Sociedad Española de Química Terapéutica

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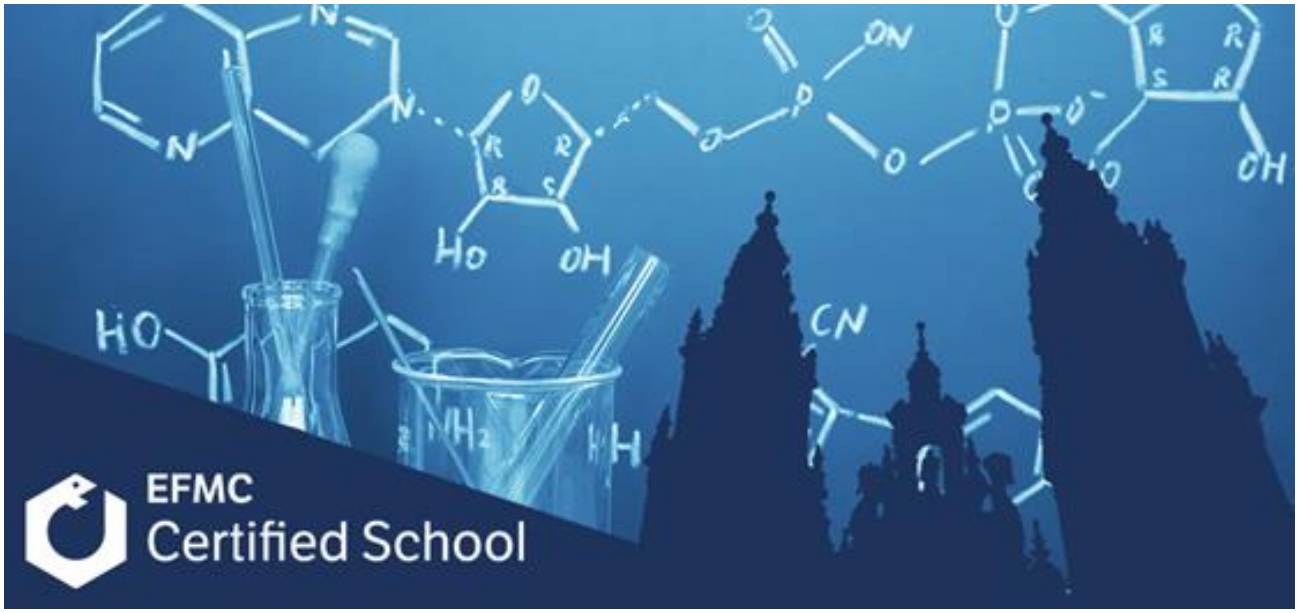

VIII SEQT Summer School

MEDICINAL CHEMISTRY AND CHEMICAL BIOLOGY IN DRUG DISCOVERY: THE PHARMA PERSPECTIVE

19-21 June 2023, Santiago de Compostela

Co-organized by

GalChimia

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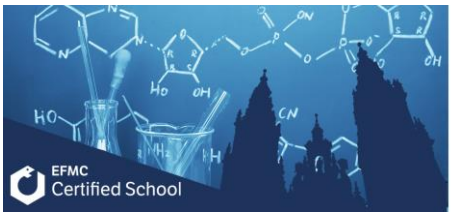

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Sociedad Española de Química Terapéutica GalChimia

19-21 June 2023, Santiago de Compostela

Dear Colleagues,

The Spanish Society of Medicinal Chemistry (SEQT), member of the European Federation for Medicinal Chemistry and Chemical Biology (EFMC), and GalChimia welcome you to the VIII SEQT Summer School "Medicinal Chemistry and Chemical Biology in Drug Discovery: the Pharma Perspective" in Santiago de Compostela, Spain.

This is our second edition as EFMC Certified School, which has contributed to its internationalization. Since its first Edition in 2009 (Janssen, Toledo), the SEQT, in collaboration with different pharma and biotech companies, has organized biannual Summer Schools that constitute a springboard for scientific discussions with the aim of approaching the pharma and biotech industry to young researchers, both graduate students and post-doctoral associates, working in the chemistry and health sciences related fields. During the Summer School, the participants have the opportunity to learn about the latest research trends in pharmaceutical drug discovery and development.

Following the tradition of previous SEQT Summer Schools, in order to foster these discussions, all students are required to participate in flash presentations (two-minute/1-slide presentation of poster highlights) and poster sessions. Among them, the Scientific and Advisory Boards will select 5 students for a short oral communication that will be presented in the final day of the school.

The scientific program will include several workshops covered by speakers from Almirall, CeTPD, GalChimia, Janssen, Kaetor Foundation, Lilly, Novartis and SpiroChem AG.

We would like to wish you an enjoyable stay in Santiago de Compostela, and we hope you will actively participate in the scientific sessions and networking activities, which will provide an optimal forum for scientific debate.

The organizing committee,

Beatriz, Jacobo, Marta, Mónica & Eva

SEQT Sociedad Española de Química Terapéutica

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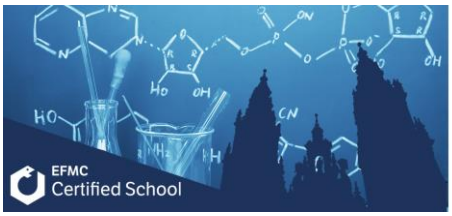
SCIENTIFIC PROGRAMME



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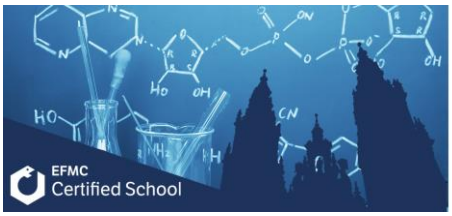
SCIENTIFIC PROGRAMME

Monday, June 19	
12:30 – 13:30	Registration
13:30 - 14:30	Opening and cocktail
14:30 - 15:45	**Workshop 1: Chemical Biology. Targeted Protein Degradation** **Willian Farnaby (CeTPD, University of Dundee)**
15:45 – 17:00	**Workshop 2: Modern Medicinal Chemistry: the lamppost effect and premature conclusions** **Gerhard Müller (SpiroChem AG)**
17:00 - 17:30	Coffee Break
17:30 - 18:30	Flash Poster Session
19:30-20:30	**Poster Session**
21:00	Networking time: Welcome Dinner. Announcement of the selected posters

Tuesday, June 20	
09:00 – 10:15	**Workshop 3: Best Practices in Medicinal Chemistry. Medicinal Chemistry and Chemical Biology for drug candidate identification** **Yves Auberson (EFMC delegate, Novartis)**
10:15-11:30	**Workshop 4: New technologies in Organic Chemistry and their application to Medicinal Chemistry** **José Enrique Gómez Pulido (Janssen)**
11:30-12:00	Coffee Break
12:00-13:15	**Workshop 5: Scale-up in Drug Discovery: from a Route to a Process** **Jacobo Cruces and Mónica Carreria (Galchimia)**
13:15-14:30	Lunch
14:30 -15:45	**Workshop 6: ADME properties and designing by purpose** **Jordi Bach (Almirall)**
15:45-17:00	**Workshop 7: Discovery and use of novel photoredox reactions to transform Medicinal Chemistry (Photo4MedChem)** **Juan A. Rincon (Lilly)**
20:15 – 21:00	Historic downtown Tour (Santiago de Compostela)
21:00	Networking time: Gala Dinner



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SCIENTIFIC PROGRAMME

Wednesday, June 21	
09:00 – 10:15	**Workshop 8: Cancer Innova: a Business Factory Medicines initiative** **Mabel Loza (Kaertor Foundation)**
10:15 – 12:00	Selected Oral Communications
12:00 - 12:30	Trip to GalChimia
12:30 – 14:00	Coffee and GalChimia Tour
14:00 – 14:15	Closing remarks
14:10 - 15:30	Lunch (Cocktail)
	End of the School

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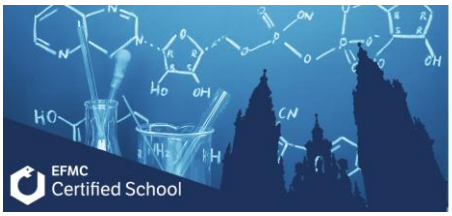
WORKSHOPS & SPEAKERS

WORKSHOP 1. Targeted Protein Degradation



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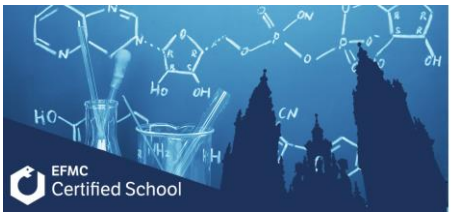
William Farnaby

w.farnaby@dundee.ac.uk

Will Farnaby is a Principal Investigator within the Centre for Targeted Protein (CeTPD) at the University of Dundee. He uses multi-disciplinary small molecule discovery methods for controlling protein homeostasis. His group has a primary focus on discovering chemical probes to further our understanding of how to treat Central Nervous System (CNS) diseases, where there are currently unmet needs for conditions affecting hundreds of millions of people globally.

Previously, whilst working as a medicinal chemist at Takeda Pharmaceutical company, Will contributed to the discovery of multiple CNS focussed clinical candidates, including Soticlestat, a Cholesterol 24-Hydroxylase inhibitor used to treat Dravet's syndrome. More recently, he led a large Targeted Protein Degradation drug discovery team as part of a collaboration between the University of Dundee CeTPD and Boehringer-Ingelheim that produced a number breakthrough discoveries in structure based bifunctional degrader discover.



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Design and Discovery of Targeted Protein Degraders

William Farnaby

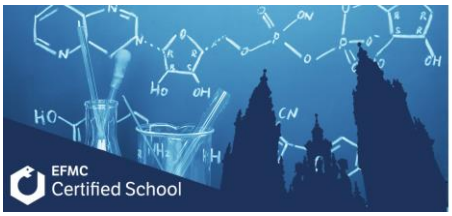
Centre for Targeted Protein Degradation, University of Dundee, UK

wfarnaby@dundee.ac.uk

Small molecule Targeted Protein Degradation has made major clinical impact in recent years, first in the context of IMiD Molecular Glues and more recently with several bifunctional PROTAC degraders now in Phase1/2 trials. These new modalities have brought both opportunity and challenge when considering how we can discover and design molecules as probes or drugs. In this workshop we will explore how medicinal chemistry and chemical biology can be applied towards targeted protein degradation. We will discuss why and when TPD approaches may be relevant for a given project, the pros and cons of different modalities (e.g. Molecular Glues or PROTACs) and how their mechanisms of action may influence preference for one over the other in a given circumstance. Best practice for benchmarking and evaluation of degrader molecules will be presented as well as discussing what parameters can be measured and how to interpret them when identifying hits and optimising them. Finally, we will work through a case study together focussed on designing bifunctional PROTAC degraders to find potent and selective chemical probes.

References:

[1] Kofink, C et al *Nat Commun* **2022**, 13, 5969
[2] Farnaby *et al*, *Nat Chem Biol* **2019**, 15, 672-680



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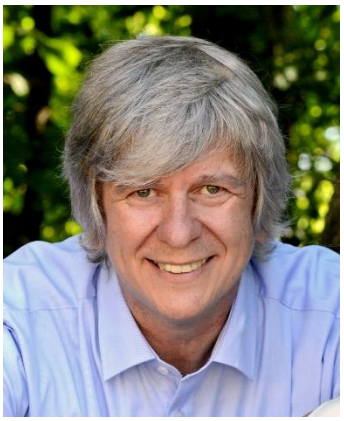
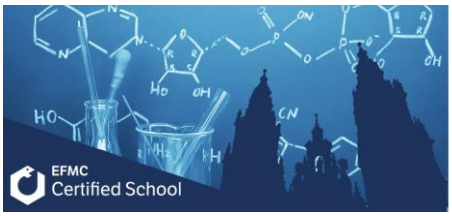
Gerhard Müller

SpiroChem AG



Gerhard has recently joined SpiroChem AG in Basel as their Chief Scientific Officer. He has proven expertise in small-molecule drug discovery and strong entrepreneurial skills supported by 25 years of practical and managerial experience in the European pharmaceutical, transatlantic biotech, and CRO industries. Throughout his career, Gerhard has worked on a wide range of different target classes in numerous disease areas. Gerhard's expert knowledge in medicinal chemistry allowed him to establish novel design paradigms, proven by over 75 peer-reviewed publications. Prior to joining SpiroChem AG, he co-founded Gotham Therapeutics in New York, and Anavo Therapeutics in Heidelberg. Gerhard raised close to 100 Mio € venture capital for three different biotech companies. He held key positions at Mercachem, GPC Biotech, Axxima Pharmaceuticals, Glaxo, Bayer, and Organon. Gerhard received his PhD in organic chemistry from the Technical University of Munich, where he worked with Prof. Dr. Horst Kessler on anti-adhesive integrin antagonists.



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Modern Medicinal Chemistry: *the lamppost effect and premature conclusions*

Gerhard Müller[1]

[1]*SpiroChem AG, Basel, Switzerland*

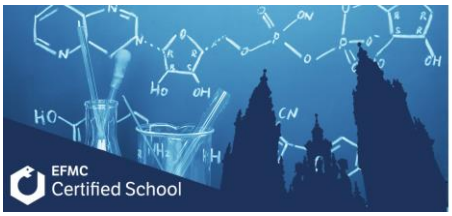
gerhard.mueller@spirochem.com

According to the title of the VIII SEQT summer school, i.e. "*Medicinal Chemistry in Drug Discovery: the Pharma Perspective*", the introductory part of the lecture will provide a number of key facts associated to today's pharmaceutical industry. Special emphasis will be laid on the so-called streetlight (lamppost) effect that still widely dominates the chemical space and the target space that is heavily scrutinized by the majority of drug discovery campaigns.

In this context, the research areas of kinase inhibitors will be compared to phosphatase inhibitors, thus demonstrating that once established stigmas can have a major impact on the way we select drug targets for novel drug discovery projects.

The field of RNA and RNA-modifying enzymes is used to highlight the relevance of thorough operational excellence in the hit confirmation phase for novel targets by utilizing novel methodologies from the field of biophysics. It will be shown, that only the rigorous application of orthogonal technologies helped to avoid premature conclusions on the confirmation level of chemotypes for two target classes, i.e., methyltransferases and YTH domains.

WORKSHOP 3. Best Practices in Medicinal Chemistry.
Medicinal Chemical Biology for drug candidate identification



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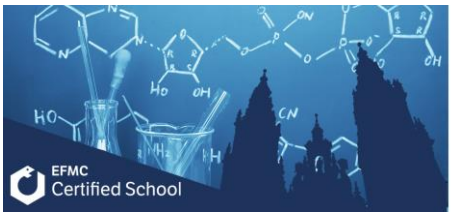
Yves P. Auberson

Novartis institutes for BioMedical research, Basel , Switzerland

Yves P. Auberson obtained his Ph.D. in 1990 at the Swiss Federal Institute of Technology in Lausanne, Switzerland. He joined the Novartis Institute for BioMedical Research in Basel, Switzerland, in 1992, after a post-doctoral training in chemical biology with Peter Schultz, at Affymax, in Palo Alto, USA.

He is currently Executive Director in Global Discovery Chemistry, where his research group develops tracers for clinical imaging, with the aim to facilitate and improve the quality of clinical trials. Previously, he was Head of Chemistry for Neuroscience, supporting projects for psychiatry and neurodegeneration.

Yves played a direct role in the discovery and development of several drug candidates for epilepsy and narcolepsy, as well as of clinical tracers for positron emission tomography. He is actively involved in the medicinal chemistry and chemical biology community, acting as the Past President of the European Federation for Medicinal Chemistry and Chemical Biology (EFMC), and Vice-president of the Swiss Chemical Society.



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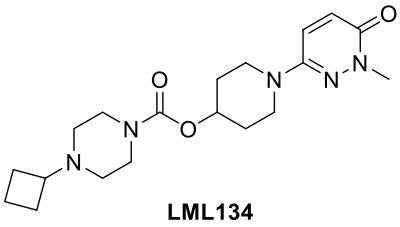
Medicinal Chemistry and Chemical Biology for drug candidate identification

Yves Auberson[1]

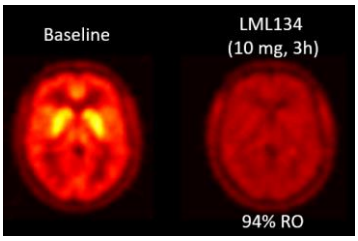
[1]*Novartis Institutes for BioMedical Research, 4056 Basel, Switzerland*

yves.auberson@novartis.com

Histamine H3 receptor (H3R) inverse agonists are efficacious for the treatment of narcolepsy but have a long duration of action. This leads to insomnia on the night following administration. Our aim was to identify a drug candidate with high efficacy (as determined by a receptor occupancy above 85%), and a fast elimination from the receptor in the brain, to avoid any effect on sleep quality.
We will discuss the medicinal chemistry program that led to the identification of the clinical development compound LML134, and how the team solved the issues associated with brain penetration, receptor binding kinetics, hERG, phospholipidosis and several challenges that appeared along the way. The comparison of the preclinical profile of LML134 with its phase I clinical data will show how the strategy of addressing toxicity alerts early, and optimizing receptor occupancy, allowed to reach the criteria set at the onset of this program: safety, efficacy, and a short duration of action.



LML134



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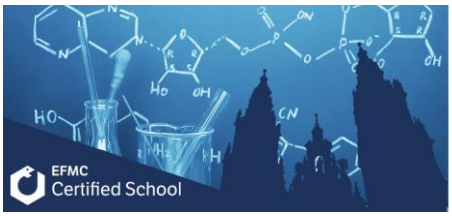
[2] Auberson Y. P., Troxler T. J., Zhang X., Yang C. R., Feuerbach D., Liu Y. C., Lagu B., Perrone M., Lei L., Shen X., Zhang D., Wang C., Wang T.-L., Briner K., Bock M. G. *ChemMedChem* **2015**, 10(2), 266-275.
[3] Auberson Y. P., Troxler T. J., Zhang X., Yang C. R., Fendt M., Feuerbach D., Liu Y.-C., Lagu B., Lerchner A., Perrone M., Lijun L., Zhang C., Wang C., Wang T.-L., Bock M. G. *ChemMedChem* **2014**, 9(8), 1683-1696.

WORKSHOP 4. New technologies in Organic Chemistry and their application to Medicinal Chemistry



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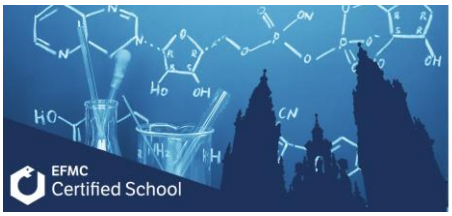
José Enrique Gómez, PhD.

Janssen Research & Development, Janssen-Cilag, S.A., Jarama, 75A, Toledo, 45007, Spain.

José Enrique Gómez, former alumni of the University of Valladolid, received his bachelor's and master's degrees in Chemistry in 2015. He later obtained his PhD in Organic Chemistry, in 2019, working on transition-metal-catalyzed stereocontrolled transformations under the supervision of Prof. Arjan W. Kleij at the Institute of Chemical Research of Catalonia (ICIQ). During his PhD studies, he also spent four months at Eli Lilly (United Kingdom, UK) working at the Discovery Chemistry and Synthesis Group, working in the development of a workflow for the automated late-stage functionalization and structure elucidation of drug-like molecules. As a recognition of his doctoral studies, he was awarded with the 2019 RSEQ-Lilly Award, the 2019 Reaxys-RSEQ Early Career Researcher Award and the Josep Castells 2019 Award.

José Enrique worked at Albany Molecular Research Inc. (AMRI) for one year in the Process Research and Development department (Valladolid, Spain) prior to joining Janssen Cilag (Toledo, Spain) as a Scientist.

In Janssen Cilag, José Enrique is part of the Global Chemical Capabilities group contributing to accelerate medicinal chemistry programs through the use of automated parallel chemistry and enabling technologies.



