Sociedad Española de Química Terapéutica

SEQT

YRS

YOUNG RESEARCHERS SYMPOSIUM

VII YOUNG RESEARCHERS SYMPOSIUM

JUNE 18TH 2021

ONLINE EVENT

Sociedad Española de Química Terapéutica

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YOUNG RESEARCHERS SYMPOSIUM

SCIENTIFIC PROGRAMME

09:00 — 09:15	**Opening**
09:15 — 10:00	**Plenary lecture L1:** Prof Marcos G. Suero, Institute of Chemical Research of Catalonia (ICIQ) New carbene & carbyne transfer catalysis Sponsored by Molecules
10:00 — 11:00	**Oral communications: Session 1** **O1: Francesco Calzaferri**. Design, synthesis and pharmacological evaluation of novel blood-brain barrier-permeable non-nucleotide purine derivatives as P2X7 antagonists **O2: Vanesa Nozal**. Improved controlled release and brain penetration of small molecules with therapeutic potential using PLGA nanoparticles **O3: Ainoa Sánchez Arfelis**. Design and synthesis of novel Brd4-targeting molecules with computer-assisted FBDD
11:00 — 11:15	**Morning break**
11:15 — 12:15	**Poster session 1**
12:15 — 13:15	**Oral communications: Session 2** **O4: Silvia Panarello**. Development of selective photoswitchable PAMs for the metabotropic glutamate receptor subtype 1 **O5: Adrián Gironda Martínez**. The power of big numbers: DNA-encoded libraries as a powerful technology in drug discovery **O6: Ana Gomes**. Peptide-based therapeutics to tackle skin and soft-tissue infections: antimicrobial, antibiofilm and collagenesis-boosting activities
13:15 — 14:15	**Lunch and break**
14:15 — 15:45	**Workshop:** Dr Manolo Castellano, Carreras Científicas Alternativas Strategies to explore new professional horizons Sponsored by Juste
15:45 — 16:25	**Oral communications: Session 3** **O7: Matteo Borgini**, Stereoselective synthesis of δ-fluorinated L-isoleucines exploiting C-H bond activation **O8: Chiara Borsari**, From pan to PI3Kα-selective inhibitors: a covalent strategy to fine-tune isoform-specific targeting
16:25 — 16:40	**Afternoon break**
16:40 — 17:40	**Poster session 2**
17:40 — 18:25	**Plenary lecture L2:** Prof Cristina Nevado, University of Zurich Complex Motifs via N-centered Radical Sponsored by EFMC
18:25 — 18:45	**Closing session and awards**

Sociedad Española de Química Terapéutica

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To all current board members of the Spanish Society of Medicinal Chemistry (SEQT), particularly to:

Beatriz de Pascual –Teresa: President

Marta Gutiérrez Rodríguez: Secretary

Eva María Priego Crespo: Treasurer

To our speakers: Dr. Cristina Nevado from University of Zurich, Dr. Marcos G. Suero from ICIQ and Dr Manolo Castellano

Special thanks to Antonio M. Rodríguez García from University of Castilla-La Mancha for his technical support and Brieuc Matagne from EFMC Young Scientists Network (EFMC-YSN).

To all participants for contributing to the field.

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SPEAKERS

Dr. Marcos G. Suero from ICIQ.

Dr. Marcos G. Suero was graduated in Chemistry from the Universidad de Oviedo in 2003 and introduced to organometallic chemistry in the laboratory of Prof. José Gimeno and Prof. Pilar Gamasa. In February 2009 he obtained his PhD degree at the Institute of Organometallic Chemistry Enrique Moles (Universidad de Oviedo), where he worked under the direction of Prof. José Barluenga and Prof. Josefa Flórez on Fischer carbene chemistry. During the summer of 2005 he joined the laboratory of Prof. Andrew Myers at Harvard University working on the synthesis of novel tetracycline antibiotics as a PhD visiting student. In May 2010 he moved to the University of Cambridge to work with Professor Matthew Gaunt on copper (III) catalysis and methionine bioconjugation as a Postdoctoral Marie Curie Fellow and in October 2014 he started his independent research career at the Institute of Chemical Research of Catalonia (ICIQ) within the CELLEX-ICIQ starting career programme.

Webpage:

www.iciq.org/dr-marcos-g-suero/

Plenary lecture L1: New carbene & carbyne transfer catalysis. Sponsored by Molecules.

Dr. Cristina Nevado from University of Zurich.

Dr. Cristina Nevado graduated in chemistry at the Autónoma University of Madrid in 2000. In October 2004 she received her PhD in organic chemistry from the same University working with Prof. Antonio M. Echavarren in late transition metal catalyzed reactions. After a post-doctoral stay in the group of Prof. Alois Fürstner at the Max-Planck-Institut für Kohlenforschung (Germany), she joined the University of Zürich as an Assistant Professor in May 2007. In 2011, Cristina was awarded the Chemical Society Reviews Emerging Investigator Award and the Thieme Chemistry Journal Award in recognition of her contributions in the field of synthetic organic chemistry. In 2012 she received an ERC Junior Investigator grant and has been awarded the Werner Prize of the Swiss Chemical Society. In 2013 she became Full Professor at the Organic Chemistry Institute of the University of Zürich. Rooted in the wide area of organic chemistry, her research program is focused on complex chemical synthesis and new organometallic reactions.

Webpage:

http://www.nevadogroup.com/cristina-nevado

Plenary lecture L2: Complex Motifs via N-centered Radical. Sponsored by EFMC.

Dr Manolo Castellano:

Dr Manolo Castellano is career consultant for scientists and researchers and a selection consultant for R&D companies. All the information about him is available at:

Webpage:

carrerascientificasalternativas.com

Workshop: Strategies to explore new professional horizons. Sponsored by Juste.

PLENARY LECTURES

PL1 NEW CARBENE & CARBYNE TRANSFER CATALYSIS

Marcos G. Suero[1]

[1] Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, Països Catalans 16, 43007 Tarragona, Spain, mgsuero@iciq.es

The art of organic synthesis and reaction discovery relies on logic-guided thought processes that often involve hypovalent carbon reactive species and their corresponding stabilized equivalent forms. However, not all of the possible carbon reactive intermediates and their reactivity rules have attracted the same attention by the synthetic community. This is mainly because of the perception of the lack of synthetic utility and importantly, because of the challenges associated with controlling their extreme reactivity and lack of efficient sources. In this lecture, I will show the discovery and development of new chemical processes based on underexplored carbyne and triplet carbene equivalents using bespoke sources and their use in solving important synthetic problems in the field of (late-stage) C–H and C–C bond functionalizations of feedstock and drug molecules as well as in radiolabeling.

PL2 COMPLEX MOTIFS VIA N-CENTERED RADICAL

Cristina Nevado[1]

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Nitrogen center radicals present divergent features: while highly reactive and thus difficult to control, they can also offer an excellent platform towards the formation not only of C-N but also remote C-C bonds. Here, we present ongoing efforts in our group to generate and harvest these valuable intermediates in synthetically relevant contexts, including recent results towards their application in asymmetric transformations.[1]

[1] Hervieu, C.; Kirillova, M.S.; Suárez, T.; Müller, M; Merino, E.; Nevado, C. *Nat. Chem*. **2021**, *13*, 327.

