIN INDEX

P - 95

cis-DICHLORO-4,5-DIAZAFLUORENE PLATINUM (II) COMPLEXES: SYNTHESIS AND ANTIPROLIFERATIVE ACTIVITY

Leonardo Sandin-Mazzondo [1], Jesús Martínez de Ilarduya [1], Camino Bartolomé [1] and Concepción Alonso [2]

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Coordination compounds are of great interest in medicinal chemistry, especially in cancer research since the approval of cisplatin as an antitumoral drug. After the approval of cisplatin, other platinum coordination complexes, oxaliplatin and carboplatin for example, have reached the market as anticancer medicines. Given the success of platinum complexes, many other platinum compounds are being studied as potential new antitumoral drugs. The substitution of the ammonia group of cisplatin for *N*-heterocycles ligands has proven to be succesfull.[1] Based on that, our research focuses on the synthesis of bipyridines derived from 4,5-diazafluorene and the corresponding cis-dichloro platinum(II) complexes.

The synthesis of the 4,5-diazafluorene derivatives mentioned is presented. These compounds have an aromatic group substitution at the C9 position of 4,5-diazafluorene. These compounds have been used as ligands to synthesize *cis*-dichloro Pt(II) complexes with a molecular ratio of 1:1 ligand:Pt (Fig. 1). The antiproliferative evaluation of ligands and complexes in different cancerous cell lines is presented and compared to cisplatin´s. The selectivity towards lung carcinoma cells and the Pt cellular uptake are also discussed. These results highlight the importance of inorganic medicinal chemistry and serve as a foundation for further investigation on bioactive coordination compounds.

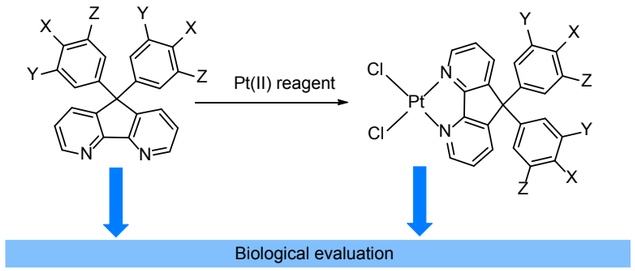

Figure 1. *Schematic presentation of the workflow in this work*

Acknowledgements

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P - 96

NEW LIBRARY OF SALICYLIC ACID DERIVATIVES AS DUAL INHIBITORS OF GO AND LDHA FOR THE TREATMENT OF PRIMARY HYPEROXALURIA

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The term primary hyperoxalurias (PHs) gathers a group of rare diseases characterized by an endogenous overproduction of oxalate.[1,2] Oxalate is a toxic end-product of metabolism. Its overproduction leads to accumulation in tissues (oxalosis) and urine (hyperoxaluria), both of which are clinical manifestations of PHs. Crystallization of calcium oxalate in kidneys leads to oxalate urolithiasis and impairment of the renal function until end-stage renal disease (ESRD). Enzymes glycolate oxidase and lactate dehydrogenase, which catalyze consecutive steps in the biosynthesis of oxalate, are therapeutic targets for the treatment of PHs.[1–2] In our previous work, we have prepared salicylic acid derivatives with dual inhibitory activity of the human enzymes *h*GO and *h*LDHA.[3] Compound **1** (Figure 1) produces a decrease of urinary oxalate when it is administered orally to PH1 mice. However, the inhibitory potency of 1 against *h*GO and *h*LDHA remains in the micromolar range.[3] We have prepared 5-[5-(3-oxo-3-phenylpropenyl)-2-furyl] salicylic acids (OPPFSAs) as structural derivatives of **1** with dual inhibitory activity of *h*GO and *h*LDHA in the nanomolar range. We characterized the biological profile of OPPFSAs on recombinant enzymes and studied their binding mode using *in-silico* studies (Fig. 1).