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AUTOMATION IN PARALLEL MEDICINAL CHEMISTRY AND NEW ENABLING TECHNOLOGIES AT JANSSEN R&D

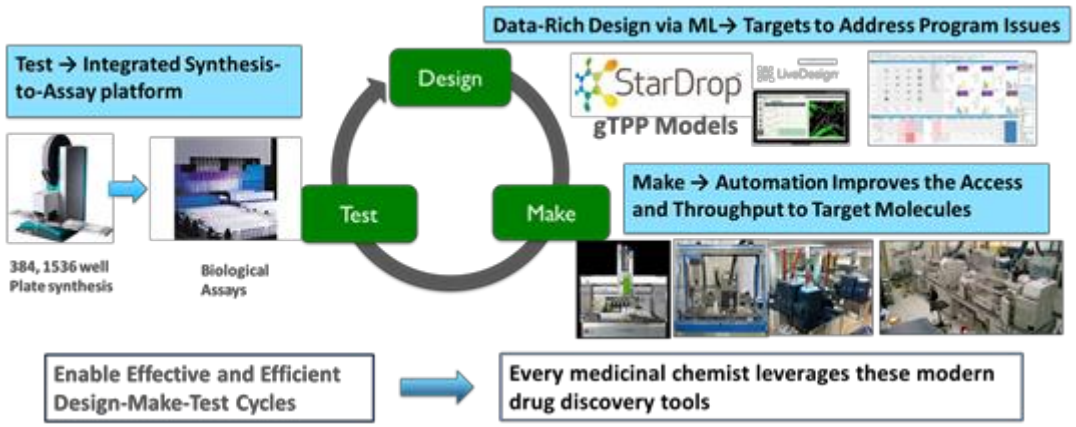
José Enrique Gómez[1]

[1]*Janssen Research & Development, Janssen-Cilag, S.A., Jarama, 75A, Toledo, 45007, Spain.*

jgomezpu@its.jnj.com

Small molecule medicinal chemistry relies on iterative learning cycles composed of a compound design, synthesis, testing, and data analysis to provide new chemical probes and lead compounds for novel and druggable targets. Using traditional approaches, the time from hypothesis to obtaining the results can be protracted, thus limiting the number of compounds that can be advanced into clinical studies. This challenge can be tackled with the recourse of enabling technologies that are showing great potential in improving the drug discovery process.

In this talk, we highlight automation equipment and representative examples of automated end-to-end prototypes that are currently employed at Janssen R&D to expedite medicinal chemistry discovery cycles.



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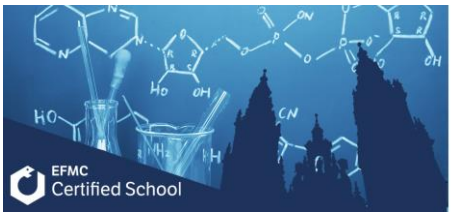

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Jacobo Cruces

CSO and Co-founder, GALCHIMIA S.A., Touro, Spain

Jacobo Cruces obtained his PhD in Organic Chemistry in 2001 from the University of Santiago de Compostela. Soon after, he founded GalChimia with Dr Carme Pampín and two of their professors, where he is the Chief Scientific Officer (CSO).

Throughout these years, he has managed more than 2700 synthesis projects, most of them related to drug development. His 21-year experience as R&D Manager and Chief Scientific Officer has given Jacobo ample expertise in both medicinal chemistry and process development, and a real know-how in the practicalities required for the establishment of successful processes.

His entrepreneurial career is completed with the creation of three other companies within the biotechnology sector: AMSLab, ChemoSapiens, and Origo Biopharma (now AgomAb Therapeutics).

In addition, he participates in several innovation projects at national and European level. In particular, his interests lie in projects that address the synthesis and scale up of complex molecules for specific applications related to medicine and biotechnology through the development of new chemical methodologies.

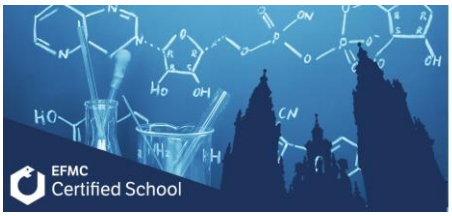
Monica Carreira

Scientific Innovation Officer, GALCHIMIA S.A., Touro, Spain

Monica Carreira is a Chemistry graduate from the University of Santiago de Compostela (Spain). She obtained a PhD in Homogeneous Catalysis from the University of Bristol (UK), and later moved to the United States to work on anticancer compounds as a Research Associate in Brooklyn College (The City University of New York).

In 2013, she made the move from the bench to a desk after joining the Royal Society of Chemistry (Cambridge, UK) as a Publishing Editor. She later continued her career in Scientific Communication as a freelance Scientific Writer.

Monica joined GalChimia in 2019 as Scientific Innovation Officer, helping outline the innovation strategy of the company by supporting the CSO and CGO. In this role, she manages the R&D collaborative projects at national and international level, as well as leading the communication and disseminaton activities of the company.



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SCALE-UP IN DRUG DISCOVERY: FROM A ROUTE TO A PROCESS

Monica Carreira and Jacobo Cruces

GalChimia S.A., Parque Empresarial de Touro, Parcelas 26-27, Fonte Díaz, 15822, Touro, A Coruña (Spain)

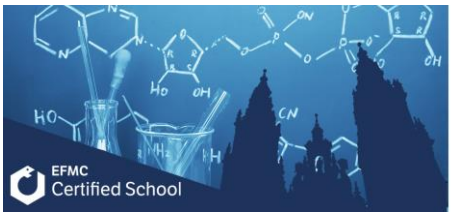
monica.carreira@galchimia.com, jacobo.cruces@galchimia.com

Process chemistry enables the safe, sustainable, and economical manufacturing of organic compounds that are required in large amounts. It not only involves every aspect of organic chemistry, but it also takes from analytical and solid-state chemistry, and even chemical engineering.

During drug discovery, medicinal chemistry and process chemistry have very different objectives. While medicinal chemists are concerned with synthesizing a large number of compounds as quickly as possible from easy-to-tune building blocks (usually for SAR studies), process chemists are tasked with identifying a chemical process that is cost and labor efficient, safe, sustainable, and reproducible, among other considerations. Often, in the search for the “ideal” route, process chemists must think "out of the box" and develop creative synthetic solutions.

In this talk, we will cover the different aspects to consider when transferring a synthesis route for a drug (discovery chemistry) into an actual process viable for manufacture at pre-clinic scale (process development). Such transference involves several crucial considerations, from the cost and supply of raw materials to regulatory and safety aspects.

WORKSHOP 6. ADME properties



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Sociedad Española de Química Terapéutica · GalChimia

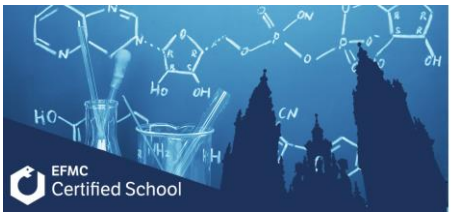
19-21 June 2023, Santiago de Compostela

Jordi Bach

NCE Discovery & Early Development, Almirall R&D, Sant Feliu de Llobregat, Spain

Jordi Bach graduated in Chemistry from the University of Barcelona (UB) in 1991. After a short stay in Prof. Steve Davies group at Oxford University (UK), he obtained his PhD in Organic Chemistry at the University of Barcelona under the supervision of Prof. Jordi Garcia (1997). From 1998 to 1999 he carried out postdoctoral research in Prof. Ian Paterson's group at the University of Cambridge (UK) before joining Almirall's Medicinal Chemistry Department where he has risen to become a Principal Scientist.

In Almirall, Jordi has led or has been directly involved in numerous discovery programs for autoimmune, respiratory and dermatological diseases, several of which have delivered Development Candidates. He has also been involved in diverse research collaborations with industrial and academic groups. Jordi is co-author of 21 peer-reviewed publications and co-inventor of 14 patents and has given several lectures at various international Conferences.



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ADME PROPERTIES AND DESIGNING BY PURPOSE

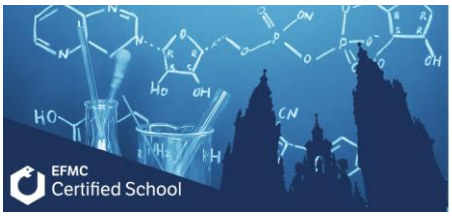
Jordi Bach[1]

[1]*NCEs Discovery & Early Development, Almirall R&D, Sant Feliu de Llobregat, Spain*

jordi.bach@almirall.com

In addition to therapeutic efficacy and safety, a New Chemical Entity (NCE) needs to have favorable ADME properties to become a marketable drug. These properties refer to the processes Absorption, Distribution, Metabolism and Excretion of the drug in the body. Characterization and optimization of the ADME properties become increasingly important as a project progresses from lead finding to lead optimization and finally to candidate selection. In this workshop, the discovery of the inhaled JAK inhibitor LAS194046 will be presented to illustrate the relevance of the route of administration and the ADME properties in the design of bioactive compounds. After reviewing the most relevant *in vitro* and *in vivo* ADME assays for compound profiling, the workshop will focus on the design, synthesis, and biological activity of a novel series of potent JAK inhibitors with a suitable profile for inhaled administration. Work in this series culminated in the identification of LAS194046 as a preclinical candidate. Strategies followed to improve potency, selectivity and lung retention of initial hits will be discussed along with the overall profile (ADME, safety/tox, formulability and efficacy) of the candidate compound. This case study illustrates some of the key challenges that medicinal chemists face in discovery programs and highlights the relevance of ADME properties in drug design.

WORKSHOP 7. Photochemistry



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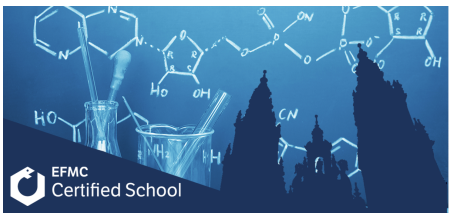
Juan A. Rincón

Centro de Investigación Lilly, S.A.U. Alcobendas, Madrid

Juan A. Rincón, PhD. Advisor-Research received his doctorate in Organic Chemistry at University of Valladolid (Spain, 1999) working in organotin-mediated stereoselective synthesis. During that period, he spent short stays at University of Cambridge (UK) working in the group of Prof. Ian Fleming. After that, he performed post-doctoral studies at the Organic Chemistry Institute (CSIC, Madrid) working in the field of catalysis supported on new materials. Then, he joined Lilly (2002-present) where he is currently Advisor at the Medicinal Chemistry Alcobendas Team. Since then, he has acquired broad experience in route development, process safety and synthetic and medicinal chemistry. Juan was key to establish and consolidate the flow chemistry group in Alcobendas and played a pivotal role in growing the technical capabilities in this area (flow chemistry platforms, reaction monitoring and semi-automated continuous processing). He possesses an extensive external network and has sponsored multiple LRAP collaborations with key professors in the field of photochemistry (Prof. David W.C. MacMillan) and flow chemistry processes (Prof. Timothy Noël). He is currently leading the implementation of the Photo4MedChem initiative in Alcobendas site.

Publications: **42 + 1 book chapter** (ISBN: 978-3-527-34689-9)



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DISCOVERY AND USE OF NOVEL PHOTOREDOX REACTIONS TO TRANSFORM MEDICINAL CHEMISTRY (Photo4MedChem)

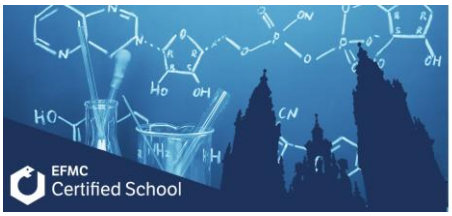
Juan A. Rincón

Centro de investigación Lilly, S.A.U. Alcobendas, Madrid

rincon_juan_antonio@lilly.com

Light-induced and photoredox catalytic transformations have emerged as powerful tools to readily access complex molecules through innovative mechanistic pathways by using sustainable sources of light. This approach enables new chemical transformations in terms of identifying novel bond disconnections by providing synthetic shortcuts with a special interest in Late-Stage Functionalization (LSF). This seminar describes the impact that this strategy can have in drug discovery programs, with an emphasis of the use of flow chemistry to get more efficient and scalable processes. The learnings coming from different collaborations with key professors in this area have been key to achieve these goals.

WORKSHOP 8. Entrepreneurship



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MABEL LOZA

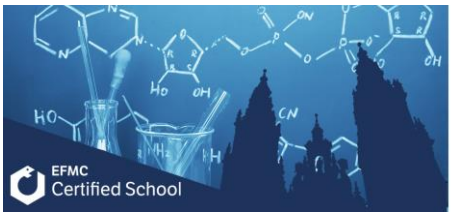
Professor of Pharmacology, Head of BioFarma research group at the University of Santiago de Compostela (USC). Promoter and founding trustees of the Kærtor Foundation. Coordinator of DPT unit (Diagnostic, prognostic and therapeutics tools) from the Biomedicine area of the Spanish Research Agency. Galician Coordinator of the Complementary Plan for Biotechnology applied to Health (https://www.pcbasgalicia.es/). Loza participates in the creation of four small technological companies, two of them with drugs in clinical trials.

Mabel Loza profoundly believes in interdisciplinary collaboration and networks. Her activity is mainly focused on international collaborations in drug discovery networks, participating in think-tanks and debates on strategic solutions like Keystone and advisory boards. With Dr. Angel Carracedo from Genomic Medicine, they lead the pharmacogenomics screening platform INNOPHARMA one of the seven of high capacities from the ERIC EU-OPENSCREEN (www.eu-openscreen.eu), where she is the scientific Spanish representative. She also created and leads the Galician and Spanish Drug Discovery Networks (REGID and REDEFAR), and ES-OPENSCREEN

Mabel Loza research field is applied pharmacology, especially in new drug discovery for unmet clinical needs. She has worked on more than ninety research projects, seventy of them as principal researcher, founded by public and private, local, Spanish and international institutions. Her research has contributed with 17 new clinical entities (NCE) that have reached clinical trials through Public-Private-Partnerships (PPP), the last one for repositioning in COVID-19 developed jointly in the joint unit from the team that she promoted with the ESTEVE Pharmaceutical Company.

She is Scientific Director of the Kærtor Foundation focused on accelerating the application of drug discovery to patients, connected with the second generation of open innovation that has allowed them to be recognized internationally (www.jnjinnovation.com/johnson-johnson-innovation-spotlight-2021-emea) and create inclusive/mission like drug discovery programs to accelerate disruptive science to transformational therapeutics, i.e. I2D2 or Cancer Innova (www.kaertorfoundation.org).

Author of more than 230 articles in indexed journals in the Journal Citation Report and more than 300 contributions at national and international congresses in Pharmacology, Medicinal Chemistry and Drug Discovery. She has participated, as Principal Researcher, in 13 European



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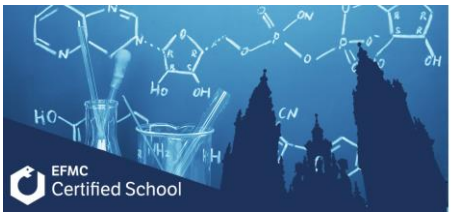
Projects, among them: DRUGtrain, EU-OPENSCREEN-DRIVE, SmallDrugRheuma, Open PHACTS IMI project, EU-ADR projects, etc.

Prizes and distinctions: International LOréal-Unesco “For Women in Science”, including in the book entitled “Nosotras biocientíficas españolas". Selected in EFPIA (European Federation of Pharmaceutical Industries and Associations) among the “30 scientists from 30 countries in Europe” in the initiative Portraits of Science-Scientists of Tomorrow (Paris, June 19, 2008). Recognized as Researcher-Innovator recognition 2018 by the Forum of Innovative Companies. Awarded with María Josefa Wonenburger Planells Galician award in 2019.



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CANCER INNOVA: A BUSINESS FACTORY MEDICINES INITIATIVE

Maria Isabel Loza,[1,2,3].

[1]Kaertor Foundation, Santiago de Compostela, Spain. [2]Innopharma Drug Screening and Pharmacogenomics Platform. BioFarma research group. Center for Research in Molecular Medicine and Chronic Diseases (CiMUS). Department of Pharmacology, Pharmacy and Pharmaceutical Technology. University of Santiago de Compostela, Santiago de Compostela, Spain. [3]Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain.

cancerinnova@kaertorfoundation.org

Cancer Innova Program (CIP) is the first initiative framed in the new Business Factory Medicines of Galicia [1]. The Kærtor Foundation and the Scientific Foundation of the Spanish Association Against Cancer, in collaboration with the Galician Innovation Agency (GAIN), and the pharmaceutical companies Janssen, of the Johnson&Johnson Group, and Lilly have created this program for the development of new drugs against cancer and for the consolidation of a biotechnological ecosystem close to patients.

Its background was the I2D2 program, a collaboration between GAIN, Kærtor Foundation, and Janssen/ J&J, which incubated early research projects in new drug discovery and validated a new incubation methodology based on five validated work packages. This resulted in an 80% reduction in time and costs, compared to the industry averages.

CIP supports innovation in cancer and accelerates the translation of research to patients. To this end, a drug discovery program was created aligned with the Cancer Mission of the Horizon Europe [2] framework program, which represents a landmark in the biotechnology sector.

In CIP, the most disruptive research of the highest scientific quality on cancer was selected to be carried out, with the aim of achieving proof of concept in humans through research planned by milestones. More than one-hundred expressions of interest from eight different countries were applied. Four projects were prioritized to execute the first phase of intensive R+D developed in Galicia coordinated by the Kærtor Foundation.

Currently, CIP is developing the acceleration phase and bringing the projects closer to the pharmaceutical industry to license, carry out a proof of concept, or create a new spin-off.

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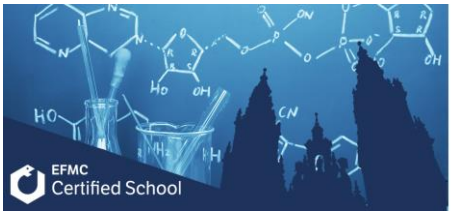
ABSTRACTS



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CONJUGATION OF SIDEROPHORE MIMETICS WITH EFFLUX PUMP INHIBITORS: A NEW STRATEGY TO TACKLE ANTIBACTERIAL RESISTANCE

Mariana C. Almeida,[1,2] Paulo M. da Costa,[2,3] Emília Sousa,[1,2] and Diana I. S. P. Resende [1,2*]

[1]Laboratório de Química Orgânica e Farmacêutica, Departamento de Ciências Químicas, Faculdade de Farmácia, Universidade do Porto, Porto, Portugal. [2]CIIMAR- Centro Interdisciplinar de Investigação Marinha e Ambiental, Matosinhos, Portugal. [3]ICBAS – Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal.

up201605347@edu.ff.up.pt

Antimicrobial resistance to traditional antibiotics must be addressed urgently, through innovative approaches to combat this global threat to public health [1,2]. The conjugation of antibiotics with siderophores/siderophore mimetics, constitutes a promising strategy for the discovery of novel compounds.[3] Inspired by the huge potential of siderophore conjugates, in this work we aim to conjugate siderophore mimetics with efflux pump inhibitors (EPIs) to obtain “Trojan Horse” compounds that might have potential in the fight against antibacterial resistance.

Herein, several siderophore mimetics were synthesized through diverse pathways. Then, two sequential reactions were performed to couple the EPI, the linker portion and the siderophore mimetic to obtain novel conjugates. Structure elucidation of the synthesized molecules was made by nuclear magnetic resonance techniques. Current work includes the screening of the synthesized compounds for their antibacterial activity against both human and fish pathogens. Future goals will also involve the assessment of the compounds’ capacity to inhibit bacterial efflux pumps and their potential synergism with antibiotics.

Acknowledgements: This research was supported by national funds through FCT - Foundation for Science and Technology within the scope of UIDB/04423/2020, UIDP/04423/2020 (Group of Marine Natural Products and Medicinal Chemistry, CIIMAR) and project EXPL/CTA-AMB/0810/2021, under the PORTUGAL 2020 Partnership Agreement. Mariana C. Almeida acknowledges FCT for the individual PhD grant (2021.05224.BD) and Diana I. S. P. Resende for her individual researcher contract (2022.00379.CEECIND).