ORAL COMMUNICATIONS

O1 DESIGN, SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF NOVEL BLOOD-BRAIN BARRIER-PERMEABLE NON-NUCLEOTIDE PURINE DERIVATIVES AS P2X7 ANTAGONISTS

F. Calzaferri[1], P. Narros-Fernández[1,2], R. de Pascual[1], A.M.G. de Diego[1], J. Egea[1,2], A. Nicke[3], A.G. García[1,2], C. de los Ríos[1,2]

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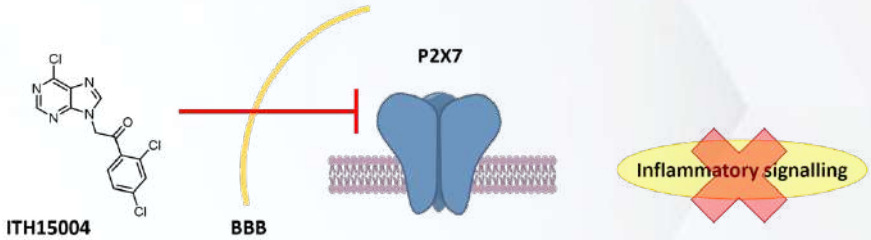
Keywords: *purine, P2X7 antagonists, neuroinflammation, CNS disorders*

The purinergic P2X7 receptor participates in the inflammatory signalling of several central nervous system (CNS) disorders [1]. In this work, we rationally designed and synthesised 3 main series of blood-brain barrier (BBB)-permeable non-nucleotide purine derivatives as P2X7 antagonists [2]. Their inhibitory activities were assessed by both cytosolic calcium measurements and YO-PRO-1 dye uptake in human P2X7-expressing HEK293 cells. Two-electrode voltage clamp in *X. laevis* oocytes was employed to validate the screening results and define the selectivity of the active compounds over other P2X subtypes. The arylpurinylethanone ITH15004 showed a consistent P2X7 inhibition in all the employed assays. It also reduced the release of IL-1β, an anti-inflammatory marker, in mouse peritoneal macrophages, and showed a good permeability profile as assessed by parallel artificial membrane permeability assay (PAMPA). Additionally, we observed that ITH15004 is not substrate of the efflux pump P-glycoprotein, differently from the BBB-permeable P2X7 antagonist JNJ-47965567. ITH15004 is thus a novel pharmacological tool whose optimisation, guided by the structure-activity relationships described in this work, may lead to the development of new drugs for the treatment of inflammatory-based CNS disorders.



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O2 IMPROVED CONTROLLED RELEASE AND BRAIN PENETRATION OF SMALL MOLECULES WITH THERAPEUTIC POTENTIAL USING PLGA NANOPARTICLES

V. Nozal, E. Rojas-Prats, D.I. Pérez, C. Gil, A. Martínez

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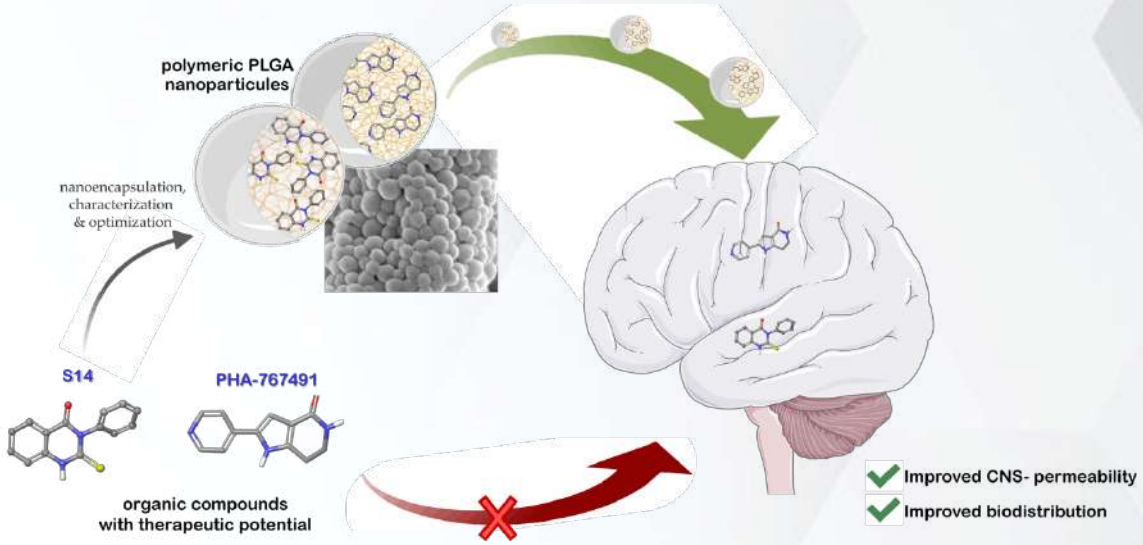
Keywords: *nanoparticles, neurodegeneration, kinase, phosphodiesterase, inhibitor*

One of the main hurdles in the design and development of drugs for neurodegenerative diseases is the penetrance to the central nervous system (CNS), protected by the blood-brain barrier. Recently, polymeric nanoparticles have been used as new formulations to target specific organs and produce controlled release of certain drugs. In this work, we describe poly(lactic-co-glycolic acid) (PLGA) based polymeric nanoparticles loaded with two interesting drugs: S14 and PHA-767491.

Phenyl-2-thioxo-(1H)-quinazolin-4-one, called S14, is a PDE7 inhibitor that has shown very promising results to treat Parkinson's disease. [1] Encapsulation of this drug inside PLGA-PVA nanoparticles resulted in improved CNS penetrance and biodistribution in mice. [2]

1,5,6,7-Tetrahydro-2-(4-pyridinyl)-4H-pyrrolo[3,2-c]pyridin-4-one, also known as PHA-747691, is a CDC-7 inhibitor which could have potential in the treatment of amyotrophic lateral sclerosis, since this kinase has recently been proposed as a new therapeutic target for this fatal disease. Preparation of PLGA-PVA nanoparticles has shown, not only improvement in the predicted CNS permeability but also reduced levels of hyperphosphorylated TDP-43 protein compared to the free drug. [3]



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O3 DESIGN AND SYNTHESIS OF NOVEL BRD4-TARGETING MOLECULES WITH COMPUTER-ASSISTED FBDD

A. Sánchez-Arfelis[1], S. G. Piticchio[1], M. Martínez-Cartró[1], S. Scaffidi[1], A. Bertran-Mostazo[1], S. Rodríguez-Arévalo[2]. C. Escolano[2], C. Galdeano[1], X. Barril[3].

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Keywords: *BET bromodomains; BRD4; Chemical probes; Fragment-based drug discovery, Crystallography; Medicinal chemistry; Drug discovery.*

Epigenetic proteins are highly sought-after targets in medicinal chemistry and drug discovery. In the recent years, research efforts were focused on developing small molecules binding to bromodomains (BRD), the readers of acetyl-lysine modifications, due to their implication in numerous of diseases [1,2].

From the structural point of view of BRD, crystallographic studies describe five water molecules as an integral part of the acetyl-lysine binding pocket, which are essential for its druggability and functional part of the protein [3,4]. Following a fragment-based drug design, with the help of computational techniques, a series of fragments with 5-phenylthiazolo[2,3-c][1,2,4]triazole scaffold with a substituent at the 3-position were proposed, probing the hydrophobic properties of the water network site of BRD4(BD1) [5,6]. Using time-resolved fluorescence energy transfer assays and X-Ray crystallography, the most active fragment, SSR4 (IC_{50} 26 µM), was characterized.

In a following computational study with the help of NAOMInext software [7], optimized derivatives of SSR4 and a synthetic route were suggested, leading to a 650-fold potency jump. In this study, we will describe the computational studies and chemical approaches applied to obtain a potent lead candidate for BRD4 (BD1).