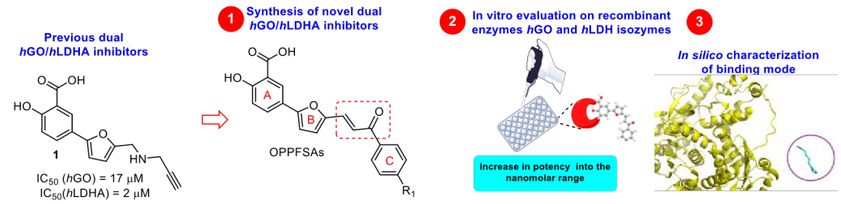

Figure 1. *Work plan followed for the development of new compounds for the treatment of PH.*

Acknowledgements

We would like to acknowledge Project PID2022-141783OB-C21, funded by MCIN/AEI/10.13039/501100011033/ and by FEDER A way to make Europe.

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BACK TO MAIN INDEX

P - 97

DESIGN, SYNTHESIS AND BIOLOGICAL STUDIES OF N-PHENYLBENZAMIDE DERIVATIVES TARGETING INTRACELLULAR TRYPANOSOMATID PARASITES.

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Neglected tropical diseases caused by kinetoplastid parasites, such as *Trypanosoma cruzi*, *Trypanosoma brucei*, and *Leishmania*, represent a significant global health burden. The AT-rich mitochondrial DNA (kDNA) of trypanosomatid parasites serves as a target for DNA minor groove binders (MGBs). In this work, we synthesised symmetric and non-symmetric N-phenylbenzamide-derived molecules having different heterocyclic (Het) moieties and analysed their biological and physicochemical properties in order to perform SAR studies (*Figure 1*). The binding affinity to AT-rich oligonucleotides was analysed by SPR, which allowed ranking the new compounds based on their DNA binding affinity. The efficacy of these series was assessed *in vitro* against African trypanosomes (i.e., *T. brucei* and *T. congolense*), American trypanosomes (*T. cruzi*), and *L. donovani*, as well as the apicomplexan parasite *Plasmodium falciparum.* Additionally, nonspecific cytotoxicity was evaluated across various mammalian cell lines, including MRC-5, L929 fibroblasts, and THP-1, to calculate the selectivity indexes (SI) for the parasites.

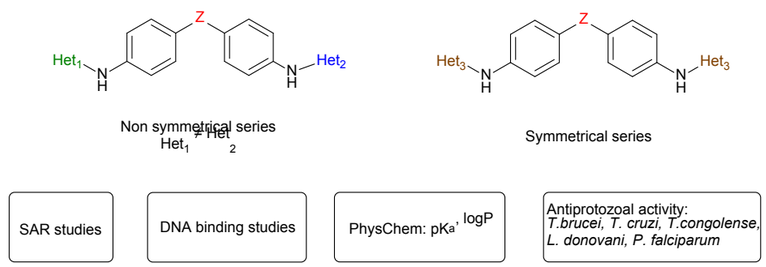

Figure 1. *New MGBs developped for series. Chemical strategies applied in this work to improve activity and selectivity towards neglected tropical diseases caused by kinetoplastid parasites.*

Acknowledgements

We gratefully acknowledge COMUNIDAD DE MADRID (CAMPREDOC22 PIPF-2022SAL-GL-24344) and Agencia Estatal de Investigación (MCIN/AEI/10.13039/501100011033), through the project PID2022-136438OB-I00 (Co-funded by European Regional Development Fund. ERDF, “A way to build Europe”) for financial support.

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AUTHORS INDEX

* Corresponding poster

BACK TO MAIN INDEX

* Corresponding poster

BACK TO MAIN INDEX

* Corresponding poster

* Corresponding poster

BACK TO MAIN INDEX

* Corresponding poster

* Corresponding poster

BACK TO MAIN INDEX

* Corresponding poster

BACK TO MAIN INDEX

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