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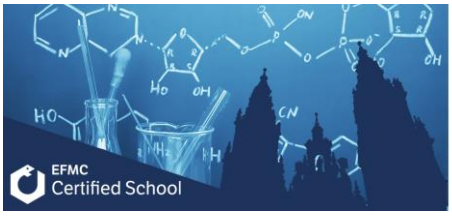

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DESIGN AND OPTIMIZATION OF NOVEL H_4 HISTAMINE ANTAGONISTS

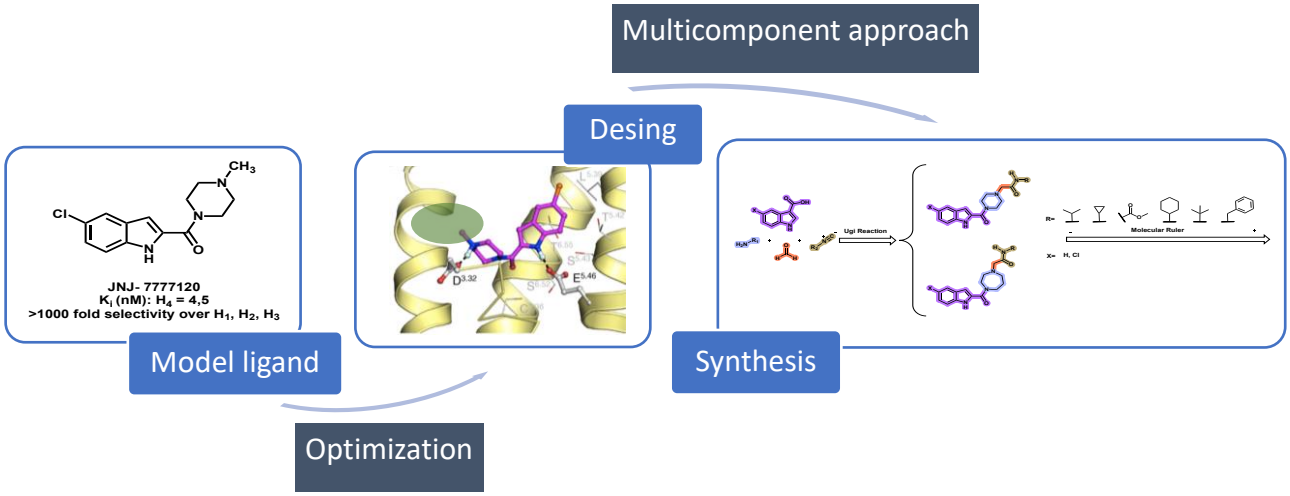
Antonio Andújar-Arias,[1,2] Tania Serlenga,[2] Jhonny Azuaje,[1,2] Mateo Osoro[1] and Eddy Sotelo.[1,2]

[1] Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Santiago de Compostela, Santiago de Compostela, España. [2] Centro de Investigación en Química Biológica y Materiales Moleculares, Universidad de Santiago de Compostela, Santiago de Compostela, España.

antonioandujar.arias@usc.es

Histamine is an endogenous substance that is widely distributed throughout the body and acts as agonist of a series of four subtypes of G protein-coupled Receptors (GPCRs), the H_1, H_2, H_3 and H_4. It plays a crucial role in the immune response, as well as in regulating key physiological processes such as digestion, sleep, and sexual function. H_4 is the most recently discovered subtype, and it is highly expressed in a variety of organs, including immune cells such as eosinophils, dendritic cells and Th2 cells, playing an important role in allergic immune responses and diseases.

Atopic dermatitis (AD) is a pruritic inflammatory skin disease, which is characterized by itching, eczema, epidermal thickness, and a predominant expression of the inflammatory Th2 cytokines, such as IL-4, IL-5 and IL-13. The skin injuries caused by scratching exacerbate the defects in the sking barrier and lead to a boost in the liberation of pro-inflammatory cytokines. Several studies with H4R Knockout mice models showed reduced skin inflammation and antagonists of this receptor significantly limited Th2 cytokines liberation, pruritus, and skin inflammation in AD murine models. Therefore, potent, and selective H_4 histamine antagonists are presented as a promising therapeutical approach for the treatment of atopic dermatitis. Herein we document a multicomponent-assisted program that enabled the design, synthesis, and optimization of a collection of new H4R histamine antagonists inspired by JNJ-7777120. The novel derivatives explore new regions in the receptor by potentiating non-orthosteric interactions.



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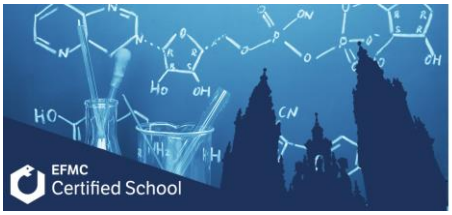

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Bicyclic α-phosphoprolines as imidazoline I_2 receptor ligands

Carla Barbaraci[1], Andrea Bagán[1], Sònia Abás[1], Alba Irisarri[2], Christian Griñán-Ferré[2], Mercè Pallàs[2], Itziar Muneta-Arrate[3], Carolina Muguruza[3], Luis F. Callado[3,4], Belén Pérez[5], Elies Molins[6], José Ángel Morales[7], and Carmen Escolano[1,*]

[1]Laboratory of Medicinal Chemistry (Associated Unit to CSIC), Department of Pharmacology, Toxicology and Medicinal Chemistry, Faculty of Pharmacy and Food Sciences, and Institute of Biomedicine (IBUB), University of Barcelona, Barcelona, Spain; [2]Pharmacology Section, Toxicology and Medicinal Chemistry, Faculty of Pharmacy and Food Sciences, and Institut de Neurociències, University of Barcelona, Barcelona, Spain; [3]Department of Pharmacology, University of the Basque Country, UPV/EHU, and Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Leioa, Bizkaia, Spain; [4] Biocruces Bizkaia Health Research Institute; [5]Department of Pharmacology, Therapeutic and Toxicology. Autonomous University of Barcelona, Cerdanyola, Spain; [6]Institut de Ciència de Materials de Barcelona (CSIC), Campus UAB, E-08193 Cerdanyola, Spain; [7]Department of Cell Biology. School of Medicine. Complutense University (UCM), Madrid, Spain, and The Network Center for Biomedical Research in Neurodegenerative Diseases (CIBERNED).

cbarbaraci@ub.edu

Imidazoline I_2 receptors (I_2-IR) are not specified molecular identities that can be found in the central nervous system and many other organs such as heart and liver. The modulation of I_2-IR by standard ligands evidenced their role in analgesia, inflammation, and human brain disorders, encompassing glial tumors, depression, Alzheimer's disease (AD) and Parkinson's disease (PD), amongst others. The chemical structure of I_2-IR ligands is restricted to 2-heterocyclic-2-imidazolines in the standards idazoxan, tracizoline, BU224, 2-BFI and BU99008 (clinical candidate, Phase I) or an *N*1-imidazole heterocyclic scaffold in CR4056 (clinical candidate, Phase II). We have contributed to the disclosure of the pharmacological role of I_2-IR by their modulation with structurally original I_2-IR ligands and observing *in vivo* physiological responses and modifications of molecular AD-biomarkers in treated murine model animals [1,2,3]. Here we report a new family of bicyclic α-phosphoprolines that showed high affinity and selectivity upon I_2-IR and good BBB permeation. We evaluated three selected new compounds in dopaminergic neurodegeneration and neuroinflammation cellular models. The good results led us to take the challenge to carry out the first study of I_2-IR ligands in *Caenorhabditis elegans* as an *in vivo* AD model organism.

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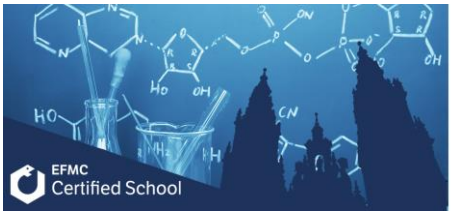

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Towards a new strategy for fighting Mycobacterium tuberculosis through the reductase-trHbN complex

Katerina Barmpidi,[1] Carolina Estarellas,[1] and F. Javier Luque.[1]

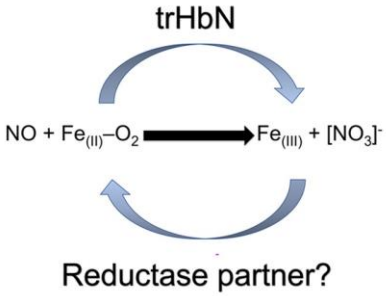
[1]*Department of Nutrition, Food Science and Gastronomy, Faculty of Pharmacy and Food Sciences, Institute of Theoretical and Computational Chemistry (IQTCUB) and Institute of Biomedicine, University of Barcelona, Spain.*

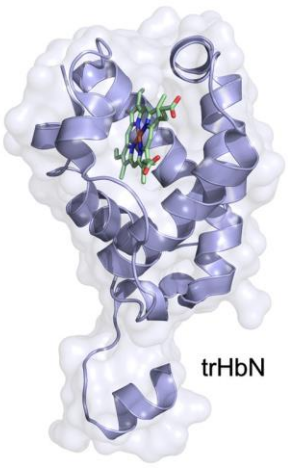
kbarmpidi@ub.edu

Tuberculosis (TB) continues to be a cause of significant morbidity and mortality worldwide due to numerous factors, including the rise of multidrug-resistant and extensively drug-resistant of *Mycobacterium tuberculosis (Mtb)* strains and the absence of an effective vaccine. To forestall this trend, development of innovative strategies targeting novel pathways is currently demanding.

Truncated hemoglobin N (trHbN) of *Mtb* protects its host from the toxic effects of nitric oxide (NO) due to its potent O2-dependent NO dioxygenase (NOD) activity. This protein converts NO produced by macrophages into the harmless nitrate anion.[1] Studies of our research group regarding the structure of trHbN and the migration of NO and O_2, revealed that a protein tunnel system composed of short and long branches facilitates ligand entry to the distal heme site.[2] On the other hand, the oxyferrous heme interacts with NO producing nitrate and ferric heme. To recover the ferrous state and thus enabling the protein to start the cycle again a reductase partner, which has not been identified yet, is required.

Herein, we suggest the putative reductase partner needed for the efficient NOD activity of *Mtb*. Computational methods have been utilized to obtain the complex of trHbN and the putative reductase partner disclosing its structure and eventually molecular docking of four potent inhibitors to this complex which exert antimycobacterial activity[3] has been performed. Our aim is to reveal if its inhibitory effect over the reductase will also affect the NOD activity of trHbN, and thus designing a more potent antimycobacterial drug for this complex.





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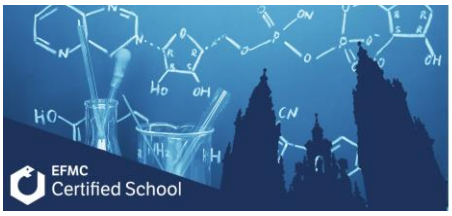

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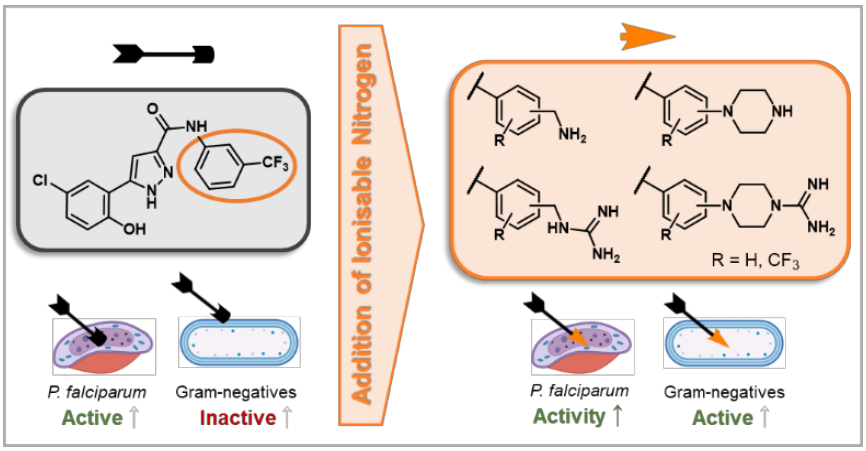
A POSITIVE CHARGE IN AN ANTIMALARIAL COMPOUND UNLOCKS GRAM-NEGATIVE ACTIVITY

Maria Braun-Cornejo[1,2], Mitchell Platteschorre[1], Vincent de Vries[1], Dennis Piet[1], Eleonora Diamanti[3], Jörg Haupenthal[3], Patricia Bravo[4], Vidisha Sonawane[5], Norbert Reiling[5], Matthias Rottmann[4], Peter Maas[1] and Anna K. H. Hirsch.[2,3]

[1] Specs Research Laboratory, Specs Compound Handling, B.V., Bleiswijkseweg 55, 2712 PB, Zoetermeer, The Netherlands. [2] Department of Pharmacy, Saarland University, Campus Building E8.1, 66123 Saarbrücken, Germany. [3]Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) – Helmholtz Centre for Infection Research (HZI), Campus Building E8.1, 66123 Saarbrücken, Germany. [4]Swiss Tropical and Public Health Institute Socinstrasse 57, 4002 Basel, Switzerland. [5]Microbial Interface Biology, Research Center Borstel, Leibniz Lung Center, 23845 Borstel, Germany.

maria.braun.cornejo@specs.net

With the aim of obtaining activity against Gram-negative bacteria, we added ionisable nitrogen-containing functional groups (amines and *N*-alkyl guanidiniums) to an antimalarial compound. The focused library of pyrazole-amides has good broad-spectrum anti-infective potency and is easily accessible synthetically. Overcoming the cell envelope of Gram-negative pathogens is one of the major difficulties in antibacterial drug development. By following Hergenrother's recent findings, the so called "eNTRy-rules" (N = ionisable nitrogen, T = low three-dimensionality, R = rigidity), we obtained anti-Gram-negative activity from an anti-plasmodial starting point. Additionally, the results of phenotypic assay screenings of diverse pathogens (*P. falciparum, E. coli, A. baumannii, P. aeruginosa,* and *M. tuberculosis*) reveal that the studied library, not only gained activity against Gram-negative pathogens but also *M. tuberculosis* and we boosted *P. falciparum* inhibition to the double-digit nanomolar range.



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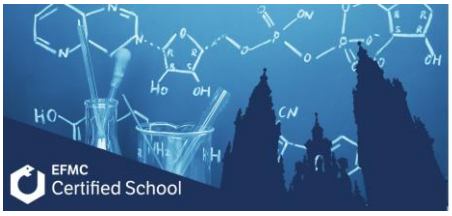

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SMALL-MOLECULE INHIBITORS AS ANTIVIRALS AGAINST DISEASES CAUSEDBY CORONAVIRUSES

D. Cabrera-Torrejón[1], F. F. Castro-Navas[1,2], V. Castro[3], P. Bueno-Fernández[2,3], U. Garaigorta[2,3], P. Gastaminza[2,3] and M. Gutiérrez Rodriguez [1,2]

[1]Instituto de Química Médica (IQM-CSIC) 28006 Madrid, Spain; [2]PTI+ Global Health, CSIC; [3]Centro Nacional de Biotecnología (CNB-CSIC) 28049 Madrid, Spain.

daniel.cabrera@iqm.csic.es

The COVID-19 pandemic has had a profound impact on the world, resulting in millions of lives lost and countless others affected[1]. Although vaccination efforts have made significant progress, the emergence of new variants has highlighted the urgent need for effective antivirals against SARS-CoV-2.

However, the importance of developing antivirals against COVID-19 goes beyond the current pandemic. The threat of future pandemics caused by different coronaviruses is a very real possibility, and the development of potent and safe antivirals is crucial for preparedness for future outbreaks. It is clear that investing in antiviral research is essential for both the current and future global health crises. Therefore, we must prioritize this effort to protect ourselves and future generations.

Considering that the therapeutic armamentarium of specific antiviral drugs to fight against these coronaviruses-caused diseases is limited, it is of capital importance the discovery of new lead molecules with novel mechanism of action, which allow the identification of clinical candidates. This should be the way to arrive in medium/long term to efficient drugs for their treatment, and potentially, also for other coronaviruses infections that could emerge.

As part of our involvement in the emergency plan established by CSIC to fight COVID-19 pandemic, with the aim to increase the antiviral armamentarium against SARS-CoV-2, we started a drug discovery program in collaboration with the CNB Antiviral Platform.

In this communication, we will present the hit-to-lead process of one of the identified families that has allowed us to obtain candidates with EC_{90} values of 2 μM against SARS-CoV-2 and CC_{50}≥ 50 μM in different human cell lines. Additionally, they demonstrated a selectivity profile against other viruses, with no antiviral activity against recombinant human West Nile virus and vesicular stomatitis virus. Moreover, the selected candidates effectively prevented the propagation of SARS-CoV-2, resulting in a viral load reduction of 10^5, values comparable with remdesivir[2].

This study was funded by the European Union - NextGenerationEU, PTI+ Salud Global - CSIC, SGL2103050 "Generación de diversidad química", and CSIC (CSIC-COVID-153; PIE 202080E221).

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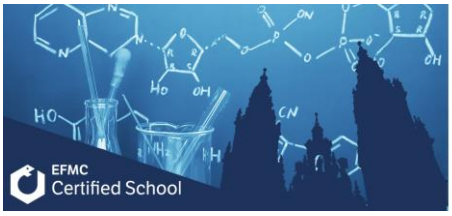

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THE EUROPEAN PROJECT PANACHE: SYNERGIZING *IN SILICO*, *IN VITRO*, AND *IN VIVO* METHODS TO DEVELOP INNOVATIVE INHIBITORS OF MEMBRANE-BOUND PROTEINS AS POTENTIAL ANTI-INFLAMMATORY DRUGS

Laureano E. Carpio,[1] Pravin Ambure,[1] Eva Serrano-Candelas,[1] Brenda Kwak,[2] María D. Mayán,[3] Steven Ballet,[4] Rafael Gozalbes[1,5] and Mathieu Vinken[6]

[1]ProtoQSAR SL, CEEI (Centro Europeo de Empresas Innovadoras), Parque Tecnológico de Valencia, Valencia, Spain, [2]Department of Pathology and Immunology, University of Geneva, 1211 Geneva, Switzerland, [3]CellCOM Research Group, Instituto de Investigación Biomédica de A Coruña (INIBIC), Servizo Galego de Saúde (SERGAS), Universidade da Coruña (UDC), A Coruña, Spain, [4]Research Group of Organic Chemistry, Vrije Universiteit Brussel, Pleinlaan 2, Brussels, Belgium, [5]MolDrug AI Systems SL, Valencia, Spain, [6]Department of Pharmaceutical and Pharmacological Sciences , Vrije Universiteit Brussel, Brussels, Belgium

lcarpio@protoqsar.com

The modulation of membrane-bound proteins, in particular connexins and pannexins, by pharmaceutical drugs is receiving increasing attention due to their importance in cellular communication and inflammation [1-2]. However, the lack of suitable connexin and pannexin inhibitors of cellular channels composed of these proteins has hindered clinical exploration as potential drug targets [3]. The European project PANACHE aims to overcome this challenge by generating a novel generation of connexin and pannexin (hemi)channel inhibitors through the collaboration of academic and industrial scientists from the chemical, chemo-informatics, and biomedical fields.

To accomplish this goal, the PANACHE consortium is applying *in vitro, in vivo*, and *in silico* techniques in order to test and develop new inhibitors with high selectivity and metabolic stability. The targets of this project are the pannexin 1 (Panx1) and connexins 32 and 43 (Cx32 and Cx43), which have been shown to play a key role in inflammation. *In vitro* and *in silico* testing is being used to assess the efficacy of the inhibitors, while *in vivo* testing allows to evaluate their therapeutic potential. The accomplishment of these objectives will represent a significant step forward in developing new, innovative strategies for treating inflammatory diseases.

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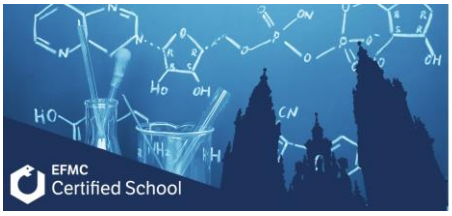

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γ-HYDROXY LACTONE BASED PPARγ NON-AGONISTS AS SAFE AND INNOVATIVE ANTI-DIABETIC AGENTS.