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O4 DEVELOPMENT OF SELECTIVE PHOTOSWITCHABLE PAMS FOR THE METABOTROPIC GLUTAMATE RECEPTOR SUBTYPE 1

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Keywords: *G Protein-Coupled Receptor, mGlu$_1$, Positive Allosteric Modulator, Photo-pharmacology, Photochromic ligands, Structure- activity relationship (SAR), Selectivity*.

Positive allosteric modulators (PAMs) for metabotropic glutamate receptor 1 (mGlu$_1$) have been postulated to treat neuropsychiatric diseases associated to mGlu$_1$ dysfunction. Besides, obtaining a reversible and efficient spatiotemporal control of mGlu$_1$ activity would be therapeutically advantageous. Photopharmacology may provide a solution on this topic, since it is based on the use of light and photoswitchable ligands to modulate a protein activity. This approach offers new perspectives for drug discovery and promises a better drug action control reducing side effects to unattained levels. We have focused on developing photoswitchable PAMs in order to precisely switch on/off the activity of the mGlu$_1$ receptor with light. Replacing the phtalimide moiety of a known mGlu$_1$ PAM [1] with a N=N bond led to azobenzene candidates. Subsequent *in vitro* assays revealed that MCS1186 is a mGlu$_1$ PAM ligand in the dark, whereas it loses activity under 380 nm light. It derived from a "molecular switch" converting the equipotent mGlu$_{1/4}$ ago-PAM MCS0242 into a highly selective mGlu$_1$ PAM [2]. The reversible photocontrol of mGlu$_1$ activity may be advantageous to study the pharmacological and physiological implications of mGlu$_1$ with an unprecedented precision, which may lead to unexpected findings in neuro-science.

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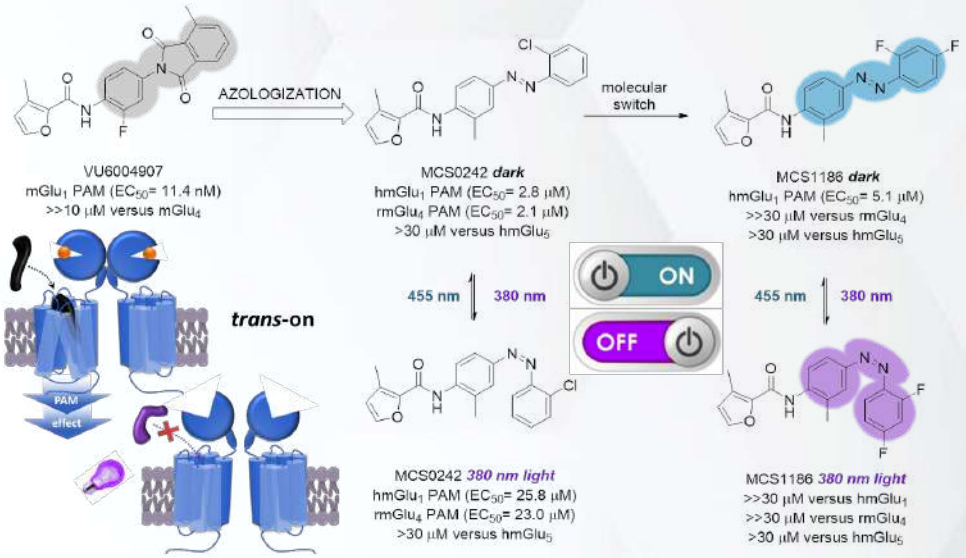

O5 THE POWER OF BIG NUMBERS: DNA-ENCODED LIBRARIES AS A POWERFUL TECHNOLOGY IN DRUG DISCOVERY

A. Gironda-Martínez[1], E. M. D. Gorre[1], E. J. Donckele[1], D. Neri[2,3] and F. Samain[1]

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Keywords: *DNA-Encoded Libraries, ESAC technology, Diazo-transfer*

Since Sydney Brenner and Richard Lerner theoretically proposed the concept, DNA-encoded library (DEL) technology has become a useful tool for drug discovery. The encoding of individual organic molecules with DNA fragments, serving as amplifiable identification barcodes, allows the construction and screening of compound libraries of unprecedented size. [1, 2]

DELs can be classified in terms of their synthesis strategy (e.g., "DNA-recorded" and "DNA-templated" synthesis) or in terms of the number of molecules displayed on DNA (e.g., "single-pharmacophore" and "dual-pharmacophore" libraries). Encoded Self-Assembling Chemical (ESAC) libraries make use of DNA hybridization in order to generate DNA-encoded assemblies of small-molecule fragments in a sequence-programmed fashion. [2]

In this presentation, novel advances in ESAC technology will be described. First, a new ESAC setting will be presented (ESAC 2+1) based in a single pharmacophore sub-library A, comprising two building blocks, and the complementary sub-library B. As an extension of this concept, we designed ESAC Plus, a novel cyclized ESAC library. The combinatorial self-assembling of both sub-libraries may yield a repertoire of very large libraries of high purity and diversity, which keep the initial purity of the original sub-libraries. [3] For the construction of ESAC Plus libraries, a new robust DNA-compatible diazo-transfer reaction has been developed and optimized. [4] The new constructs have been validated against a model target like Carbonic Anhydrase IX (CAIX), a well-known tumor-associated antigen. [5]

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O6 PEPTIDE-BASED THERAPEUTICS TO TACKLE SKIN AND SOFT-TISSUE INFECTIONS: ANTIMICROBIAL, ANTIBIOFILM AND COLLAGENESIS-BOOSTING ACTIVITIES

Ana Gomes,[1] Lucinda Bessa,[1] Iva Fernandes,[1] Ricardo Ferraz,[1,2] Nuno Mateus,[1] Paula Gameiro[1], Cátia Teixeira, [1] Paula Gomes[1]

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Keywords: *antibiofilm; antimicrobial peptide; collagenesis; multidrug-resistant bacteria; skin and soft-tissue infections*

Complicated skin and soft tissue infections (cSSTI) are often associated to bacterial biofilms that are hard to eliminate and contribute to tissue destruction, delayed wound-healing, and other serious complications. The most severe cases of cSSTI culminate in impatient hospital admission, where infections can be exacerbated by hospital acquired pathogens, in particular if caused by the so-called ESKAPE pathogens, for which few efficient antibiotics are available.[1, 2] New options for management and treatment of cSSTI are urgently needed, and the current biomedical approaches aim at providing protection against multidrug resistant (MDR) bacteria to the open wound together with a matrix scaffold, often collagen-based, to boost reestablishment of a healthy skin.[3] Having this in mind, we designed a dual-action chimera peptide, encompassing an antimicrobial sequence and a collagen-boosting sequence covalently linked to each other through different spacers and orientations. The resulting constructs displayed potent *in vitro* action against reference strains of Gram-positive and, especially, Gram-negative bacteria, with minimal inhibitory concentration (MIC) values as low as, e.g., 1.0 and 2.1 μM against *Escherichia coli* and *Pseudomonas aeruginosa*, respectively. The best construct also presented activity against MDR clinical isolates of *K. pneumoniae, E. coli* and *P. aeruginosa*, and hampered the formation of/disaggregated biofilms of MDR clinical isolates of *K. pneumoniae.* Relevantly, the hybrid peptide retained the collagenesis-inducing behavior of the parent collagen-boosting building block.[4] A more detailed report on this promising construct, along with preliminary results on other peptide-based constructs currently in development will be communicated.