Giulia Cazzaniga,[1] Matteo Mori,[1] Davide Capelli,[2] Roberta Montanari,[2] Antonio Laghezza,[3] Fulvio Loiodice,[3] Ivan Bassanini,[4] Sergio Romeo,[1] Enrico M.A. Fassi,[1] Giovanni Grazioso,[1] Martina Quaglia,[1] Fiorella Meneghetti,[1] Stefania Villa[1]

[1]Department of Pharmaceutical Sciences, University of Milan, Via L. Mangiagalli 25, 20133 Milano, Italy. [2]Istituto di Cristallografia, Consiglio Nazionale delle Ricerche, Strada Provinciale 35d, n. 9 - 00010 Montelibretti (RM), Italy. [3]Department of Pharmaceutical Sciences, Università degli Studi di Bari "Aldo Moro", Via Orabona 4, 70125 Bari, Italy. [4]Istituto di Scienze e Tecnologie Chimiche "Giulio Natta" Consiglio Nazionale delle Ricerche, Via Mario Bianco 9, 20131 Milano, Italy.

giulia.cazzaniga@unimi.it

Peroxisome proliferator-activated receptor γ (PPARγ) represents a key target for the treatment of type 2 diabetes and metabolic syndrome. PPARγ takes part in the control of many cellular functions and pathways related to the regulation of fatty acid metabolism and glucose homeostasis.[1] To avoid the serious adverse effects related to the PPARγ agonism profile of traditional antidiabetic drugs, a new opportunity is represented by the development of molecules acting as inhibitors of PPARγ phosphorylation by the cyclin-dependent kinase 5 (CDK5). Their mechanism of action is mediated by the stabilization of the PPARγ β-sheet containing Ser245.[2]

We performed a biological screening, through Surface Plasmon Resonance (SPR), of an in-house library of synthetic γ-hydroxy-lactone derivatives, among which 4-(4-bromophenyl)-3-hydroxy-5-(3-hydroxyphenyl)furan-2(5H)-one (**1**) emerged as a promising candidate. The library was screened for the ability to prevent PPARγ phosphorylation by CDK5 given the structural similarity with BLI, a natural product, isolated from *Aspergillus terreus*, reported in literature as both PPARγ partial agonist and CDK5 inhibitor.[1] Compound **1**, endowed with a promising K_d of 3.75 μM, showed also an effective inhibition of CDK5-mediated phosphorylation of PPARγ *in vitro* by a kinase assay. The agonist and antagonist activities on PPARγ, and the direct inhibition on CDK5 were dismissed by assays that validated the non-agonist profile of our compound.[3]

We deeply investigated the interaction mode of **1** with PPARγ, by performing crystallographic experiments. The co-crystal structure of **1**-PPARγ showed that the compound occupies the canonical partial agonist hydrophobic binding region between the helix 3 (H3) and β-sheets of the PPARγ LBD (PDB: 8ADF).[3] These data were used in the computational studies for the design of optimized derivatives of **1**.

Overall, this study represents the starting point for the development of novel anti-diabetic drugs based on γ-hydroxy-lactone scaffold, effective for the treatment of diabetes, but without adverse effects.

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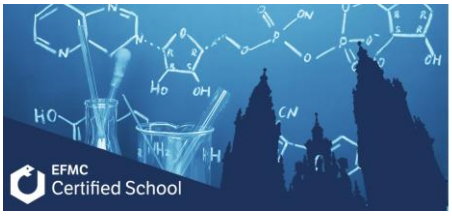

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NOVEL TRIMERIC FUSION INHIBITORS OF HEMAGGLUTININ OF INFLUENZA VIRUS H1N1

Álvaro de la Cruz,[1] Sonia de Castro,[1] Lieve Naesens,[2] F. Javier Luque,[3] María-José Camarasa,[1] Sonsoles Velázquez.[1]

[1]Instituto de Química Médica (IQM, CSIC), E-28006 Madrid, Spain; [2]Rega Institute for Medicinal Research, K.U. Leuven, B-300 Leuven, Belgium; [3]Instituto de Biomedicina (IBUB) e Instituto de Química Teórica y Computacional (IQTCUB), Universidad de Barcelona, E-08921 Barcelona, Spain,

alvaro.dlcruz@iqm.csic.es

Outbreak of influenza epidemics and pandemics caused by (re)emerging influenza A viruses is a constant major threat to public health. Currently available controls of seasonal influenza in humans are vaccination and antiviral medications. Given the challenges with generated effective influenza vaccines and the potential for drug resistance to reduce effectiveness of the limited number of currently available antiviral drugs, new influenza therapeutic strategies directed to novel targets/mechanisms of action are urgently needed. An attractive anti-influenza strategy is to block the virus entry into the host cell, a process in which the viral hemagglutinin (HA) plays a key role.(1) HA is an homotrimeric envelope glycoprotein.

We have recently identified a unique class of *N*-benzyl-4,4-disubstituted piperidines as influenza A virus fusion inhibitors with specific activity against the H1N1 subtype in the low micromolar range(2). Mechanistic and computational studies with the prototype compound **DICAM180** revealed that the inhibitory activity is mediated through binding to a so-far unexplored pocket in the HA_2 subunit of HA close to the highly conserved fusion peptide. A direct π-stacking interaction of the *N*-benzylpiperidine moiety with the Phe9 HA_2 residue of the fusion peptide and a stable salt bridge of the protonated piperidine N with the Glu120HA_2 of the protein represent the most relevant ligand-protein interactions. In the proposed binding mode **DICAM180** interacts only with the fusion peptide of one of the monomers of the homotrimeric structure of HA(2).

Development of small-molecule fusion inhibitors targeting the receptor binding pocket is challenging since multivalent or complex natural analogues are preferred. However, development of this type of fusion inhibitors has been hindered by their subtype dependent influenza virus activities, and low barriers to resistance.

We herein report the design and synthesis of innovative trimeric influenza virus fusion inhibitors by taking advantage of the threefold symmetry of the HA homotrimer. The general structure of the proposed compounds involved a central scaffold (core) "decorated" with three identical arms bearing aromatic recognition motifs to establish π-stacking interactions with the Phe9 of the fusion peptides and an amino group at the focal point to form a salt bridge with the three Glu120. A variety of scaffolds, covalent linker groups and spacers of appropriated lenght will be explored. Achieving interaction with all three fusion peptides would likely enhance the inhibitory potency of the new molecules. The synthesis and antiviral evaluation will be reported.

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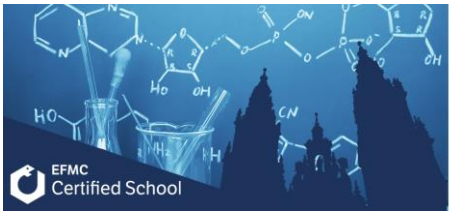

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ANTIBODY-DRUG CONJUGATES AS A NEW APPROACH FOR THE TREATMENT OF INFECTIOUS DISEASES

Andrea Escobar-Peña[1], Laura Lerma[2], Rafael Prados-Rosales[2], Mar Martín-Fontecha[1], María Luz López-Rodríguez[1]

[1]Dpto. de Química Orgánica, Facultad CC. Químicas, Universidad Complutense de Madrid, Spain, [2]Dpto. de Medicina Preventiva, Salud Pública y Microbiología, Facultad de Medicina, Universidad Autónoma de Madrid, Spain

anaescob@ucm.es

Antibody-drug conjugates (ADCs) are a promising strategy for effective drug delivery since they combine the specificity of antibodies with the potency of the drug. Therapeutic ADCs are broadly employed in cancer[1] and have been proposed for the treatment of infectious diseases.[2] These facts suggest that this approach may be promising for the treatment of other infections such as tuberculosis (TB), the leading cause of death due to bacterial infections worldwide with 1.6 million deaths reported in 2021.[3]

In this sense, our research group is carrying out a project aimed at the development of ADCs for the treatment of TB in order to overcome the poor efficacy of the current drugs.[4] This strategy involves the attachment of a monoclonal antibody (mAb) directed to *M. tuberculosis* or to antigens in the surface of the macrophages of infected mammalian cells, to an anti-TB drug through a cleavable linker, which selectively releases the active drug into the infected cells (Figure 1). In order to maximize the therapeutic potential of our conjugates, each of their components - antibody, linker and drug - is being optimized according to the flowchart shown in Figure 1, since they play crucial roles in the safety, target specificity, stability and efficacy of the conjugates. The validation of this strategy could open a new avenue towards the development of more effective treatments for TB.

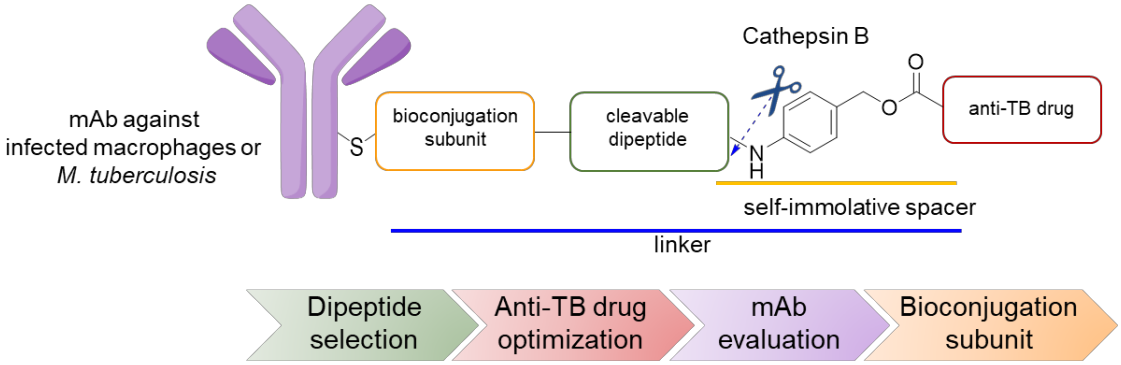

Figure 1. General structure of antibody-drug conjugates for the treatment of tuberculosis.

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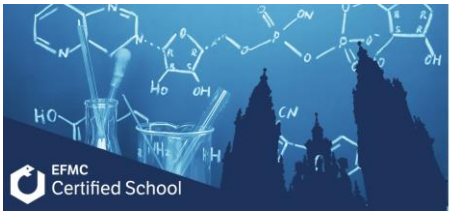

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METAL COMPLEXES OF SMALL POLYAZAMACROCYCLIC LIGANDS AND THEIR INTERACTION WITH MONO/OLIGONUCLEOTIDES

Jesús Escobar,[1] Esther Navarro,[1] Enrique García-España,[1] Begoña Verjdejo,[1] Salvador Blasco.[1]

[1]*Instituto de Ciencia Molecular (ICMol), Universitat de Valencia, C/Catedrático José Beltrán nº2, 46980, Paterna, Valencia, Spain.*

jesus.escobar@.uv.es

In recent years, research on platinum coordination chemistry has aroused great interest due to their potential biological applications.[1,2] Thus, one of the most important platinum complexes is cis-platin, which contains two chloride leaving groups in cis positions allowing its anchoring to DNA, being used effectively for the treatment of different cancer types. In fact, this complex has served as a starting point for the development of a large number of derivatives with similar properties. [3,4,5]

Herein, we report the interaction of $PtCl_4^{2-}$ and $PdCl_4^{2-}$ with different small tetraazapyridinacyclophane ligands (Figure 1), by UV-Vis, NMR spectroscopy and X-ray diffraction analysis. For Pt(II) and Pt(IV), different coordination modes have been observed as function of the macrocyclic cavity size. The interaction of the platinum and palladium complexes with different mononucleotides and polynucleotides poly A/U and Calf thymus DNA has been analyzed.

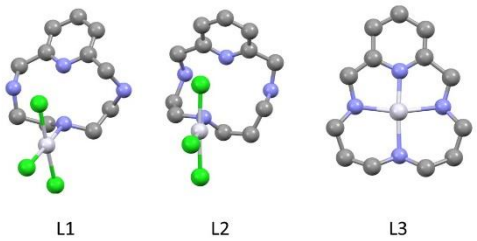

Figure 1. Structures of the studied Pt(II) tetraazapyridinacyclophanes complexes solved by X-ray diffraction.

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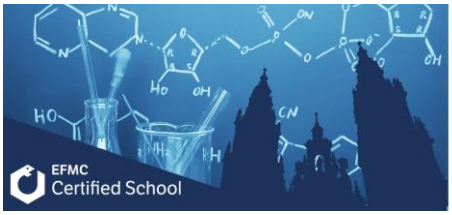

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Discovery of new progerin ligands

Daniel Fernández, Jon Macicior-Michelena, Marta Vizuete, Ana I. Manzano, Mª Ángeles Canales and Silvia Ortega-Gutiérrez

Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, Plaza de las Ciencias s/n, 28040 Madrid, Spain

dafern12@ucm.es

Hutchinson-Gilford progeria syndrome (HGPS) or progeria is an extremely rare disease that affects around 1 in 7 million new-borns causing their death at 14-15 years resulting from heart failure. Some of its characteristic symptoms are accelerated aging, alopecia and altered skin pigmentation. Progeria is caused by a mutant protein, called progerin, which abnormal accumulation in the nuclear membrane promote permanent structural changes in cells.[1] Recent studies have shown that the reduction of progerin levels in the nuclear membrane improves the phenotype of this disease.[2] Unfortunately, as of today there are not effective treatments for this disease. On this basis, our research group has started a project aimed at the direct reduction of progerin levels based on the development of proteolysis targeting chimeras (PROTACs) directed to this protein. A PROTAC molecule contains three moieties: (i) A ligand that binds to the protein of interest, (ii) a subunit responsible for the recognition of the E3 ligase that labels the protein of interest for degradation and (iii) a linker between these two fragments.[3]

Previous work developed in our group has validated this approach with PROTAC UCM-18142,[4] based on decursinol, the only progerin ligand described so far.[5] However, considering the drawbacks associated to this natural product such as lack of selectivity and limited drug-like properties, the discovery of new progerin ligands is of utmost importance. Towards this end, we have screened ~30 compounds selected from part of our in-house library, using saturation-transfer difference nuclear magnetic resonance (STD-NMR) and cellular thermal shift assays (CETSA). As a result, we have identified hit compound UCM-91, able to bind progerin. In this work we will show the medicinal chemistry program we are carrying out around this ligand (Figure 1) to optimize affinity for progerin and our efforts for the development of new PROTACs directed to progerin.

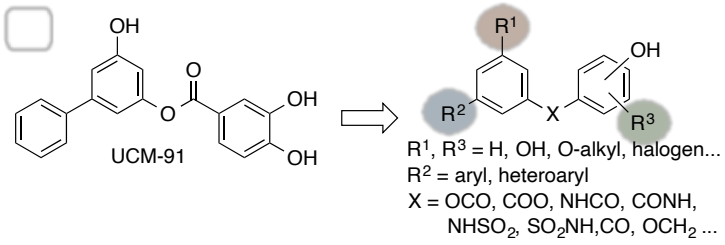

Figure 1. Structural exploration around hit **UCM-91**

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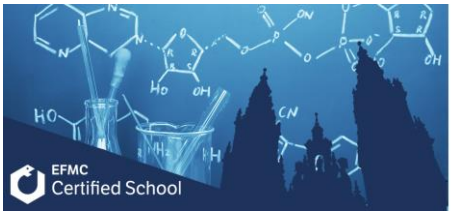

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SYNTHESIS OF NEW ANTIMITOTIC SULFONAMIDES FOR NANOPARTICLE FORMATION

Noelia Fernández-Ceballos, Laura Gallego-Yerga, Marta López-Rubio, Raquel Álvarez and Rafael Peláez.

Pharmaceutical Sciences Department, University of Salamanca, Faculty of Pharmacy, Salamanca, Spain.

nferceb@usal.es

Cancer is a very complex group of diseases and one of the main causes of death in the world, evincing that the current treatments are still not enough effective. Among the available treatments, colchicine site antimitotics, such as combretastatin A-4 (CA-4), are very potent anticancer and antiangiogenic agents that block cellular proliferation when binding to the colchicine site, inhibiting tubulin polymerization and thus, all the processes where microtubules are involved including mitosis [1]. Although they have good properties, they also show low aqueous solubility and side effects when administered to patients, being necessary to modify them to avoid this.

In this work we have designed and synthesized new antimitotics based on the structure of CA-4, by introducing new modifications such as a sulfonamide group and alkyl chains with polar heads to increase water solubility. This also confers them amphiphilic properties that can be used to self-assembly into nanoparticles (NPs) as micelles [Fig. 1]. It can be a good strategy to improve solubility problems since NPs preserve the hydrophobic moiety inside and hydrophilic heads on the surface. This also increases their penetration in tumors thanks to the enhanced permeability and retention effect (EPR). The EPR effect allows the massive entrance of NPs in the tumoral tissues due to the defective angiogenic process, and their accumulation because of the high demand of irrigation, rising the concentration of anticancer agents [2]. The antiproliferative activity of the new compounds in human tumor cells (HeLa, HT-29, MCF7) has been evaluated, and some of them have shown activity in the submicromolar range.

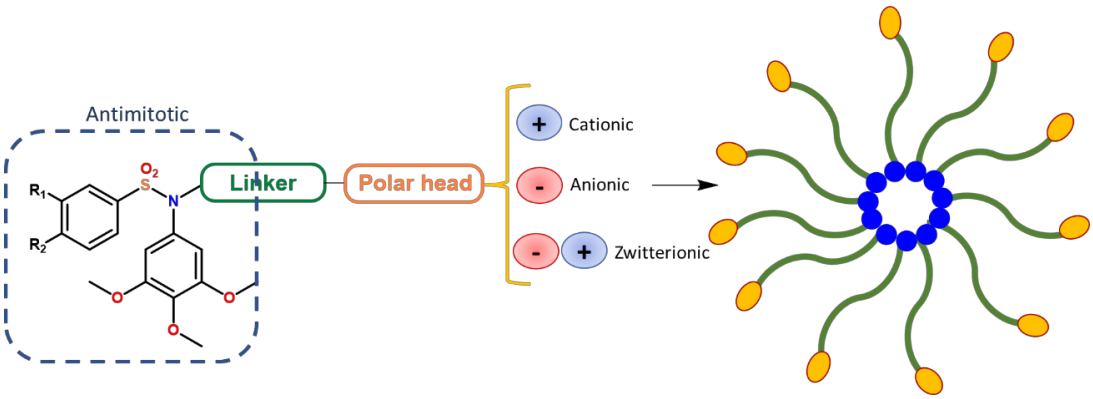

Fig 1. Representation of the new antimitotics and the expected assembly into nanoparticles.

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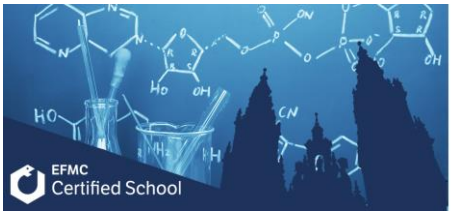

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MMV'S BENZOFURAN SERIES: PRELIMINAR SAR STUDIES AND IDENTIFICATION OF STRUCTURAL ALERTS

Mariana Ferrer-Casal,[1] Anees Ahmad,[1] Anwar Shamim,[1] Sarah Maluf,[2] Guilherme de Souza,[2] Anna C.C.Aguiar,[2] Rafael V. C. Guido,[2] Tom von Geldern,[3] Dominique Soldati-Favre,[4] Delphine Baud,[3] Paul Willis,[3] Luiz Carlos Dias,[1]

[1]Instituto de Química, Universidade Estadual de Campinas, Campinas, Brazil, [2]Instituto de Física de São Carlos, Universidade de São Paulo, São Carlos, Brazil, [3]Medicines for Malaria Venture, Geneva, Switzerland, [4]Faculté de Médecine, Université de Genève, Geneva, Switzerland

mferrer@unicamp.br

Medicines for Malaria Venture (MMV) is a not-for-profit organization globally recognized for its work on malaria drug discovery and malaria elimination. To develop a drug that could be used as a Single Encounter Radical Cure and Prophylaxis for malaria, several research projects are ongoing. In this context, compound **MMV1747770**, containing a benzofuran scaffold, was identified as a hit compound (**Figure 1**). Besides being active against *P. falciparum* in the nanomolar range (*Pf*3D7-IC_{50}=180nM), compound **MMV1747770** has a fast rate killing profile (low risk of resistance development) and no cross resistance against several resistant panels. However, it has a very low metabolic stability.

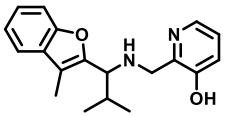
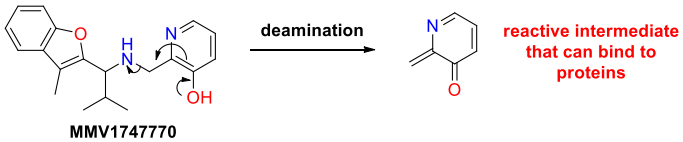


Figure 1. Benzofurane series Hit compound.

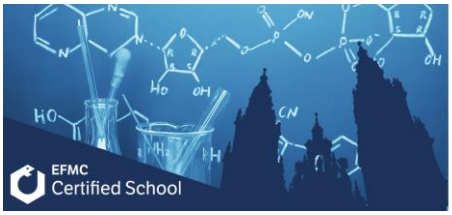
After identifying the essential moieties required for the activity, work on this series focused on the design and synthesis of analogs that couldn't lead to the formation of Quinone-type reactive intermediates (**Scheme 2**). Quinone-type reactive intermediates can bind to proteins leading to toxicity issues. For this reason, successful replacement of the Mannich base constitutes a STOP/GO decision for the series.



Scheme 2. Formation of reactive intermediates.

Herein, we will summarize our efforts towards the Hit Validation of compound **MMV1747770**, including the design and synthesis of analogues in which the Mannich base has been replaced to avoid the formation of quinone type reactive intermediates.

Acknowledgements:
The authors thank Medicines for Malaria Venture (MMV) for financial support of this research. Further financial support from FAPESP (The State of São Paulo Research Foundation, grants #2013/07600-3, #2015/50655-9, #2018/24344-4, and #2020/10494-4) is gratefully acknowledged. We also thank UNICAMP and USP for support and infrastructure.



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DEVELOPMENT OF NEW TYPE 2 LYSOPHOSPHATIDIC ACID RECEPTOR (LPA_2) ANTAGONISTS

Román Foronda-Sainz[1], Henar Vázquez-Villa[1], Rubèn López-Vales[2], María L. López-Rodríguez[1] and Silvia Ortega-Gutiérrez[1]

[1]Dpto. de Química Orgánica, Universidad Complutense de Madrid, España; [2]Dpto. de Biología Celular, Fisiología e Inmunología, CIBERNED, Universidad Autónoma de Barcelona, España.

roforond@ucm.es

Lysophosphatidic acid (LPA) is a lysophospholipid that acts as a signalling molecule inside the body. LPA produces its effects through interaction with LPA_1-LPA_6 receptors, which belong to the family of G protein-coupled receptors (GPCRs) [1]. Among all of them, LPA_2 receptor has recently attracted attention due to its involvement in different processes related with neuroinflammation and the regulation of functions of the central nervous system [2].

In our research group, we have already validated this receptor as an interesting therapeutic target for treating spinal cord injury (SCI) by developing compound UCM-14216 (Figure 1). Despite being the most potent and selective LPA_2 receptor antagonist with in vivo efficacy described so far [3], it has a relatively moderate stability that does not allow its oral administration. In order to obtain new potent and selective antagonists with good oral bioavailability, we have carried out a medicinal chemistry program around UCM-14216, which has allowed us to identify a new family of selective LPA_2 receptor antagonists, with increased potency and good pharmacokinetic properties both *in vitro* and *in vivo*.

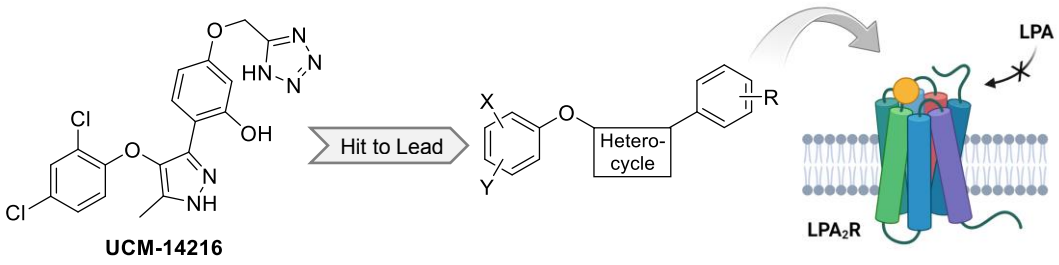

Figure 1. Development of new potent and selective LPA_2 receptor antagonists.

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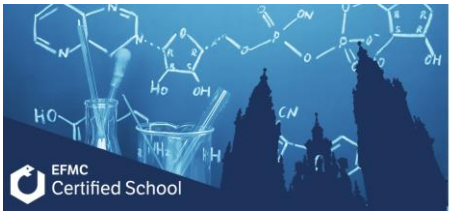
Acknowledgments: This work has been funded by Ministerio de Ciencia e Innovación (PID2019-106279RB-I00) and by Comunidad de Madrid (Grant PEJ-2020-AI/BMD-18172 to R.F.-S.)



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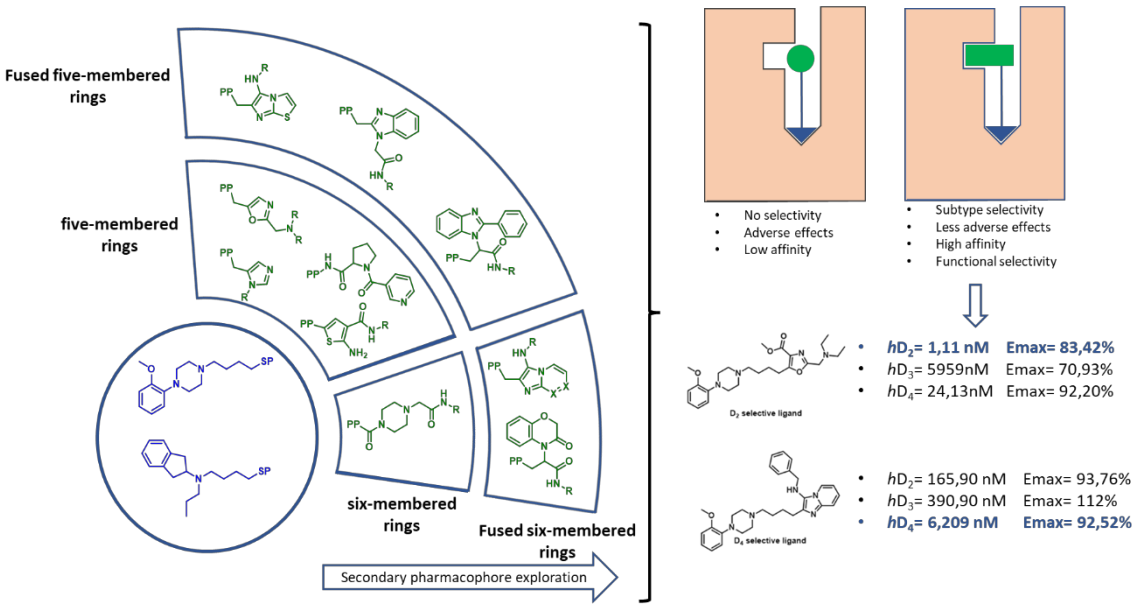
Multicomponent Assisted Bitopic Discovery: Proof-of-concept Study with the Dopamine D_2 Receptor Family.

Aitor García-Rey,[1,2] Ana Mallo Abreu,[1,2] Sergio Lence,[1,2] Jhonny Azuaje,[1,2] M.Rita Paleo,[1] Gemma Brugal,[3,4] Rafael Franco,[3,4] Xerardo García-Mera,[1,2] and Eddy Sotelo.[1,2]

[1]Center for Research in Chemical Biology and Molecular Materials, University of Santiago de Compostela, Santiago de Compostela, Spain, [2]Faculty of Pharmacy, University of Santiago de Compostela, Santiago de Compostela, Spain, [3]Department of Biochemistry and Physiology, Barcelona, Spain, [4]Faculty of Pharmacy and Food Science, Barcelona, Spain.

aitor.garcia.rey0@usc.es

Bitopic ligands are a class of drugs that concomitantly bind orthosteric and allosteric sites in a single receptor monomer. Bitopic ligands constitute tailored therapeutics that provide superior selectivity profiles, thus enabling to target specific receptor subtypes in the central nervous system, potentially leading to improved treatments for neurological disorders. Bitopic ligands are particularly suited to tackle challenging central nervous system diseases such as Alzheimer's and schizophrenia. Aripiprazole is a pharmacological agent used to treat psychiatric disorders, with a bivalent ligand structure. In recent years, several ligands similar to aripiprazole have been synthesized, but none of them have been found to be selective, possibly due to conservative strategies and lack of diversity.[1] Inspired by the structure of aripiprazole, this work employs a novel multicomponent methodology focused on generating diversity to synthesize 41 new ligands with novel structures. Eight new ligands were found to be selective for the D_4 subtype, and three were selective for the D_2 subtype. These new selective structures allow for a more precise identification of the involvement of each subtype in the pathology of neurological diseases.



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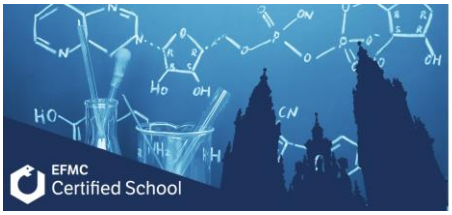

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STRUCTURE-ACTIVITY RELATIONSHIP STUDIES OF A NEW GENERATION OF CK2/HDAC DUAL INHIBITORS

Alba Gil-Rivas, Irene Ortín, Claire Coderch, José María Zapico, Beatriz de Pascual-Teresa and Ana Ramos

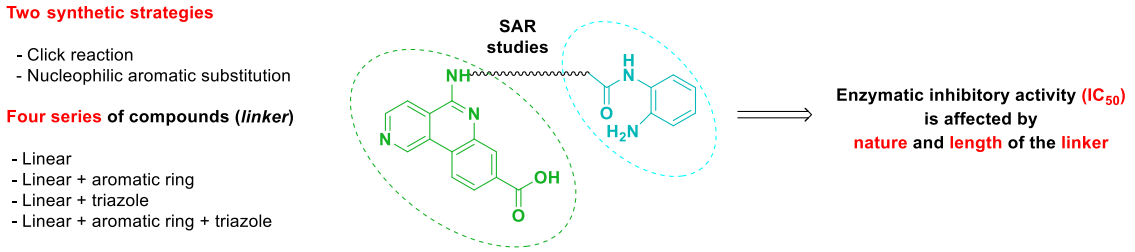
Departamento de Química y Bioquímica, Facultad de Farmacia, Universidad San Pablo-CEU, CEU Universities, Urbanización Montepríncipe, 28668, Boadilla del Monte, España.

alba.gilrivas@usp.ceu.es

The multi-target approach is based on the combination of two pharmacophores (dual inhibitors) in a single entity, to allow an efficient and simultaneous inhibition of two targets involved in a multifactorial disease. This strategy not only improves patients' adherence to therapy, but also reduces drug-drug interactions, side effects, and the manufacturing costs of drugs.[1] Protein Kinase (CK2) and Histone DeACetylases (HDACs) are two proteins overexpressed in cancer. They are related to each other under hypoxic conditions due to the fact that, for cell growth processes, HDACs need to be activated by CK2 phosphorylation.[2]

Following our previous research,[3] and taking into consideration the synergistic effect that we can achieve with this strategy, we have designed and synthesized a novel generation of CK2/HDAC hybrid molecules using a convergent chemical synthesis. The design proposed connects, through linkers of different lengths and nature, a derivative of CX-4945, which serves both as a CK2 ligand and a surface recognition site of HDACs, with *o*-aminoanilides, as the zinc-binding group (ZBG) of HDACs. The use of *o*-aminoanilides has several advantages over other ZBGs such as higher selectivity for class I HDACs, less toxicity and an improved metabolic profile.[4,5]

We have carried out enzymatic inhibitory studies against CK2 and HDAC for all synthesized compounds, which together with computational studies, allowed us the analysis of the structure-activity relationship (SAR) for this series. Based on these studies, we have optimized the length of the linker that best matches the Zn^{2+} in the HDAC catalytic site, achieving a good balance in the inhibitory activity (IC_{50}) against the two target enzymes.



Basic structure of the CK2/HDAC dual inhibitors synthesized for SAR analysis.

Financial support from PID2021-123786OB-I00 *(MICIU/FEDER, UE) is kindly acknowledged. A.G. is supported by a predoctoral research fellowship granted by CEU-Santander.*

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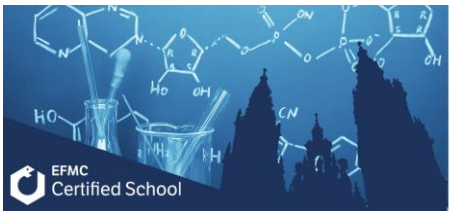

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NEW INDUCERS OF SELECTIVE DEGRADATION OF ESSENTIAL PROTEINS AS AN ALTERNATIVE TO CONVENTIONAL CHEMOTHERAPY IN THE SEARCH FOR NEW ANTITUMOR AND ANTIPARASITIC AGENTS

S. Gonzalez-Pelayo[1], L. Gallego[1], R. Álvarez[1], P. Puebla, R. Peláez[1]

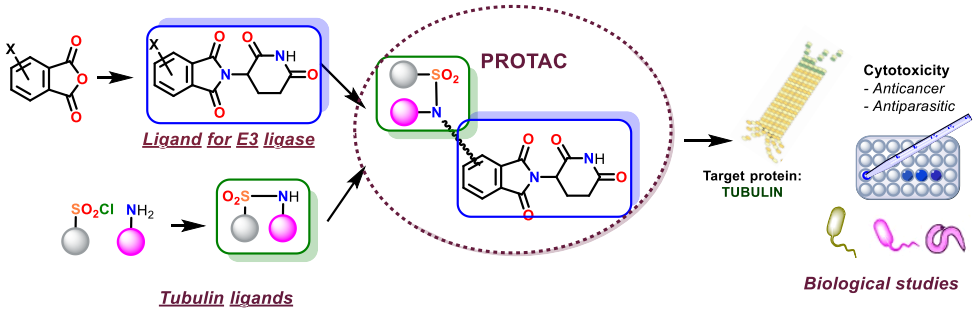
[1]*Pharmaceutical Sciences Department, Faculty of Pharmacy, University of Salamanca. Campus Miguel de Unamuno, 37007. Salamanca, Spain*

gonzalezpsilvia@usal.es

Drug-induced selective protein degradation is a new therapeutic strategy based on the simultaneous binding of heterobifunctional drugs (proteolysis-targeting chimaeras or PROTACs) to the target proteins whose degradation is pursued for therapeutic and to the proteins of the cell degradation machinery, in this particular case by ubiquitination by ubiquitin ligases or E3 proteins. [1]

In comparison with conventional drugs, PROTACs possess several advantages such as selectivity that increased when binding to two different targets. Moreover, PROTACs behave catalytically due to their successful dissociation after promoting ubiquitination of the protein, thereby providing great potential for allowing action at very low doses. The induction of protein degradation reduces the required contact time with the target, thus reducing toxicity. [2]

The objective of this work is synthetizing **new PROTACs for the degradation of tubulin** as an alternative to conventional chemotherapy. Sulfonamides have been chosen as antimitotic target [3] and Cereblon as the E3 degradatory partner. [4]



PROTACs will **be evaluated as anti-proliferative, anti-leishmaniasis and anti-strongyloidiasis agents**. The action mechanism and the possible toxicity will be studied for the active compounds and the pharmacokinetic properties will be optimized.

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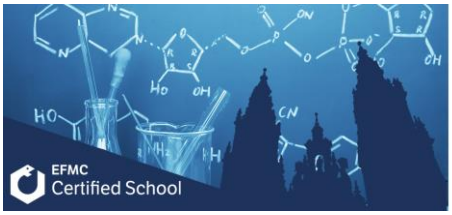

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SYNTHESIS, DNA INTERACTION AND ANTITUMOR ACTIVITY OF 2-(ACRIDIN-9-YL)-1*H*-IMIDAZO[4,5-f][1,10]PHENANTHROLINE AND p-CYMENE RUTHENIUM(II) METAL COMPLEXES

Patricia Gratal, Adrián Pérez-Redondo, Zoila Gándara, Lourdes Gude

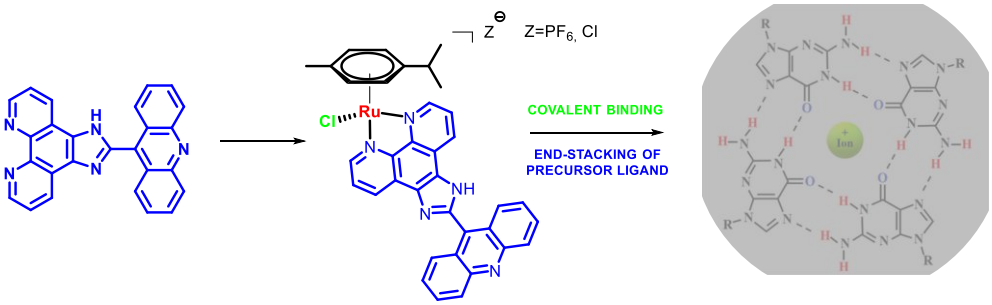
Department of Organic Chemistry and Inorganic Chemistry, Andrés M. del Río Chemistry Research Institute (IQAR), University of Alcalá, 28805, Alcalá de Henares, Madrid, Spain.

patricia.gratal@uah.es

Cancer is a leading cause of death worldwide, posing a challenge for the development of novel and efficient therapeutics. In the field of metallodrugs, platinum(II) complexes such as cisplatin and analogues (i.e. carboplatin and oxaliplatin) have played and still play a relevant role as chemotherapeutic agents of choice for some type of tumors. However, these metal complexes have several disadvantages, namely low selectivity and significant toxicity, especially nephrotoxicity and neurotoxicity, among other adverse effects. Consequently, the last years have witnessed increasing scientific efforts towards the development of alternative anticancer metallodrugs with lower toxicity and higher efficacy profiles, often targeting metastatic processes.[1]

Among them, Ru-based drugs have deserved special attention. Ruthenium(II) complexes of the type $[(\eta 6\text{-arene})Ru(XY)Z]_n$, which possess a characteristic 'piano-stool' structure that allows to modulate the activity and interaction with nucleic acids through their multiple components constitute a good example.[2] The two principal motifs normally used in their design are: 1) a bidentate chelating heterocyclic system (for example, a bipyridine or a phenanthroline ligand) that enables the incorporation of additional groups that can interact with DNA through π-stacking interactions, and 2) a labile chlorine group that may facilitate covalent binding with DNA bases.

In this communication, we report our recent results with a novel aromatic ligand, 2-(acridin-9-yl)-1*H*-imidazo[4,5-f][1,10]phenanthroline and some related p-cymene Ru(II) complexes. In addition, preliminary interaction studies, with dsDNA and with the telomeric G-quadruplex, as well as cytotoxic activity in cultured cells, will be discussed.



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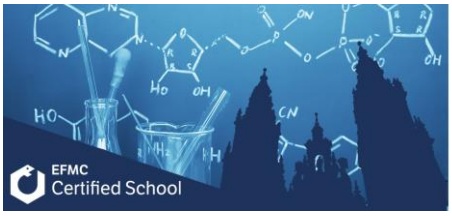

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COMPUTER-AIDED DRUG DESIGN OF HEMAGGLUTININ FUSION PEPTIDE INHIBITORS

Francisco J. Hermoso Pinilla[1]

[1]*Computational Biology Chemistry and Gastronomy Group, Facultat de Farmàcia i Ciències de l'Alimentació, Institut de Biomedicina, Universitat de Barcelona, Santa Coloma de Gramenet, Barcelona, Spain.*

fjhermoso@ub.edu

During the last century, Influenza has become a challenging infectious disease due to the occurrence of several pandemics such as the Spanish (1918), Hong Kong (1957), Russian (1968) and swine (2009) flu. Several targets and new drugs have been studied over the last decades, but with limited success. This effort is exemplified by arbidol, which is approved and commercialized in Russia and China as Umifenovir ®.

The present project is focused on hemagglutinin (HA), a homotrimeric membrane protein of Influenza A virus (IAV) responsible of the host-cell recognition and the subsequent endosomal membrane fusion process, which ultimately promotes the release of the genetic material through the cytoplasm. In collaboration with Profs. MJ Camarasa and S Velázquez (IQM-CSIC), we are working in the design of novel compounds expected to bind to a novel pocket located at the bottom of the HA stem region. Noteworthy, the proposed binding mode for the parent compound, DICAM180, involves a direct interaction with Phe9 in the fusion peptide (FP), thus allowing us to justify the inhibitory activity in preventing the fusion process.