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O7 STEREOSELECTIVE SYNTHESIS OF δ-FLUORINATED L-ISOLEUCINES EXPLOITING C-H BOND ACTIVATION

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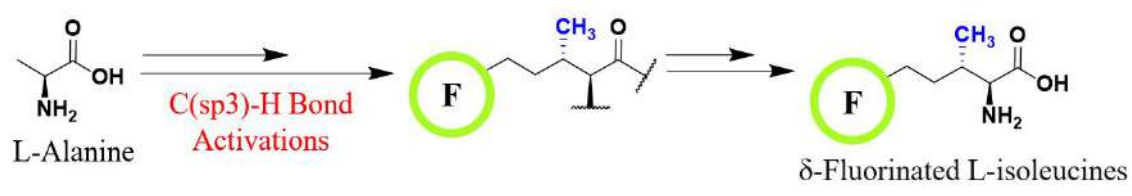
Keywords: *Fluorine-containing amino acids, C-H bond activation, protein engineering*

While the first synthesis of fluorinated amino acids (F-AAs) was reported almost a century ago, the study of F-AAs continues to expand.
This increased interest can be attributed to the altered physicochemical properties of F-AAs compared to their hydrogen-substituted analogs, resulting in different biological properties when F-AAs are incorporated into more complex molecules. Accordingly, F-AAs have been used in protein and peptide engineering, as well as drug discovery.[1,2] Despite the increasing number of F-AA syntheses reports, methods for the asymmetric preparation of α-F-AAs with multiple stereocenters are still limited.[3] In this regard, the stereoselective syntheses of δ-fluorinated L-isoleucines represent a challenge that needs to be addressed. Inspired by a better understanding of transition metal-mediated C-H bond activation,[4] we exploited C-H bond functionalization to introduce both methyl and fluorinated ethyl groups into the L-alanine scaffold to obtain δ-fluorinated L-isoleucines in a stereoselective fashion. The latter have found applications in protein structure determination and molecular biophysics.



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O8 FROM PAN TO PI3Kα-SELECTIVE INHIBITORS: A COVALENT STRATEGY TO FINE-TUNE ISOFORM-SPECIFIC TARGETING

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Keywords: Cysteine targeting, covalent compounds, chemical probes, PI3K pathway, cancer

Inhibitors of the phosphatidylinositol 3-kinase (PI3K) – protein kinase B (PKB/Akt) - mechanistic target of rapamycin (mTOR) axis are considered as valuable assets in cancer therapy.[1-4]

Herein we present a strategy to convert a phase II clinical candidate, a pan-PI3K inhibitor (PQR309, bimiralisib)[1,5], into highly selective PI3Kα-covalent inhibitors aiming to minimize the on-target metabolic side effects of PI3K inhibitor cancer therapy. We exploited a rational approach to increase target selectivity by covalently targeting a PI3Kα non-conserved nucleophilic amino acid side chain, namely Cys862. A reactive moiety, so called warhead, was introduced into a chemically modified bimiralisib.

A combination of warhead activity design, proximity and orientation allows a tight control of reversible inhibitor binding and isoform selective covalent binding. To avoid off-target reactions, we have set up a method to quantitatively evaluate warheads' reactivity and optimize for selective Cys862 modification. An extensive Structure Activity Relationship (SAR) study was performed and a wide range of linear and restricted rotation linkers introduced. A comprehensive understanding of the kinetics of irreversible inhibition allowed to interpret SAR and identify compounds with optimal kinact (maximum potential rate of inactivation). X-ray crystallography and mass spectrometry experiments validated the covalent modification of Cys862. Our pilot compounds exceed specificity and potency over an experimental dimethyl-substituted enone, CNX-1351[6]. Moreover, they are metabolically stable in rat liver microsomes and outperform the rapidly metabolized CNX-1351.

Our strategy to investigate and tune warheads' reactivity represents a major step forward in the rational design of covalent chemical tools. Moreover, we provide highly selective chemical tools to dissect PI3K isoform signaling in physiology and disease.

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POSTER PRESENTATIONS

P1 DEVELOPMENT OF MATRIX METALLOPROTEINASE TYPE 13 (MMP-13) INHIBITORS AS CANDIDATES FOR OSTEOARTHRITIS TREATMENT

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MMP-13 inhibitors, osteoarthritis

Osteoarthritis is a degenerative disease of the joint cartilage for which there are only symptomatic treatments [1]. Participation of MMP-13 in type II collagen degradation [2] proves the relationship of this enzyme with osteoarthritis [3]. Thus, its inhibition constitutes a novel therapeutic strategy to prevent the progression of this disease.

MMP-13 belongs to the family of zinc-dependent endopeptidases. Although they are all very similar, they differ in the size of the S1´pocket, which is directly related to the length of the omega loop. This pocket is larger in MMP-13 than in other MMPs, which can be used to design selective inhibitors of this enzyme [2, 4].

The strategy followed in this work consists on of using a hydroxamate as Zinc Binding Group (ZBG) to chelate the Zn atom present in the active site, linked to a large group designed to interact with the S1´ pocket.

In a previous work, we described polybrominated triazole derivatives 1 and 2 (figure 1) with nanomolar inhibitory activity against MMP13 and promising selectivity profiles against other MMPs [5].

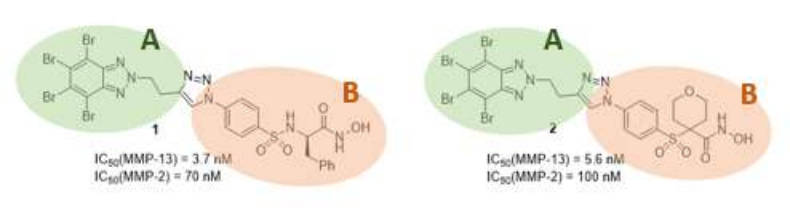

Figure 1. Structures of compounds **1** and **2**. Highlighted in green the scaffold A and in orange the scaffold B.

In this work we have extended the study to inhibitors based on the substitution of the benzotriazole scaffold by a phthalimide structure. In this new type of compounds, we also evaluated the influence of the bromine atoms with the aim of improving the pharmacokinetic and solubility properties of these inhibitors. Finally, modifications in scaffold B were performed. In this case, the hydroxamic acid was replaced by a weaker ZBG, such as a carboxylic acid to improve the selectivity.

Financial support from RTI2018-093539-B-I00 *(MICIU/FEDER, UE) is kindly acknowledged. L.A is supported by PEJ-2020-AI/BMD-17635 (CAM research support).*

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P2 MOLECULAR HYBRIDIZATION TO DESIGN NEW LIGANDS OF NS5 METHYLTRANSFERASE OF FLAVIVIRUS

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Keywords: *antivirals, flavivirus, methyltransferases*

Flavivirus are an important class of human pathogens that includes Zika virus (ZIKV), Dengue virus (DENV), Yellow fever virus (YFV) and Went Nile virus (WNV), among others. These flavivirus are transmitted by the bites of infected mosquitos mostly belonging to the *Aedes* and *Culex* species. Unfortunately, no antivirals have been approved for the treatment of these (re)emerging viral infections.