The binding mode of DICAM180 has been used as a starting point for the design of the new derivatives designed to gain an additional interaction with the FP at the vicinal monomer in HA. Thus, the structure of the novel compounds has been modified to gain additional blockage of Phe9 in the second FP. Several chemical modifications have been explored by combining molecular docking and Molecular Dynamics simulations. The results support a specific chemical derivatization that would enable a dual attachment of the compounds to the FP of two monomers, and hence they are expected to exhibit a higher inhibitory activity. Antiviral assays are now being performed.

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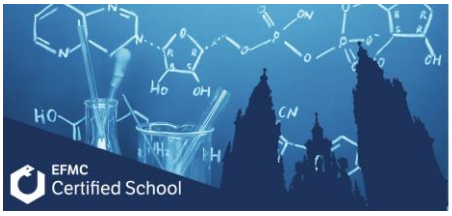

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A GENERAL AND HIGHLY SELECTIVE DEOXYGENATIVE HYDROGENATION OF CYCLIC IMIDES TO LACTAMS BY USING AN ALUMINA-SUPPORTED Ag-Re BIMETALLIC CATALYST

Carles Lluna-Galán,[1] Juan Camilo Arango-Daza,[1] Daviel Gómez-Acosta,[1] Patricia Concepción,[1] Rong Sun,[2] José Juan Calvino,[2] Laura Simonelli,[3] Rosa Adam[4] and Jose R. Cabrero-Antonino[1]

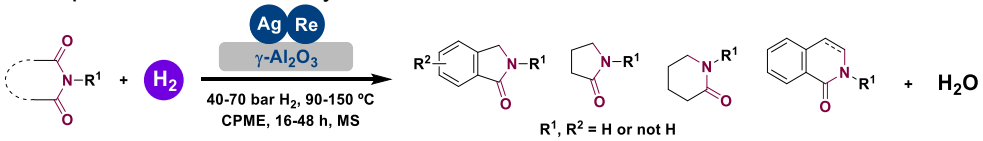
[1]*Instituto de Tecnología Química, Universitat Politècnica de València - Consejo Superior Investigaciones Científicas (UPV-CSIC), València, 46022 (Spain).* [2]*Departamento de Ciencia de los Materiales e Ingeniería Metalúrgica y Química Inorgánica, Facultad de Ciencias, Universidad de Cádiz, Puerto Real, 11510 (Spain).* [3]*CELLS – ALBA Synchrotron Radiation Facility. Cerdanyola del Vallès, 08390 (Spain).* [4]*Departament de Química Orgànica, Facultat de Farmàcia, Universitat de València, Burjassot, 46100 (Spain)*

cllugal@itq.upv.es

The rational design of nanomaterials able of acting as heterogenous catalysts in complex organic transformations is a relevant strategy to build a more sustainable fine chemistry. Hydrogenative protocols of carboxylic acid derivatives are atom-economical protocols employing readily available substrates.[1-3] However, activating these substrates is challenging, due to the low susceptibility towards hydride attack of their poorly electrophilic carbonyl group. A successful strategy to perform these transformations has been the design of bimetallic materials, combining a transition metal presenting oxophilic character (commonly V, Mo, Sn, W or Re), with another metal with the capacity to activate H_2 (usually Pd, Pt or Ru).

Cyclic imides are a particular kind of carboxylic acid derivative in which a nitrogen atom is directly connected to two carbonyl groups. The selective reduction of one carbonyl group of cyclic imides, such as phthalimides, homophthalimides and succinimides to isoindolinones, isoquinolones, dihydroisoquinolones or pyrrolidones, is a highly sought transformation because it is a very straightforward protocol to obtain these lactams, considered privileged scaffolds in medicinal chemistry. In fact, isoindolinones are present in drugs such as Lenalidomide or Indobufen. In addition, pyrrolidone-based compounds are also known for their biological activities, as in the case of Piracetam. However, this transformation still presents important drawbacks.[3]

In this work, after a rational optimization process, a nanostructured heterogeneous catalyst based on Ag and Re aggregates supported over Al_2O_3 has been developed as an active, selective, and reusable catalyst to obtain efficiently more than 60 lactams. Furthermore, exhaustive characterization has led to establishing strong structure-activity and cooperativity relationships important for the future development of heterogeneous bimetallic nanocatalysts for hydrogenative protocols with carboxylic acid derivatives.



Tailored Nanocatalyst Design and Optimization | Practical, Robust and Reusable | General Applicability (>60 cyclic lactams) | Kinetic and Mechanistic Studies

Exhaustive Characterization (XRD, UV, Raman, BET, TPR, IR-Pyr, IR-CO, XPS, XAS ...) | Total Heteroaromatic Ring Tolerability

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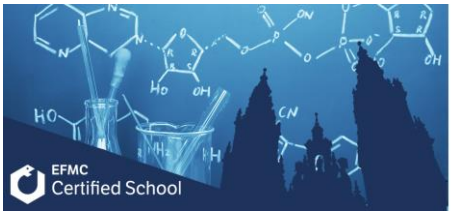

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ANTIMALARIAL ACTIVITY OF NEW DISULPHIDE INHIBITORS OVER THE *PLASMODIUM FALCIPARUM* CHOLINE KINASE (*Pf*ChoK)

Pilar María Luque Navarro,[1] Archimede Torretta,[2] Emilio Parisini,[2,3] and Luisa Carlota López Cara*.[1]

[1]Department of Organic and Pharmaceutical Chemistry, University of Granada, Spain, [2]Center for Nano Science and Technology at Polimi, Istituto Italiano di Tecnologia, Milan, Italy, [4]Latvian Institute of Organic Synthesis, Riga.

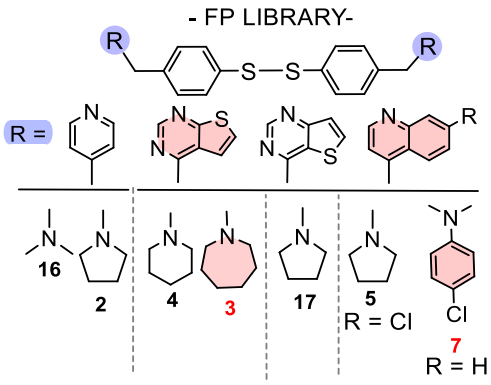
pilarluque@ugr.es

Malaria is the most widespread protozoan disease in the world, transmitted by the bite of the Anopheles mosquito.

Plasmodium resistance to some of the antimalarial drugs like Artemisinin and Chloroquine has led to the use of combination therapies. For that reason, new drugs and therapeutic pathways are needed.

In this scenario, *Vial et al*. [1] first proposed a strategy based on the different metabolic requirements between the parasite and the host. They realized that parasite replication requires the formation of new lipidic membranes that cover the new progeny. As the erythrocyte is enucleated, it is the parasite metabolism that works using the host materials.

We have focused on the inhibition of *PfChoK*, a parasite enzyme that catalysed the conversion of the *host* choline to phosphocholine, which finally led to phospholipids. The enzymatic homology of the Human ChoK and the recent crystallization of its structure [2], guide us to the design of new bioisosteric inhibitors [3]. The FP library is based on a disulphide linker and two cationic heads. The sulphur atoms have improved the molecular size and the enzyme pocket anchoring, due to the sulphur free electron pair. The cationic heads provide selectivity towards the enzyme and consist of pyridine, thienopyrimidine and quinoline moieties substituted in 4 position by cyclic, aliphatic or aromatic amines. All of them show an enzymatic inhibition in the low micromolar range, however, it seems that lipophilicity plays a key role in the infected erythrocytes. The most lipophilic heads with a hindrance amine in 4 position (as in compounds **FP3** and **FP7)** have also the best GI values.



Compounds	PfCK inhibition (µM)	GI (%)
FP 2	0.44 ± 0.03	10,289
FP 3	0.16 ± 0.01	60,105
FP 4	0.32 ± 0.02	37,674
FP 5	0.42 ± 0.01	7,933
FP 7	0,72 ± 0.12	58,826
FP 16	1,78 ± 0.39	0
FP 17	0,33 ± 0.05	46,405

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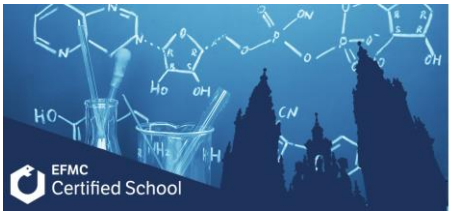

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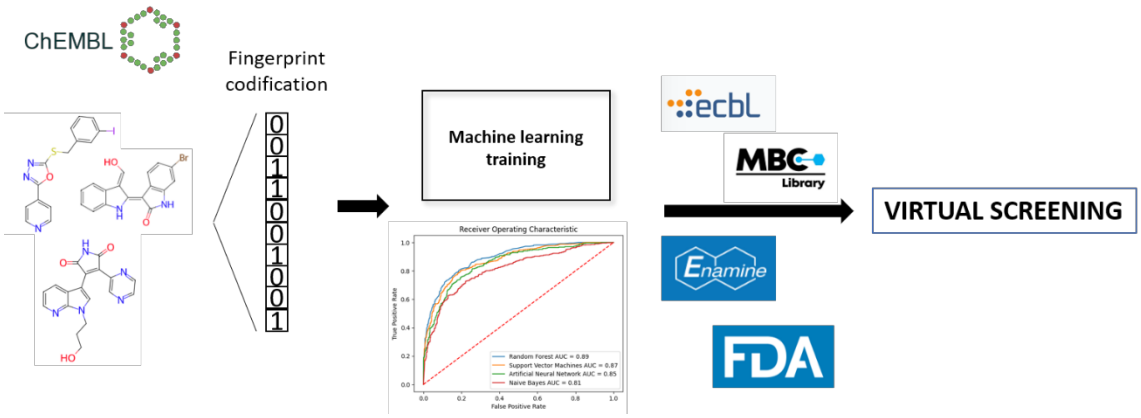
MACHINE LEARNING-ENHANCED VIRTUAL SCREENING TO FIND NEW GSK-3β INHIBITORS

Enrique Madruga,[1,2] Ana Martinez [1,2].

[1]*Centro de Investigaciones Biológicas-CSIC, Ramiro de Maeztu 9, 28040 Madrid, Spain.*
[2]*Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Instituto de Salud Carlos III, 28031 Madrid, Spain*

enrique.madruga@cib.csic.es

Glycogen synthase kinase-3 beta (GSK-3β) is a serine/threonine protein kinase that has been implicated in numerous physiological and pathological processes, including diabetes, Alzheimer's disease, cancer, and others. Therefore, the development of selective GSK-3β inhibitors is of great interest for therapeutic intervention.[1] Machine learning has become an increasingly important tool for virtual screening of large chemical libraries in a timely and cost-effective manner. Machine learning algorithms can be trained on large datasets of known active and inactive compounds, and then used to predict the activity of new compounds *in silico*.[2] In this work, we present a machine learning-enhanced virtual screening approach to identify new GSK-3β inhibitors. To generate the dataset of GSK-3β inhibitors and non-inhibitors, we compiled a list of known GSK-3β inhibitors from the ChEMBL database. Following the corresponding data treatment, a threshold of 300 nM (IC_{50}) was used to discriminate active from inactive compounds. We used four machine learning algorithms: Random Forest, Support Vector Machines, Artificial Neuronal Network and Naïve-Bayes to develop predictive models for GSK-3β inhibition. The models were trained on the dataset of inhibitors and non-inhibitors using various fingerprint descriptors, showing Random Forest as the best predictive model. Finally, four chemical libraries (MBC,[3] ECBL, FDA and HTS Collection from Enamine) were screened and the top hits based on their predicted binding affinity to GSK-3β, which are currently being tested, were identified. Overall, our machine learning-enhanced virtual screening approach is a valuable tool for identifying new GSK-3β inhibitors and can be extended to other protein targets to accelerate drug discovery efforts.



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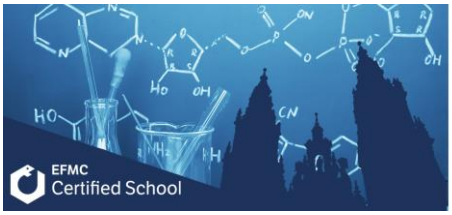

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SYMMETRICAL TRIAZOLE-PHENYL-THIAZOLE AS POTENT DISRUPTORS OF THE *Li*-TRYR INVOLVED IN THE *OXIDATIVE* REGULATORY PATHWAY OF *LEISHMANIA INFANTUM*

Miguel Maldonado,[1] Sonia de Castro,[1] Héctor de Lucio,[2] Antonio Jiménez-Ruiz,[2] Federico Gago,[2] María José Camarasa,[1] Sonsoles Velázquez[1]

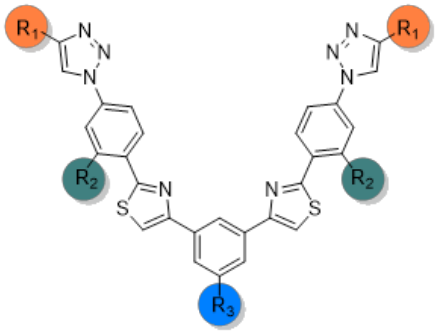
[1]Instituto de Química Médica (IQM-CSIC), Juan de la Cierva 3, Madrid, [2]Departamento de Biología de Sistemas, Universidad de Alcalá, Madrid

miguel.maldonado@iqm.csic.es

Toxicity and poor tolerance of drugs used in the treatment of Leishmaniasis[1] justifies the search of more effective and less toxic drugs.

This is where trypanothione reductase (TryR) emerges as a validated and selective therapeutic target for the treatment of the above mentioned parasitic disease.[2] This oxidoreductase enzyme is essential and exclusive for the survival of the parasite. In recent years, our group has developed an innovative strategy to inhibit TryR which consists on the disruption of the functional form of the enzyme, which is a homodimer. The proof-of-concept of this approach was performed by using peptides and peptidomimetics that mimic the 'hot spots' at the homodimer interface.[3]

In the search new non-peptide dimerization inhibitors, we herein report a series of water-soluble proteomimetics, based on an imidazole-phenyl-thiazole scaffold.[4] In further molecular modelling studies we discovered a, so-far unexplored, new drugable binding site which is located at the central interfacial cavity of the enzyme.



SAR studies of the new compounds revealed that modifications at R_1 improve the interaction with the ATP site of the homodimer interface. Also, modifications at R_3 led us to target a hydrophobic subpocket at the bottom of the central interfacial cavity. Moreover, we have carried out the optimisation of the key step of the synthetic strategy for the modifications at R_3. The results of these studies together with the biological evaluation will be reported.

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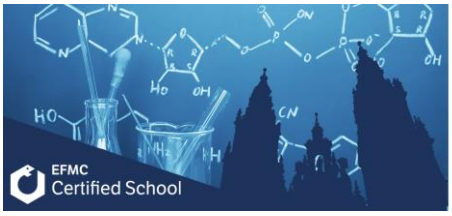

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FIRST-IN-CLASS DUAL sEH/AChE INHIBITOR FOR ALZHEIMER'S DISEASE

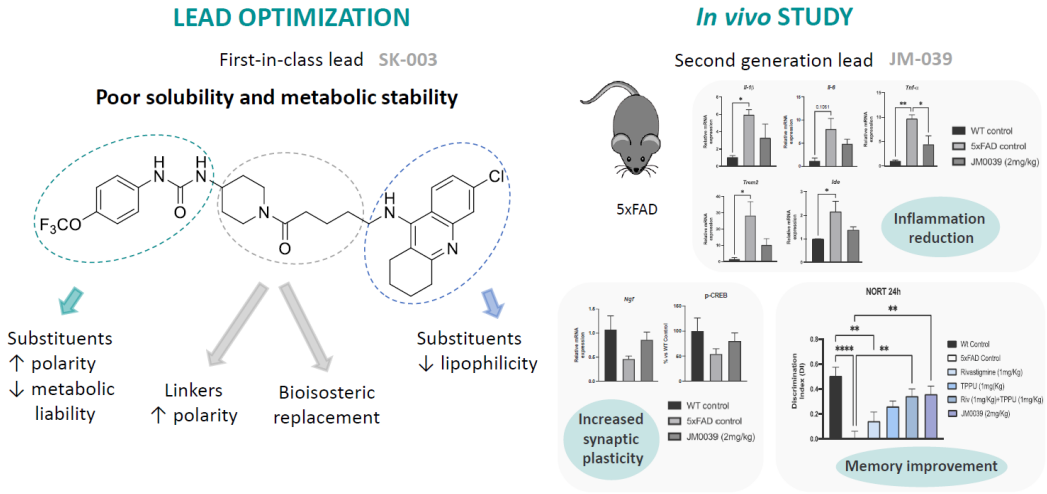
Noemí Martínez-Conde,[1] Marc Granje,[1] Francesca Digito,[1] Joseph J. Mullins,[2] Christian Griñán-Ferré,[1] Júlia Jarné-Ferrer,[1] Marina Naldi,[3] Manuela Bartolini,[3] María Isabel Loza,[4] José Brea,[4] Belén Pérez,[5] Clara Bartra,[6] Coral Sanfeliu,[6] Christophe Morisseau,[7] Bruce D. Hammock,[7] Mercè Pallàs,[1] Santiago Vázquez,[1] and Diego Muñoz-Torrero[1]

[1] University of Barcelona, Spain; [2] Le Moyne College, Syracuse, USA; [3] University of Bologna, Italy; [4] Universidade de Santiago de Compostela, Spain; [5] Autonomous University of Barcelona, Spain; [6] IIBB-CSIC and IDIBAPS, Spain; [7] University of California Davis, USA

noemimartinez@ub.edu

The multifactorial nature of Alzheimer's disease (AD) makes necessary new therapeutic approaches based on the modulation of multiple biological targets with a key pathogenic role. In this context, our group recently reported the discovery of a novel class of dual inhibitors of the enzymes soluble epoxide hydrolase (sEH) and acetylcholinesterase (AChE) [1], which display a multitarget profile *in vitro* and exerted beneficial *in vivo* effects against neuroinflammation and memory impairment. Although the lead compound showed well-balanced nanomolar potencies at both targets and good blood-brain barrier permeability, its suboptimal solubility and metabolic stability might hamper its applicability for the treatment of AD.

In this work, we describe a lead optimization campaign, mainly focused on achieving more favourable DMPK properties, while retaining the high dual potencies and brain permeation of the initial lead. To this end, we have explored the effects on biological activity and DMPK properties of the introduction of different polar substituents in diverse positions of the molecule of the first-generation lead. The optimized lead has shown superior effects on cognition and biological markers of neuroinflammation and synaptic plasticity than the first-generation lead, the reference sEH inhibitor TPPU, and the AChE inhibitor drug rivastigmine in a mouse model of AD.



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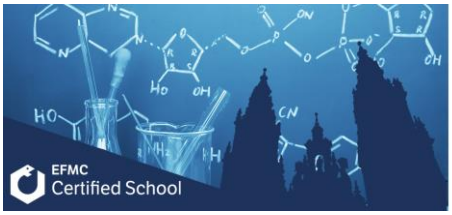

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IDENTIFICATION OF NOVEL KCHIP2 LIGANDS AS CHEMICAL TOOLS FOR UNDERSTANDING ITS PROTEIN INTERACTION NETWORK

P. Martínez-Salas[1], C. Viedma-Barba[1], Mª Ángeles Bonache[1], I. Marín-Olivero[4], M. Daniel-Mozo[5], A. Perez-Lara[4,6], J. A. Gonzalez-Vera[4], A. Orte[4], A. Albert[5], Y. Rodríguez[7], M. Martín-Martínez[1,8], C. Valenzuela[2,3] and M. Gutiérrez-Rodríguez[1,8].

[1]Inst. de Química Médica (IQM-CSIC), Spain. [2]Inst. de Investigaciones Biomédicas "Alberto Sols", CSIC-UAM, Spain. [3] CIBERCV Inst. de Salud Carlos III, Spain. [4]Nanoscopy-UGR Laboratory, Dept. de Fisicoquímica, Unidad de Excelencia de Química Aplicada a Biomedicina y Medioambiente, Fac. de Farmacia, Univ. de Granada, Campus Cartuja, Spain. [5]Instituto de Química Física Rocasolano, (IQFR-CSIC), Spain. [6]Dept. of Neurobiology, Max Planck Institute for Multidisciplinary Sciences, Germany. [7]Dept. of Natural Sciences, Hostos Community College of CUNY, NY, USA.[8]PTI-Global Health, CSIC.

pedro.martinez@iqm.csic.es

Keywords: *protein-protein interactions, KChIP2 ligands, K_V4.3 channels, atrial fibrillation*

Protein-protein interactions (PPIs) play an important role in most cellular processes. The complete map of IPPs is called interactome. Despite the progress in recent years in the knowledge of the human interactome and its relationship with disease, multiple protein-protein interactions remain to be deciphered. The knowledge of a protein interactome is essential for its validation as therapeutic target and for the discovery of drug candidates. Among the tools that can contribute to a better understanding of PPIs is the development of small molecules capable of binding to a certain protein and modulating their interactions. [1]

KChIP2 (Potassium Channel Interacting Protein 2) belongs to the calcium binding protein superfamily. It is the KChIP member predominantly expressed in heart and a key regulator of cardiac action potential duration. In the human myocardium, K_V4.3 channels generate the transient outward potassium currents (I_{TO}), which is the main responsible of the human atrial repolarization. Through its interaction with the K_V4.3 α-subunit, KChIP2 induces an increase in the traffic of K_V4.3 channels to the plasma membrane. Interestingly, this general trend is modified by the KChIP2-binding ligands. Hence, the knowledge gained from the modulation of the K_V4.3/KChIP2 complex by small molecules could open novel therapeutic opportunities for the treatment of atrial fibrillation, the most common arrhythmia. However, up to now, only three KChIP2 ligands have been described. [2] [3]

In this communication, we will describe a multidisciplinary approach that, starting with a structure-based virtual screening, followed by an iterative process of synthesis/biological evaluation/docking studies, has led to the identification of novel and potent KChIP2 ligands.

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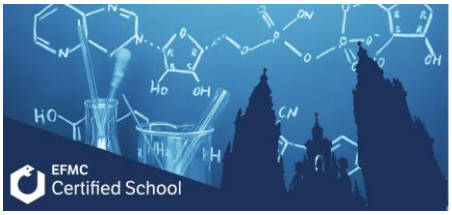

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MODULATING THE ADENOSINERGIC AXIS FOR CANCER IMMUNOTHERAPY: DISCOVERY, OPTIMIZATION AND KINETIC STUDIES OF DUAL TARGETING AGENTS

Darío Miranda-Pastoriza,[1] Rubén Prieto-Díaz,[1] Rita Paleo,[1] Xerardo García-Mera,[2] María Majellaro,[1] José M. Brea,[3] María I. Loza[3] and Eddy Sotelo[1,2*]

[1]Center for Research in Biological Chemistry and Molecular Materials (CIQUS), University of Santiago de Compostela, Santiago de Compostela, Spain, [2] Department of Organic Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, Santiago de Compostela, Spain. [3]Center for Research in Metabolic Diseases (CIMUS). University of Santiago de Compostela, Santiago de Compostela, Spain.

dario.miranda.pastoriza@usc.es

Adenosine is a metabolite that exerts important roles in the context of cancer metabolism and suppresses the anti-tumor immune response of T and NK cells via extracellular binding to adenosine A_{2A}ARs and A_{2B}ARs.[1] We have recently demonstrated that blockade of adenosine A_{2B}ARs effectively rescues lymphocyte activity[2] and promotes a potent antitumor response by employing a series of potent and selective A_{2B}AR antagonists that exhibit enantiospecific binding modes.[3] Herein we document previously unexplored series of dual anticancer drugs that simultaneously target A_{2B}ARs and HDAC enzymes. The study covers the design, optimization, kinetic studies, and preliminary evidence of the anticancer effect of selected ligands in representative cancer cell lines.

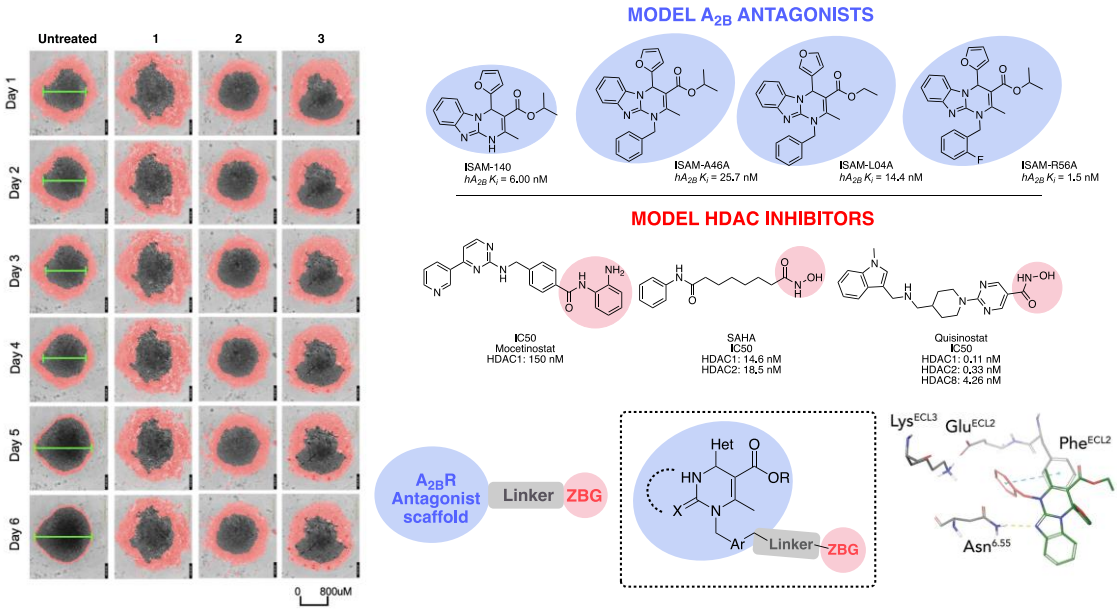

Figure 1. Antitumor effect of dual ligands on breast cancer patient-derived spheroid cultures, model A_{2B}AR and HDAC ligands and general structure of the novel dual agents herein documented.

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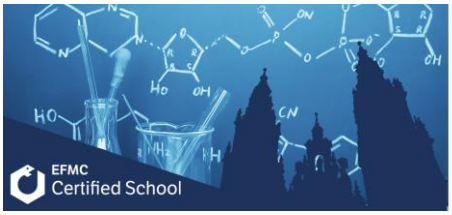

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NOVEL CANNABINOID-BASED VACCINES FOR ALLERGIC DISEASES

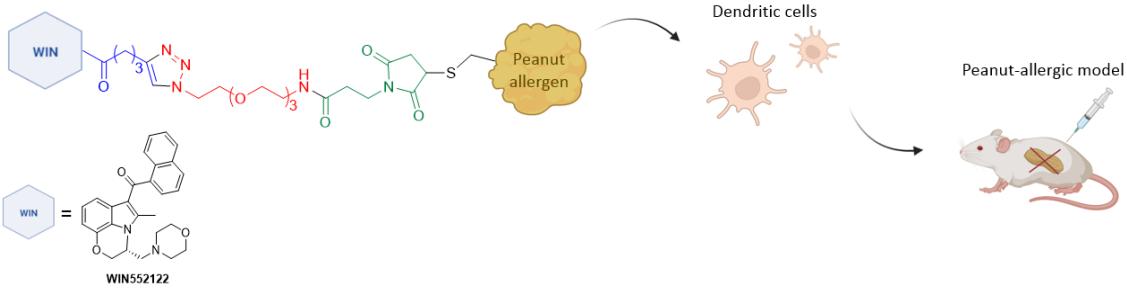
Verónica Muñoz-Canales,[1] Patricia García-López,[1] Óscar Palomares,[2] Bellinda Benhamú,[1] and Mar Martín-Fontecha[1]

[1]Medicinal Chemistry Laboratory, Department of Organic Chemistry, Faculty of Chemical Science, Universidad Complutense de Madrid, Spain ,[2] Department of Biochemistry and Molecular Biology, Faculty of Chemical Science, Universidad Complutense de Madrid, Spain.

vemuno02@ucm.es

Food allergy has become a global public health concern of increasing prevalence with high socio-economic impact.[1] Conventional management of this disease is mainly based on food avoidance and treatment of allergic reactions after accidental exposure. However, elimination diets are difficult to follow and can produce food neophobia, nutritional deficiencies and anxiety.[2] The only pharmacological treatment available to correct allergic disorders is allergen-specific immunotherapy.[3] However, this approach has several drawbacks such as low efficacy, long duration and poor patient compliance. Therefore, the development of new vaccines able to overcome these limitations is still required.

Recent studies in a mouse model of peanut allergy have demonstrated that the cannabinoid agonist WIN552122 (WIN) interferes with allergen sensitization and promotes tolerogenic responses, suggesting that co-administration of WIN with peanut allergen would prevent allergen-induced anaphylaxis.[4] In this regard, our research group is conducting a project aimed at the development of novel cannabinoid-based vaccines by crosslinking peanut allergens with WIN, as a proof of concept for immune response regulation. Toward this end, we are synthesizing different WIN derivatives linked to a maleimide subunit through a polyethylene glycol spacer, which will be subsequently conjugated with the allergen-free cysteines via thio-Michael addition. Once the WIN-allergen bioconjugates are synthesized, their ability to produce epigenetic and metabolic changes in dendritic cells will be measured. The selected candidates will be evaluated in a peanut-allergic mouse model to determine their ability to induce long-term tolerance, which would allow the development of innovative prophylactic and therapeutic strategies for peanut allergy.



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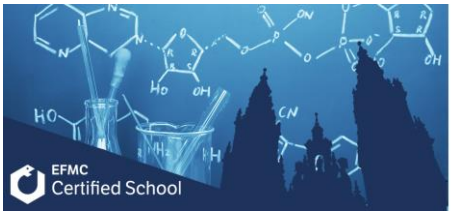

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RedMat – A Software for Fast STD-NMR-based Validation of Static and Dynamic 3D Models of Protein-Fragment Complexes

Juan C. Muñoz-García,[a] Jonathan Ramírez-Cárdenas,[a] Gabriel Rocha,[a] Samuel J. Walpole,[b] Thomas Hicks,[b] Ridvan Nepravishta,[c] Jesús Angulo[a]

[a] *Instituto de Investigaciones Químicas (CSIC—Universidad de Sevilla), 41092 Seville, Spain.*
[b] *School of Pharmacy, University of East Anglia, Norwich Research Park, Norwich, UK*
[c] *The Beatson Institute for Cancer Research, Switchback Rd, Bearsden, Glasgow G61 1BD, UK*
juan.munioz@iiq.csic.es

Saturation transfer difference (STD) NMR spectroscopy has revolutionized the study of receptor-ligand interactions. Its versatility and popularity are demonstrated by the large number of applications and developments involving this NMR technique. Ligand epitope mapping[1], the DEEP-STD methodology to gain ligand orientational information[2], or the determination of dissociation constants[3] are a few elegant examples of the strength of STD NMR in the characterization of protein-ligand binding properties. However, the development of fast relaxation matrix calculations to be efficiently combined with STD NMR experimental data for the structural validation of protein-fragment complexes remains a major milestone in the chemical biology and drug discovery fields.

We present a novel approach, implemented as a web application called *RedMat*, that takes advantage of a Reduced Relaxation Matrix (RRM) treatment of the STD NMR initial slopes (STD_0), leading to very fast calculations of the theoretical binding epitopes using the Cartesian coordinates of the receptor-fragment 3D structure, in the form of either a PDB structure or a molecular dynamics trajectory.[4] This allows for the direct comparison with experimental STD_0 factors of receptor-fragment interactions in solution. To validate our RRM approach, three protein-ligand systems previously characterized by STD NMR experiments were tested, showing excellent agreement between the theoretical and experimental STD_0 values (see Figure 1 below).

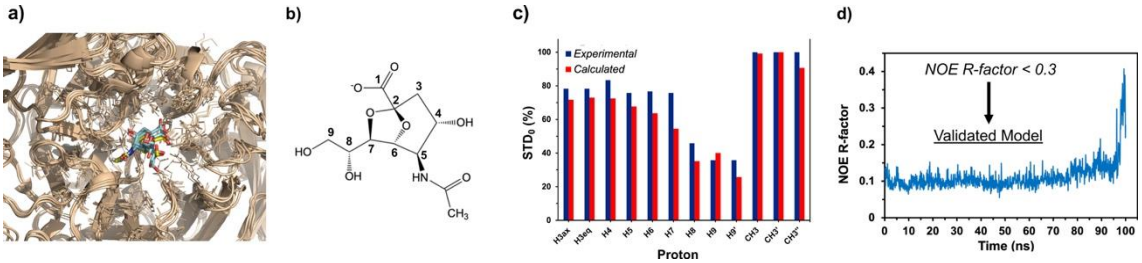

Figure 1. a) X-ray structure of the RgNanH-GH33 (coloured in green) in complex with 2,7-anhydro-Neu5Ac (in cyan; PDB 4X4A). **b)** 2D sketch of the ligand. **c)** Comparison between calculated (red bars) and experimental (blue bars) STD_0 factors for the protons of the ligand. **d)** Evolution of the NOE R-factor of the 2,7-anhydro-Neu5Ac ligand over 100 ns of MD simulation.

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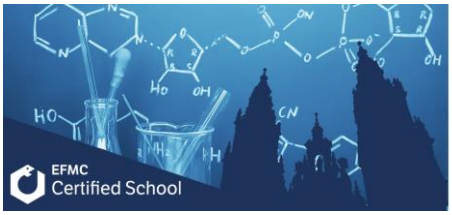

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METALLIC COMPLEXES OF HETEROCYCLIC DIAMINES WITH BIOLOGICAL ACTIVITY

E. Navarro-Blasco[1], B. Verdejo, E. Delgado, M. P. Clares, A. Martínez-Camarena, E. García-España

Instituto de Ciencia Molecular (ICMol), Universitat de Valencia, C/Catedrático José Beltrán nº2, 46980, Paterna, Valencia, Spain.

estna2@alumni.uv,es

Monoamine oxidases enzymes play a critical role in regulating the homeostasis of neurotransmitters. These enzymes oxidize amines as the first step to a degradation which keeps a balance necessary for the correct functioning of the central nervous system (CNS). [1] The use of inhibitors of MAO A and/or MAO B is a strategy that helps to restore the balance caused by the protein overexpression of malfunctioning of the catabolism of amine neurotransmitters in the brain and peripheral tissues. MAO inhibitors decrease the catabolism of neurotransmitters and therefore the neurotoxic by-products generated by this reaction (ammonia and hydrogen peroxide), related to conditions of oxidative stress and some monoamine neurotransmitter disorders.

Given the nature of the substrates and the structure of MAO, it naturally follows that polyamine derivatives are a good choice for the development of novel pharmacological agents with a diverse spectrum of action. In this sense, we report the synthesis of a series of heterocyclic diamine ligands, functionalized with pyridine or quinoline. [2] We studied the Cu^{2+} and Fe^{2+}/Fe^{3+} coordination chemistry through potentiometric titrations, as well as their catalase activity by UV-Vis spectroscopy using the ferric-xylenol orange method.

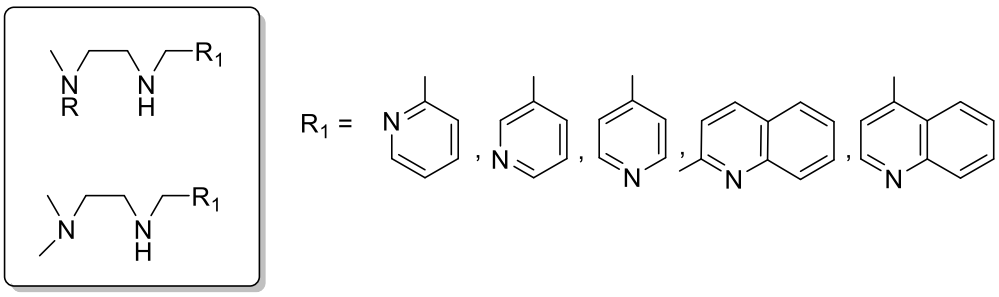

Figure 1 General structure of the.ligands studied.

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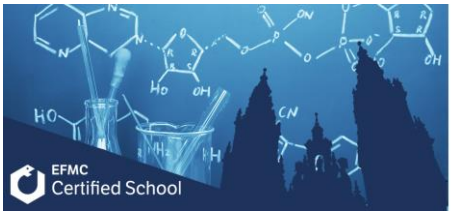

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DISCOVERY OF PROMISING NOVEL INHIBITORS FOR B4GALT6 VIA HIGH-THROUGHPUT VIRTUAL SCREENING

Claudio Papotto, Emanuela Sabato, Davide Lecca, Carlo Matera, Marco De Amici, Alessandro Pedretti, Giulio Vistoli and Clelia Dallanoce

Department of Pharmaceutical Sciences DISFARM, Università degli Studi di Milano, via L. Mangiagalli 25, 20133 Milano, Italy

claudio.papotto@unimi.it

Recently, the central role of the glycolipid Lactosylceramide (LacCer) has been evidenced in the evolution of the progressive form of Multiple Sclerosis (MS). LacCer is synthetized by the enzyme B4GALT6, a galactosyl transferase expressed mainly by reactive astrocytes, and acts in an autocrine manner, driving further inflammation and promoting neurodegeneration. The blockage of B4GALT6 caused a halt to the progression of the disease in established models of MS [1]. Despite these encouraging findings, there has been no successful development of selective inhibitors targeting this enzyme. Consequently, a virtual screening study was conducted on B4GALT6 to explore the possibility of discovering new inhibitors by screening an expanded dataset of commercially available compounds.

Since no experimental structures of the enzyme are available, two models were generated using a homology modelling approach, mimicking two significant conformational states of the enzyme. Then, a docking protocol was developed and optimized, using a purposely collected database including presumed B4GALT6 inhibitors. This protocol was based on the binding space concept and employed an enrichment factor optimization algorithm to create consensus models [2]. These models were then utilized to virtually screen the SPECS screening database, composed of over 207.000 molecules. Based on the computational results, the most promising candidates were further studied to characterize the interactions with the target enzyme. The B4GALT6 inhibition will be assessed through evaluation of the anti-inflammatory effects of the selected ligands on rat primary astrocytes.

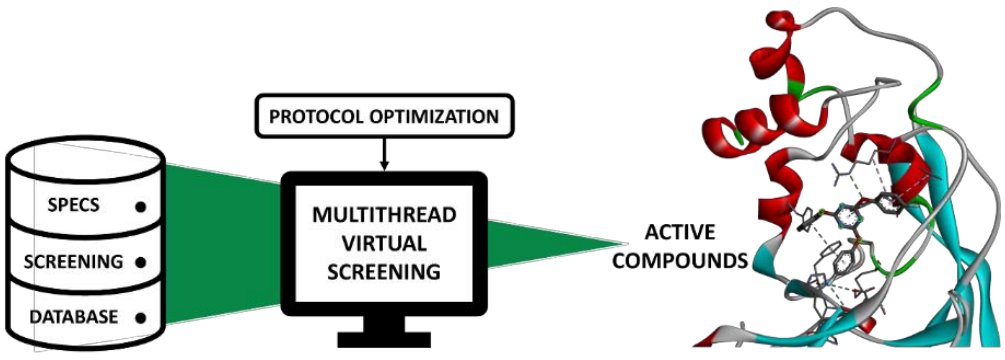

Figure 1: The step-by-step process of the screening protocol employed.

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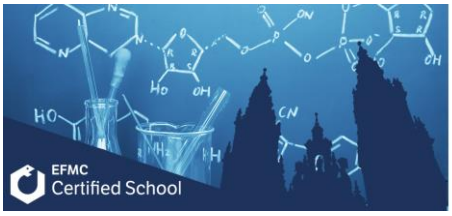

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STRUCTURE-ACTIVITY RELATIONSHIP STUDIES ON DIVALENT NAPHTHALENE DIIMIDE G QUADRUPLEX LIGANDS WITH ANTICANCER AND ANTIPARASITIC ACTIVITY.