The *N*-terminal domain of the viral non-structural protein 5 (NS5) contains the methyltrasferase (MTase) activity required for mRNA capping. This process is consideredas essential for viral replication and helps the virus to evade the host immune response[1]. The structural information available of this domain for ZIKV and DENV enzymes indicates a high degree of structural homology and sequence conservation of both the SAM (methyl donor) and the GTP binding sites, thus targeting the enzymatic activity of this domain may lead to panflavivirus antivirals [2]. Very recently, Santos el al, applyingvirtual screening protocols to ZIKV MTase, identified the 2-thioxothiazolidin-4-one ZINC1652386 as the best ligand interacting at the SAM binding site [3]. Based on the proposed binding mode, we have applied a molecular hybridization approach to construct new ligands where the 2-thioxothiazolidin-4-one has been replaced by purinebases. A small series of purine virtual ligands have been constructed and submitted to docking studies at the SAM binding site of ZIKV MTase (PDB 5ULP). The poses obtained have been useful to guide future synthetic eforts. Thus, this approach may lead to new ligands targeting the methyltransferase activity of flavivirus NS5.

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P3 BENZOFURANYLIMIDAZOLES: SYNTHESIS, AFFINITY FOR IMIDAZOLINE I2 RECEPTORS. DISEASE-MODIFYING TREATMENT WITH LSL60101 IN AN ALZHEIMER'S DISEASE MOUSE MODEL

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Keywords: *imidazoline I_2 receptors, bezofuranylimidazoles, Alzheimer's disease, 5xFAD*

Imidazoline I_2 receptors (I_2-IR) are widely distributed in the CNS and increased in the patients that suffer from Alzheimer's disease (AD). Since structural data for I_2-IR remains unknown, the discovery of selective I_2-IR ligands is necessary for their pharmacological characterization. [1] Recently, we focused our attention in the development of structurally new families of compounds endowed with an outstanding affinity and selectivity upon I_2-IR. [2,3]

Here, we describe the synthesis and full characterization of 10 members of a family embodying a 2-(2-benzofuranyl)-2-imidazole nucleus, we assessed their pharmacological profile and selectivity through competition binding studies in human tissues against the selective I_2-IR radioligand [^{3}H]-2-BFI. Then, a representative compound, LSL60101, was selected to carry out preliminary DMPK studies.

We assessed the neuroprotective effect of LSL60101 by evaluating specific oxidative stress markers and transcription factors related with OS machinery in 5xFAD, an early-onset mouse transgenic model of AD. We found a significant cognitive improvement in the treated animals and the biomarkers related to neurodegeneration (Figure 1) [4].

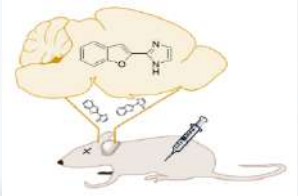

Figure 1. Neuroprotection studies

To sum up, we propose a new I_2-IR ligand that supports that I_2-IR constitute a relevant pharmacological target for the therapeutic strategy against AD.

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P4 UNLOCKING THE CF3 GROUP IN THE SYNTHESIS OF 2-MODIFIED GLYCOSIDES

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Keywords: *Fluorosugars, Trifluoromethyl, Glycosylation, Stereoselective*

Fluorinated carbohydrates are appreciated molecular fragments in chemical biology and diagnostics.[1] Available synthetic protocols are mainly restricted to the preparation of mono-fluorinated sugars,[2] whereas trifluoromethyl congeners remain virtually underdeveloped. Other easily accessible trifluoroacetamides and trifluoroacetoxy groups have been reported which are the closest-art in the CF_3-containing glycosides.[3] Herein we present a protocol for accessing a series of previously uncharted 2-deoxy-2-trifluoromethylpyranosides from the corresponding parent glycals. Exploration of the stereochemical outcome from the glycosylation step revealed that selective substrate control rendering 1,2-*trans* glycosides arises from the configuration of the CF_3 moiety. The synthetic utility was demonstrated in the preparation of CF_3-modified natural glycoside analogs, including disaccharides, steroidal aglycones, aminoacids and sphingosine analogs.

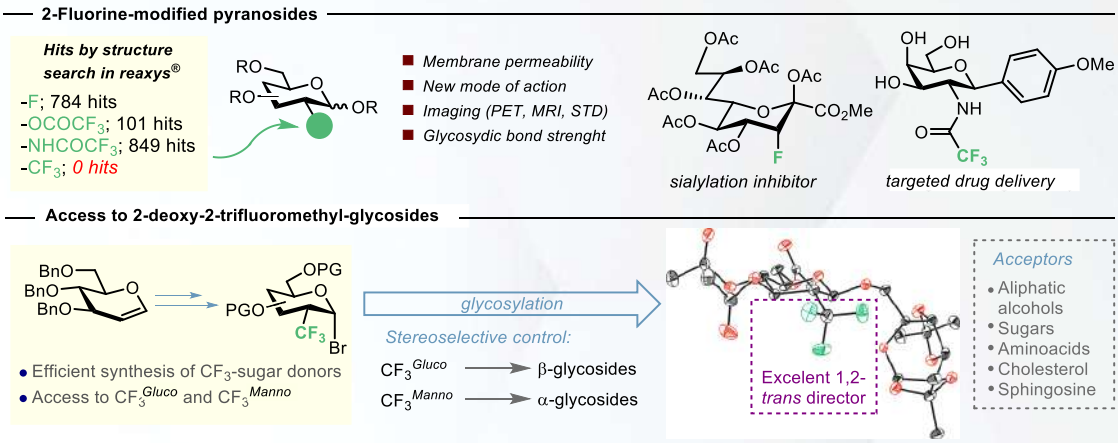

Figure 1. Top: Reported 2-deoxypyranosides bearing fluorinated groups at C-2 position and examples in medicinal chemistry. Bottom: Methodology applied for the synthesis of 2-CF_3-glycosides, stereo-chemical outcome of the glycosylation reaction and application of the method using natural analogues.

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P5 [60]FULLERENE HEXA-ADDUCTS AS DUAL HIV AND ENTEROVIRUS A71 ENTRY INHIBITORS

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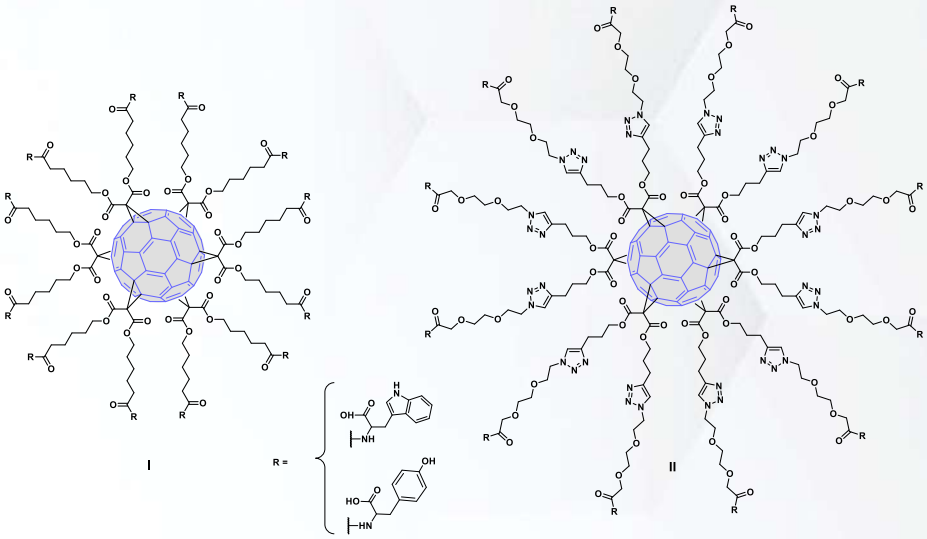
Keywords: [60]-fullerene, amino acids, HIV, EV71.

Based on the previously described dendrimer prototypes AL-385 and AL-463 [1], [60]Fullerene hexa-adducts peripherally decorated with twelve tryptophan (Trp) or tyrosine (Tyr) residues (Figure) have been synthesized by using an efficient convergent approach. These novel compounds are much more potent against HIV and equally active against EV71 than prototypes, which have the same number of Trp/Tyr residues on the periphery but attached to a smaller and more flexible pentaerythritol core.

The results demonstrate the importance of the globular 3D presentation of the peripheral groups (Trp/Tyr) as well as the length of the spacer connecting the organic addend to the central core to interact with the viral envelopes.

In addition, these studies suggest [60]fullerene can be an alternative and attractive biocompatible carbon-based scaffold for this type of highly symmetrical dendrimers [2].



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P6 SELF-ASSEMBLED PEG-SN38 NANOSYSTEMS

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Keywords: *drug delivery systems, SN-38, PEG, nanostructures, self-assembly*

The development of biocompatible and selective drug delivery systems still nowadays represents a crucial challenge for poorly soluble drugs used in cancer treatment [1]. For advanced colorectal cancer irinotecan (CPT-11), a soluble 7-ethyl-10-camptothecin (SN-38) derivative, is currently used in clinics. Since CPT-11 is only partially converted in its active metabolite, the development of other potential pro-drugs or drug delivery systems that release SN-38 in higher extension can generate more effective treatments with lower doses [2]. The covalent conjugation of SN-38 to a polymeric carrier, such as the biocompatible polyethylene glycol (PEG), generates a water-soluble conjugate with improved drug pharmacokinetic profile, protecting it from rapid degradation and stabilizing its bioactive closed-lactone form, allowing its systemic administration [3].

In this context, we have designed and synthesized diverse SN38-conjugates based on homo-bivalent and hetero-bivalent PEG-based platforms, where SN38 was conjugated through an ester bond at the C20 position. The use of a labile bond, sensitive to pH and esterases, can allow the stimuli-selective release of the intact drug. These systems have amphiphilic character due to the presence of a hydrophilic moiety of monodispersed PEG_{27} bound to a nitrilotriacetic acid core (NTA) [4] and a hydrophobic part containing SN38 and lipids (cholesterol or fatty acids). By adjusting the hydrophilic/hydrophobic ratio we obtain compounds able to self-assembly at µM concentration in aqueous media forming regular and nanostructures (10-15 nm or 40-60 nm) with different tridimensional shape, spherical or cylindrical depending on the chemical feature of the system.
The preliminary results suggest that those compounds could be versatile candidates as SN38-delivery systems.

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P7 ELECTROPHILIC REAGENTS FOR THE DIRECT INCORPORATION OF SCF_2CF_2H AND SCF_2CF_3 MOTIFS

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Keywords: *Fluorine, Fluoroalkylthiolation, Fluoroalkylation, Electrophilic reagents*

The introduction of fluoroalkylthioether groups (SRf) has attracted the attention of the drug discovery community given the special physicochemical and pharmacokinetic features they confer to bioactive compounds.[1] Synthetic advances in the field have been capitalized by methods to incorporate $-SCF_3$ and $-SCF_2H$ motifs,[2] however, longer and synthetically more challenging polyfluoroethyl chains are still underdeveloped. Here, two saccharin-based reagents have been disclosed as optimal electrophilic reagents for the introduction of $-SCF_2CF_2H$ and $-SCF_2CF_3$ motifs. The reactivity performance has been thoroughly investigated within a variety of nucleophiles, including heteroatoms, activated heterocycles, aromatic compounds, organometallic species as well as biologically relevant natural products and pharmaceutical drugs. Finally, multigram scale preparation and divergent derivatization has been explored from the unprecedented $-SCF_2CF_2H$ group.

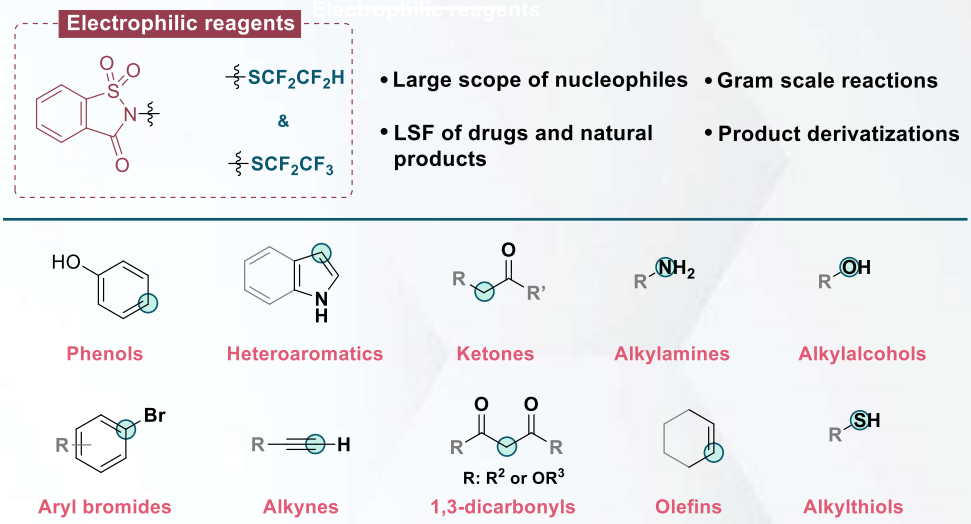

Figure 1. Electrophilic reagents for the incorporation of $-SCF_2CF_2H$ and $-SCF_2CF_3$ motifs and scope of nucleophiles.

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P8 ELUCIDATION OF THE MECHANISM OF ACTION OF NOVEL BINDERS OF THE FBW7 E3 LIGASE

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Keywords: *Fbw7*, *E3 ligase, UPS, PROTACs, protein degradation*

Fbw7 is one of the ~600 E3 ligases known in humans, which are key elements in the ubiquitination process. E3 ligases recruit specific substrates and promote their degradation by the Ubiquitin Proteasome System (UPS). [1] Fbw7 is one of the most commonly deregulated proteins in human cancers (6% of cancers present mutations in the *fbw7 gene*). The loss of its tumour suppressor activity results in an upregulation of its natural and oncogenic substrate proteins such as c-Myc, cyclin E and Notch. [2] Although, E3 ligases are attractive candidates as drug targets for specific and less toxic therapeutic intervention, the development of small-molecules against E3 ligases has been rewarded with limited success, and to date, no potent small-molecules targeting Fbw7 have been reported. [3]

A multidisciplinary approach combining computational and fragment-based was carried out in our lab to find binders for Fbw7, to (i) engineer new pharmacological strategies to treat cancer, and (ii) to serve as potential anchors to develop PROteolysis TArgeting Chimera molecules (PROTACs). A total of 8 compounds and 17 fragments with a K_D within a wide range of nanomolar and micromolar range were identified, being the first examples of confirmed Fbw7 binders.

The mechanism of action of the identified Fbw7 small-molecules binders is being now assessed. Filuorescence polarization (FP) assays are being used to determine the competition between the ligands and natural substrates of Fbw7. Moreover, the biological effect of the Fbw7 binders is being evaluated following the degradation of different Fbw7 natural substrates by western blot (WB).