Manuel Pérez-Soto [1], Pablo Peñalver [1], Steven T.G. Street [2], Dora Weenink [1], Michael P. O'Hagan [2], Javier Ramos-Soriano [2], Y. Jennifer Jiang [2], Gregory J. Hollingworth [3], M. Carmen Galan [2] and Juan C. Morales[1].

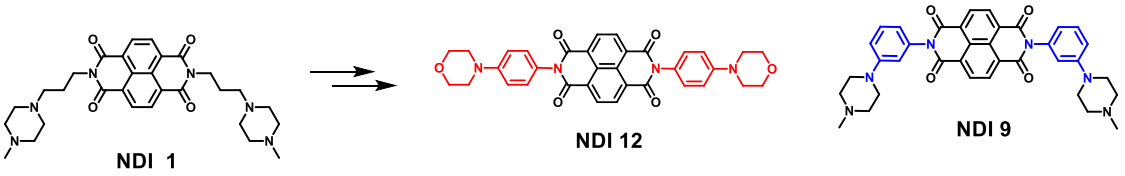
[1].Instituto de Parasitología y Biomedicina, Avenida del Conocimiento, s/n 18016, Armilla, Granada, Spain [2].School of Chemistry, University of Bristol, Bristol BS8 1TS, United Kingdom [3].Novartis Institutes for Biomedical Research, Novartis Campus, CH-4002 Basel, Switzerland

manuelperezsoto13@gmail.com

G-quadruplexes (G4) are DNA secondary structures which play important roles in the regulation of gene expression in human cells. They have been proposed as therapeutic targets in cancer [1]. At the same time, putative G-quadruplex forming sequences have also been found on the genome of parasites T. brucei, L. major and P. falciparum suggesting they could also be explored as therapeutic targets.

G-quadruplex ligands are frequently formed by a heterocyclic aromatic structure modified with positively charged groups. Here, we explore the influence of the side chains and charged groups in the well-known naphthalene diimide G-quadruplex ligands.

Our starting point is N-methyl piperazine disubstituted NDI (NDI 1), a compound that showed an IC50 value of 0.41 uM in HeLa [2] and 0.94 uM against Trypanosoma brucei parasites.



Among the synthesized compounds, a new NDI (NDI 9) containing a more conformationally restricted side chain and a piperazine group resulted in an IC50 of 0.048 uM against T.brucei with a selectivity index of 30.69 (SI= IC50 MRC5 / IC50 T.brucei) [3]. In addition, a morpholino disubstituted NDI (NDI 12) showed an IC50 of 0.17 uM against T.brucei with a selectivity index of 41.86 (SI= IC50 MRC5 / IC50 T.brucei) [3].

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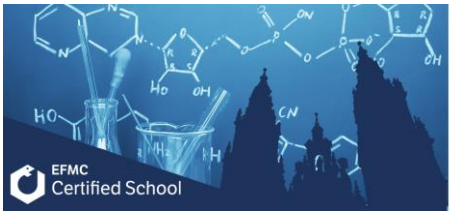

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SYNTHESIS AND EVALUATION OF BORONIC-CHALCONE DERIVATIVES AS INHIBITORS OF HEAD AND NECK CANCER

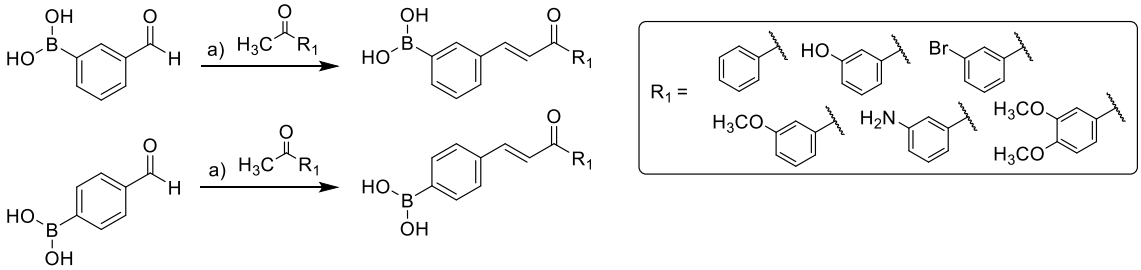
Juliana Romano Lopes,[1] Freddy Humberto Marin-Dett,[1] Paula Aboud Barbugli,[2] and Jean Leandro dos Santos.[1]

[1] School of Pharmaceuticals Science of São Paulo State University, Araraquara, Brazil, [2] School of Dentistry of São Paulo State University, Araraquara, Brazil.

romano.lopes@unesp.br

Head and neck cancer (HNC) is the seventh most common cancer globally, accounting for more than 870,000 new cases and 440,000 deaths in 2020 [1]. Approximately 90% of HNCs are squamous cell carcinoma, which comprises oral cavity, pharynx and larynx [1,2]. The principal treatment consists in surgery, radiation and chemotherapy [2]. Moreover, patients considered for immunotherapy receive pembrolizumab as the first line treatment [2] and those non-candidates for first line treatment, usually receive combinations of cetuximab or pembrolizumab plus 5-fluoracil (5-FU) and/or alkylating agent [2]. Due to the restrict therapies available, this work aimed to study small molecules in order to investigate their role against HNC. Chalcones are considered privileged scaffold in Medicinal Chemistry, exhibiting anti-cancer activity due to their inhibitory potencial against several targets involved in carcinogenesis such as: proteasome, VEGF, VEGR-2, tubulin, NF-kβ, p-53-MDM2, among others [3,4]. Twelve novel chalcones containing a boronic acid group were synthesized through Claysen-Schimidt condensation, involving the coupling between 3- or 4- formyl boronic acids and 3-functionalized acetophenones using basic condition in ethanol medium at room temperature (Figure 1). Compounds were obtained at yields ranging from 20 to 40 %, characterized by analytical methods and evaluated against HNC cell line SCC-25 (oral cavity carcinoma tumor cells) and NOK-si (oral cavity normal cells). Two most promissor compounds of the series showed IC_{50} value of 5.2 µg/mL (SI = 2.2) and 9.6 µg/mL (SI = 1.51). 5-FU showed an IC_{50} = 240 µg/mL against SCC-25 (SI < 1). Further studies will be provided in order to characterize the molecular targets of these boronic chalcones for HNC.

Figure 1. Synthetic scheme for obtaining of novel boronic-chalcones.



a) NaOH (1 mol/L), EtOH, r.t., 24 h

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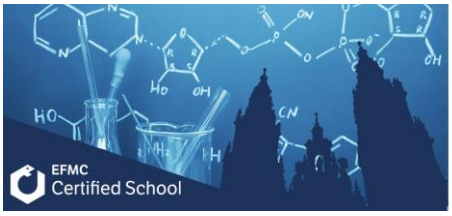

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CANCER-STEM-CELL PHENOTYPE-GUIDED DISCOVERY OF A MICROBIOTA-INSPIRED SYNTHETIC COMPOUND TARGETING NPM1 FOR LEUKEMIA

Anabel Sánchez-Merino[1], Sergio Algar[1], Henar Vázquez-Villa[1], Alberto Paradela[2], Bellinda Benhamú[1], Miguel Gallardo[3], María L. López-Rodríguez[1]

[1]Medicinal Chemistry Laboratory, Organic Chemistry Dept, Universidad Complutense de Madrid, Spain, [2]Functional Proteomics Laboratory, Centro Nacional de Biotecnología, CSIC, Madrid, Spain, [3]H12O–CNIO Haematological Malignancies Clinical Research Unit, CNIO, Madrid, Spain

anabes06@ucm.es

Microbiota plays an important role in human health and disease, in part through the secretion of metabolites that can regulate host proteins.[1] Hence, metabolites are drug-like specific modulators and represent an unexplored chemical space that can be used in the search of hits for drug discovery. In this context, we have analyzed the structures of identified metabolites[2] and explored asymmetric organocatalytic reactions as a key methodology to generate a microbiota-inspired library of structurally diverse compounds. Following a phenotypic strategy, the library was screened in a cancer-stem-cell (CSC) model and UCM-13369 was identified as a compound able of inhibiting the growth of CSCs, without cytotoxicity in non-tumor cells.[3] Proteomic experiments revealed that UCM-13369 induces a decrease in the expression of nucleophosmin 1 (NPM1), a multifunctional protein dysregulated in various hematological cancers. Notably, *NPM1* gene mutations occur in up to 30% of acute myeloid leukemia (AML) patients, representing the most frequent alteration.[4]

In this work, we have confirmed the interaction of UCM-13369 with NPM1 by confocal microscopy and in-vitro activity in two cell lines expressing the wild-type or the mutated protein. Importantly, UCM-13369 has shown in-vivo efficacy in a mouse model of NPM1-depending AML and induces cell death in hematopoietic stem cells in blood samples from AML patients without affecting differentiated cells. We are currently involved in a medicinal chemistry program based on UCM-13369, targeting optimized NPM1 inhibitors. The discovery of such drug candidates for AML treatment will contribute to the validation of NPM1 protein as a therapeutic target, and could open new avenues for precision strategies for AML with mutated *NPM1*.

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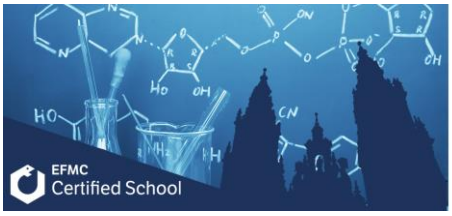

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SYNTHESIS OF 4,5-DIAZAFLUORENE DERIVATES AND THEIR Ag(I) COMPLEXES AS POTENTIAL ANTITUMORAL AGENTS

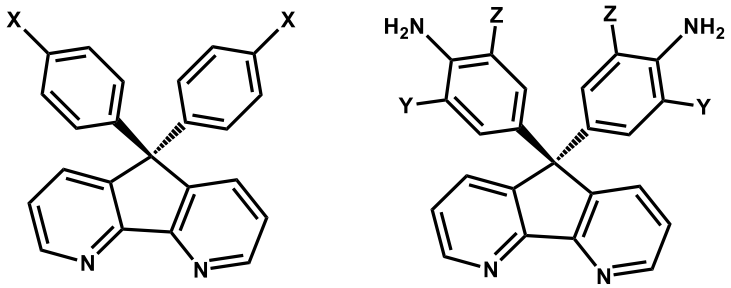
Leonardo Sandin,[1] Sandra Rico,[1] Camino Bartolomé,[1] Jesús Martínez de Ilarduya,[1] and Concepción Alonso[2]

[1]University of Valladolid, Valladolid, Spain, [2]University of Basque Country, Vitoria-Gasteiz, Spain

leonardoraphael.sandin@uva.es

Coordination compounds are of great interest in medicinal chemistry, especially in cancer research since the approval of cisplatin as an antitumoral drug. Apart from platinum, many other transition metal elements received attention due to their antitumoral properties. *N*-Heterocyclic carbenes and bipyridine silver(I) complexes, among others, have been reported to exhibit antiproliferative activities.[1] Based on that, our research focuses on the synthesis of bipyridines derived from 4,5-diazafluorene and the corresponding silver(I) complexes.

The synthesis of the 4,5-diazafluorene derivates mentioned is presented. These compounds have an aromatic group substitution at the C9 position of 4,5-diazafluorene. These aromatic groups are substituted with various functionalities (Scheme 1). The compounds were synthesized from 4,5-diazafluoren-9-one and the corresponding aryl compound. The direct synthesis of the haloderivates led to an inseparable mixture of *para*- and *ortho*-isomers. To overcome this regioselectivity issue, an alternative route was carried out, in which the *p*-amine compound was converted into the haloderivate *via* a diazonium salt strategy.



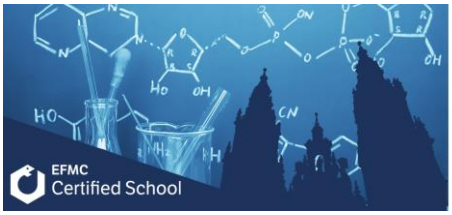
Scheme 1: Structure of the bipyridines synthesized.

These compounds were used as ligands in the synthesis of Ag(I) complexes. These complexes show a molecular ratio of 2:1 ligand:Ag. Studies are being carried out to determine the structure of the complexes.

The cytotoxicity evaluation of ligands and complexes in lung carcinoma (A-549) and fetal lung fibroblast (MRC-5) cell lines will be performed as the next step of this research.

References:

[1] Hecel, A., Kolkowska, P., Krzywoszynska, K., Szebesczyk, A., Rowynska-Zyrek, M, Kozlowski, H., *Curr. Med. Chem.*, **2019**, 26,624-647.



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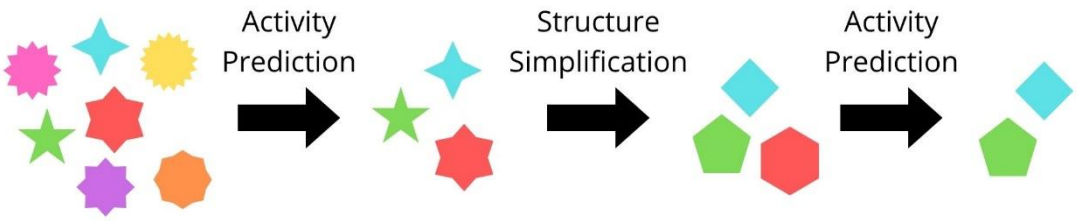
RATIONAL METHOD FOR STRUCTURAL SIMPLIFICATION AS KEY STEP IN HIT DISCOVERY

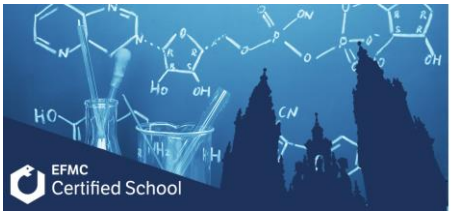
Endika Torres-Urtizberea[1], José I. Borrell[1], Raimon Puig de la Bellacasa[1], Roger Estrada-Tejedor[1]

[1]Grup de Química Farmacèutica (GQF), IQS School of Engineering, Universitat Ramon Llull, Via Augusta 390, 08017, Barcelona, Spain

endika.torres@iqs.url.edu

In a typical medicinal chemistry hit discovery, virtual libraries would undergo different filtering and prediction processes until a small group of molecules is selected for its consequent synthesis and biological testing. With the growth the availability of bibliographical data, the size of the starting molecular library can be composed of millions of molecules, making the filtering process a key step to select the most representative and promising compounds to be synthetized. Moreover, selected molecules would, ideally, have good predicted activity and be easily attainable. Here, we present a rational method for structural simplification, that allows the selection of structures in massive and complex combinatorial libraries, based on a SAR-like methodology, without compromising the biological activity. This approach has been successfully applied to develop tyrosine kinase dual inhibitors against Fibroblast Growth Factor Receptor 2 (FGFR2) and Insulin-like Growth Factor 1 Receptor (IGF1R), key proteins in the pancreatic ductal adenocarcinoma (PDAC).





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NOVEL FLUOROPHORES TO STUDY BIOMOLECULAR SYSTEMS *IN CELLULO*

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

[1]Instituto de Química Médica (IQM-CSIC), Madrid, Spain. [2]Nanoscopy-UGR Laboratory, Dept. de Fisicoquímica, Unidad de Excelencia de Química Aplicada a Biomedicina y Medioambiente, Fac. de Farmacia, Univ. de Granada, Campus Cartuja, Spain. [3]Departamento de Bioquímica y Biología Molecular II, Facultad de Farmacia, Universidad de Granada, Campus Cartuja, Granada, 18071, Spain

carmen.viedma@iqm.csic.es

Fluorescent biosensors occupy a prominent place in the development of bioimaging techniques due to the present some advantages such as high selectivity, sensitivity and versatility. In addition, compared to the contrast agents most commonly used in imaging techniques that have high background noise, fluorescent biosensors can be designed so that light emission occurs when interaction with the target of interest occurs. [1]

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. The best fluorophores are those with an emission wavelength longer than 600 nm, along with the highest quantum yield, as they would show the brightest emissions and allow non-invasive monitoring of biological material [2]. For its application in bioimaging techniques, it is necessary that the fluorophores present longer fluorescence lifetimes. However, only a few dyes with fluorescence times greater than 5 ns emit in the visible region.

In this regard, novel fluorophores to develop fluorescence probes and biosensors constitute invaluable pharmacological tools to study protein-protein interactions. We focus our attention in the study of: a) the voltage-gated potassium channel Kv4.3 channelosome and b) DNA visualization.

In this communication, we will describe the design, synthesis, photophysical properties and *in cellulo* studies of new fluorescent probes with fluorescence lifetimes around 15 ns useful for bioimaging techniques.

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LIST OF PARTICIPANTS

PARTICIPANTS

Name	Surname	Afiliation
Mariana C.	Almeida	FFUP / CIIMAR
Antonio	Andújar Arias	University of Santiago de Compostela
Yves	Auberson	Novartis
Jordi	Bach	Almirall,S.A.
Carla	Barbaraci	University of Barcelona
Aikaterini	Barmpidi	University of Barcelona
Maria	Braun Cornejo	Specs
Albert	Cabré	Lilly
Daniel	Cabrera Torrejón	Instituto de Química Médica (IQM, CSIC)
Laureano Emilio	Carpio Mulas	ProtoQSAR 2000 S.L.
Monica	Carreira	GalChimia
Jacobo	Cruces	GalChimia
Giulia	Cazzaniga	University of Milan
Álvaro	de la Cruz Potenciano	Instituto de Química Médica (IQM, CSIC)
Beatriz	De Pascual-Teresa	CEU San Pablo
Ana Andrea	Escobar Peña	Universidad Complutense de Madrid
Jesús	Escobar	Universidad de Valencia
Wiliam	Farnaby	CeTPD, University of Dundee
Daniel	Fernández Cabellos	Universidad Complutense de Madrid
Noelia	Fernández Ceballos	University of Salamanca
Mariana	Ferrer Casal	Universidade Estadual de Campinas (UNICAMP)
Román	Foronda Sainz	Universidad Complutense de Madrid
Aitor	García Rey	Universidade de Santiago de Compostela
Ana	García Souto	Universidad CEU San Pablo
Alba	Gil Rivas	Universidad San Pablo CEU
José Enrique	Gómez Pulido	Janssen Cilag S.A
Silvia	González Pelayo	Universidad de Salamanca
Patricia	Gratal Viñuales	University of Alcala
Marta	Gutierrez Rodriguez	Instituto de Química Médica (IQM, CSIC)
Md Mahbub	Hasan	King´s College London

PARTICIPANTS

Name	Surname	Afiliation
Francisco Javier	Hermoso Pinilla	Universitat de Barcelona
Carles	Lluna Galán	ITQ-UPV-CSIC
Mabel	Loza Garca	University of Santiago-Kaertor Foundation
Pilar María	Luque Navarro	University of Granada
Enrique	Madruga	Centro de Investigaciones Biológicas Margarita Salas (CIB-CSIC)
Miguel	Maldonado Menéndez	Instituto de Química Médica (IQM, CSIC)
Noemí	Martínez Conde	Universitat de Barcelona
Pedro	Martinez Salas	Instituto de Química Médica (IQM, CSIC)
Darío	Miranda Pastoriza	CiQUS-USC
Gerhard	Müller	SpiroChem AG
Verónica	Muñoz Canales	Universidad Complutense de Madrid
Patricia	Muñoz Escudero	Universidad CEU San Pablo
Juan Carlos	Muñoz García	CSIC
Esther	Navarro Blasco	Universidad de Valencia
Bárbara	Noverges Pedro	FAES FARMA
Claudio	Papotto	University of Milan
Miryam	Pastor	Lilly
Manuel	Pérez Soto	Instituto de Parasitología y Biomedicina "López-Neyra" CSIC
Eva María	Priego	Instituto de Química Médica (IQM, CSIC)
Juan Antonio	Rincón	Lilly SAU
Juliana	Romano Lopes	School of Pharmaceutical Sciences of São Paulo State University - UNESP
Anabel	Sánchez Merino	Universidad Complutense de Madrid
Leonardo Raphael	Sandin Mazzondo	University of Valladolid
Antoni	Torrens	ABAC Therapeutics
Endika	Torres	IQS
Carmen	Viedma	Instituto de Química Médica (IQM, CSIC)

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