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P9 TARGETING HYPOXIA IN TUMOUR MICROENVIRONMENT WITH SELF-IMMOLATIVE TRIAZENE PRODRUGS

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Keywords: *Triazenes; DNA alkylation; hypoxia.*

Displaying a broad-spectrum chemistry, triazenes are best known for their cytotoxic properties, as exemplified by clinical anticancer agents dacarbazine and temozolomide. They exert their chemotherapeutic activity through a unique mechanism of action that involves formation of a reactive alkyl diazonium intermediate capable of alkylating DNA and promoting cell death.[1,2] Herein we report a triazene-based platform, **1**, that can be activated by nitroreductases[3] (NTRs) to undergo a self-immolative process that culminates with the release of the cytotoxic triazene.

A series of nitro(hetero)aromatic prodrugs **1** (figure 1) of cytotoxic triazenes was synthesized and NTR-triggered activation was investigated by HPLC and LC-MS. Corroboration of the reduction reaction was attained through chemical reduction using zinc/acetic acid and by means of the synthetic des-nitro analogue. Human cancer cells A549, U-87 MG and LN-229 were treated with prodrugs **1** under either hypoxic (0.05% O_2) or normoxic (20% O_2) conditions. These experiments disclosed selective cell cytotoxicity under hypoxic conditions, whereas cells exposed to temozolomide, used as a reference compound and currently applied in glioblastoma chemotherapy, did not result in significant change of cell viability. This strategy is expected to lead to the selectivity of cytotoxic effect of triazenes, providing enhanced therapeutic agents in the field of cancer.

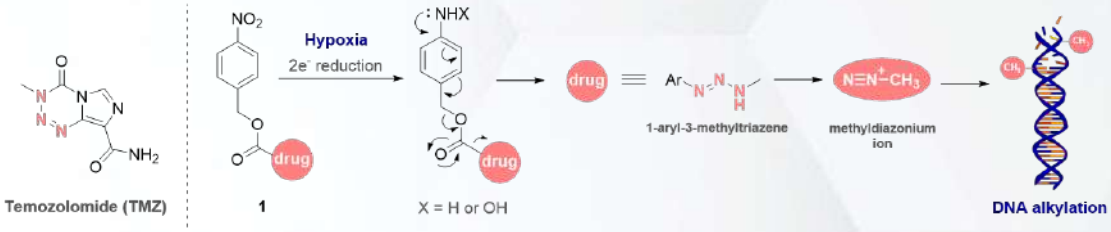

Figure 1 - Schematic representation of triazene prodrugs **1** activation under hypoxic conditions.

Acknowledgements: We thank the Fundação para a Ciência e Tecnologia for financial support through the PhD fellowship awarded (PD/BD/135286/2017) through MedChemTrain PhD Programme and through iMed.ULisboa grant, UID/DTP/04138/2019 from FCT, Portugal.

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P10 EVALUATION OF NEW BODIPYS AS PHOTOSENSITIZERS FOR THEIR APPLICATION IN PHOTODYNAMIC THERAPY

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Keywords: *BODIPY, Photosensitizers, Photodynamic Therapy, ROS*

Photodynamic therapy (PDT) is known as a low-invasive medical therapy for the treatment of neoplastic disease. The photosensitizer (PS) plays an important role inPDT for the generation of cytotoxic reactive oxygen species (ROS) upon the excitation by light irradiation. The PS is able to transfer the absorbed photon energy to the oxygen molecules in the surroundings of the tissue, thus generating cytotoxic singlet oxygen ($^1O_2$) that triggers the massive death of tumor tissue. [1]

BODIPY dyes are family of organic compounds, which present remarkable fluorescent properties, and excellent chemical and photophysical stabilities, including large molar extinction coefficients, intense photoluminescence and narrow absorption and emission bandwidths. [2]

In this work**,** we present a new family of fluorescent amino-BODIPYs-dyes as photosensitizers for PDT using the HeLa tumor cell line as an *in vitro* model, thesubcellular location of these compounds was evaluated [3].The BODIPYs scaffold present different aromatic and heteroaromatic substituents at C-3 position that allow to modulate and improve their physicochemical and photophysical properties. These compounds present high extinction coefficients, resistance to photobleaching and higher light/dark toxicity ratios. Moreover, they are capable of generating $^1O_2$ under excitation of 420-530 nm. **(Figure 1)**

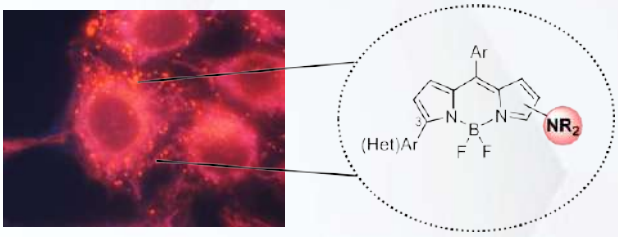

Figure 1. Fluorescence microscopy image of HeLa cells treated with amino-BODIPy (under UV light)

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P11 DEVELOPMENT OF A TWO NEW FAMILY OF SOLUBLE EPOXIDE HYDROLASE INHIBITORS FOR THE TREATMENT OF ACUTE PANCREATITIS

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Keywords: *soluble epoxide hydrolase, inflammation, urea, acute pancreatitis.*

Acute pancreatitis (AP) is a serious and life-threatening inflammatory disease and arises as one of the most common gastrointestinal disorders worldwide. Aside from palliative treatments, there is no standard therapeutic strategy for reducing inflammation in AP.

Epoxyeicosatrienoic acids are endogenous chemical mediators derived from arachidonic acid that show anti-inflammatory, antihypertensive, analgesic, angiogenic, and anti-atherosclerotic effects. [1] Soluble epoxide hydrolase (sEH) converts EETs to their corresponding dihydroxyeicosatrienoic acids, whereby the biological effects of EETs are altered. It has been proposed that the inhibition of sEH may have therapeutic effects in several diseases. Recently, it has been showed the efficacy of a potent sEH inhibitor (TPPU) on a murine model of AP. The results showed a reduction of levels of mRNA of different inflammatory cytokines, the endoplasmic reticulum stress and cell death. [2]

Herein we report the synthesis and SAR of a series of novel sEHI with excellent drug-like properties. Most of them were endowed with low nanomolar or even subnanomolar potency against the sEH enzyme. Further *in vitro* profiling and pharmacokinetic studies allowed us to select an optimized compound for an *in vivo* efficacy study in a mice model of cerulein-induced AP. We found that our candidate (0.3 mg/Kg) reduced pancreatic damage and improved the health status of the animals. In summary, these novel results suggest that sEH may be a target of clinical interest for treating acute pancreatitis. [3,4]

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P12 COMPUTATIONAL CHARACTERISATION OF A CRYPTIC POCKET IN ACHE INDUCED BY A FAMILY OF ACHE-SEH DUAL INHIBITORS

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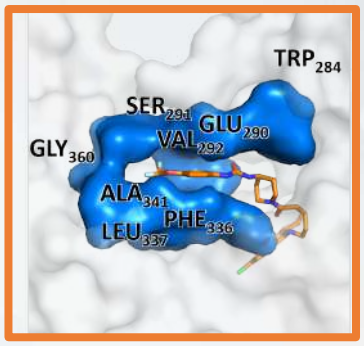
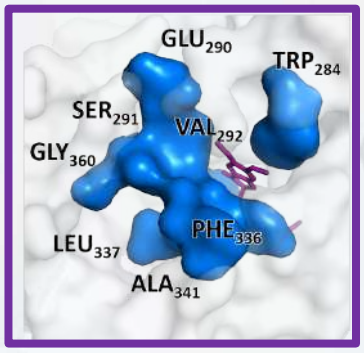
Keywords: *cryptic pockets, Multitarget Directed Ligands, Alzheimer's Disease*





AcetylCholinesterase (AChE) and soluble Epoxy-Hydrolase (sEH) have proven [1-2] effective targets against neurodegenerative diseases such as Alzheimer's Disease (AD) due to their role in cholinergic neurotransmission, amyloid-beta (Ab) aggregation, neuroinflammation, and oxidative stress. We have recently developed the first class of multitarget directed ligands able to inhibit both enzymes *in vitro* and characterised their *in vivo* efficacy, as a new family of bioactive compounds of potential interest in the treatment of neurodegenerative diseases. [3]

In this work, we have investigated by means of docking and molecular dynamics simulations, the binding of this new family of compounds to the AChE active site. While interactions at the Catalytic Anionic Site (CAS) reproduce the well-known pharmacophoric traits of other AChEi, binding of the compounds at the Peripheral Anionic Site (PAS) requires the opening of a cryptic hydrophobic cavity in the vicinity of the PAS (orange box). This cavity is not present in known crystallographic structures nor is it induced by donepezil (purple box) but is essential to accommodate the elongated hydrophobic moiety of the sEHi warhead. We hypothesize that the newly described pocket could pave the way to a new generation of ligands able to inhibit AChE by reshaping the PAS.

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P13 DE NOVO DESIGN OF SELECTIVE QUADRUPLEX-DUPLEX JUNCTION LIGANDS AND STRUCTURAL CHARACTERISATION OF THEIR BINDING MODE: TARGETING THE G4 HOT-SPOT

L. Díaz-Casado[1], I. Serrano-Chacón[2], L. Montalvillo-Jiménez[1], F. Corzana[3], A. Bastida[1], A.G. Santana[1], C. González[2], J.L. Asensio[1].

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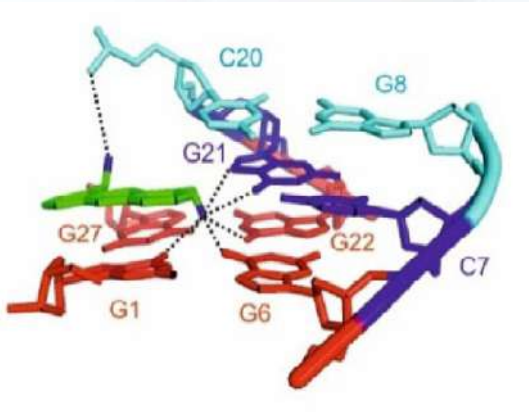
Keywords: *Nucleic Acids Ligands • Selective Molecular Recognition • Quadruplex-Duplex Junctions • NMR structure • Novel Phamacophore*

Targeting the interface between DNA quadruplex and duplex regions by small molecules holds significant promise in both therapeutics and nanotechnology. In this communication we report on a new pharmacophore that selectively binds with high affinity to quadruplex-duplex junctions, while presenting a poorer affinity for G-quadruplex or duplex DNA alone. Ligands complying with this pharmacophore exhibit a significant affinity and selectivity for quadruplex-duplex junctions, including the one observed in the HIV-1 LTR-III sequence. The structure of the complex between a quadruplex-duplex junction with a ligand of this family has been determined by NMR methods. According to these data, the remarkable selectivity of this structural motif for quadruplex-duplex junctions is achieved through an unprecedented interaction mode so far unexploited in medicinal and biological chemistry: the insertion of a benzylic ammonium moiety into the centre of the partially exposed G-tetrad at the interface with the duplex (Figure 1). Further decoration of the described scaffolds with additional fragments opens up the road to the development of selective ligands for G-quadruplex-forming regions of the genome.

Figure 1



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P14 ACE2-DERIVED PEPTIDES WITH ENHANCED EFFICACY FOR INHIBITION OF SARS-COV-2 INFECTION

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Keywords: *SARS-COV-2 spike inhibitors, ACE2- based peptides, macrocyclic peptides.*

The coronavirus disease (COVID-19) originated the current world-wide pandemic situation. This disease is caused by the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) and the structural and biochemical basis of the infection mechanism has been widely investigated showing that the receptor binding domain (RBD) of the virus surface spike protein interacts with the peptidase domain (PD) of angiotensin-converting enzyme 2 (ACE2). [1-3] Crystallographic studies of the RBD of SARS-CoV-2 with the full-length human ACE2 receptor exposed the amino acid residues that play a key role at the contact interface of the two proteins. [3,4] Most of the interactions between RBD and ACE2 receptor reside on the helix 1 of ACE2. It has been reported that the α-helix secondary structure is essential to obtain antiviral activity against the SARS-CoV-2 pseudovirus. [5] Several strategies have been published to increase the helicity content of the helix 1 peptide of ACE2. Curreli et al. designed four stapled peptides [5] while Karoyan et al. substituted the non-essential positions of the native helix 1 of ACE2 by amino acid residues such as Ala and/or Leu that display a higher helical folding propensity. [1] Both strategies showed an increase in the helical content and a potent SARS-CoV-2 inhibitory activity. Here, we report the development of a long-range macrocycle ACE2 derived peptides with the aim to stabilise the helical structure of the peptides and consequently, increase the potential ability to block SARS-CoV-2 attachment to the host cell. Chemical modifications of the peptides that show greater affinity against RBD will be conducted to obtain irreversible versions of the peptides. These modified peptides should be chemically stable and maintain the binding properties. Nonetheless, crosslinking between both components is expected due to the chemical reaction of the modified peptide with amino acid residues of the RBD that have a nucleophilic character. Finally, multivalent platforms will be synthesized following methodologies well established in our laboratory with the peptide candidates that show better results.

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P15 ANTIBACTERIAL AND ANTIBIOFILM ACTIVITY OF NOVEL QUATERNARY AMMONIUM FLUOROQUINOLONE ANTIMICROBIALS

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Keywords: *antibiotics, drug research, fluoroquinolones, antibacterial agents*

Bacterial resistance to antibiotics was identified by the WHO as one of the biggest threats to human health. Antibiotic resistance leads to higher health care costs and is a particularly serious problem for patients with compromised immune systems. Since a single drug is not always able to adequately control the illness, a combination of therapeutics with different pharmacotherapeutic profiles may be needed. Previously our research group reported the synthesis and biological action of a series of fluorescent fluoroquinolone (FQ) hybrid compounds featuring fused quinolone-triazolinium moiety [1-3]. The objective of this work was to evaluate the activity of new antibacterials incorporating a FQ drug and a quaternary ammonium moiety to confirm the hypothesis that a new class of agents exhibits an unique dual mechanism of action: destabilization of bacterial membrane structures due to the presence of quaternary nitrogen atom and inhibition of bacterial type II topoisomerases elicited by FQ portion.

The novel synthesized FQ derivatives were characterized by IR, MS, NMR, X-ray, and elemental analysis. The compounds were screened *in vitro* for their antibacterial activity against a panel of microorganisms including Gram-positive and Gram-negative bacteria. The most active derivatives exhibited MICs in the low micro- and nanomolar range towards MRSA, VRE, as well as pathogens from the ESKAPE group. Furthermore, they presented a promising inhibition effect against *S. aureus* biofilms. The molecular docking experiments revealed that all the antibacterial agents can interact at bacterial type II topoisomerases active sites in the FQ-binding mode.

The Project was financed by the Polish National Agency for Academic Exchange as part of the Bekker Scholarship Programme and Medical University of Gdańsk subsidies.

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P16 ORGANO-GOLD CATALYSIS

FOR ASYMMETRIC OR SILVER-FREE ALKYNE ACTIVATION

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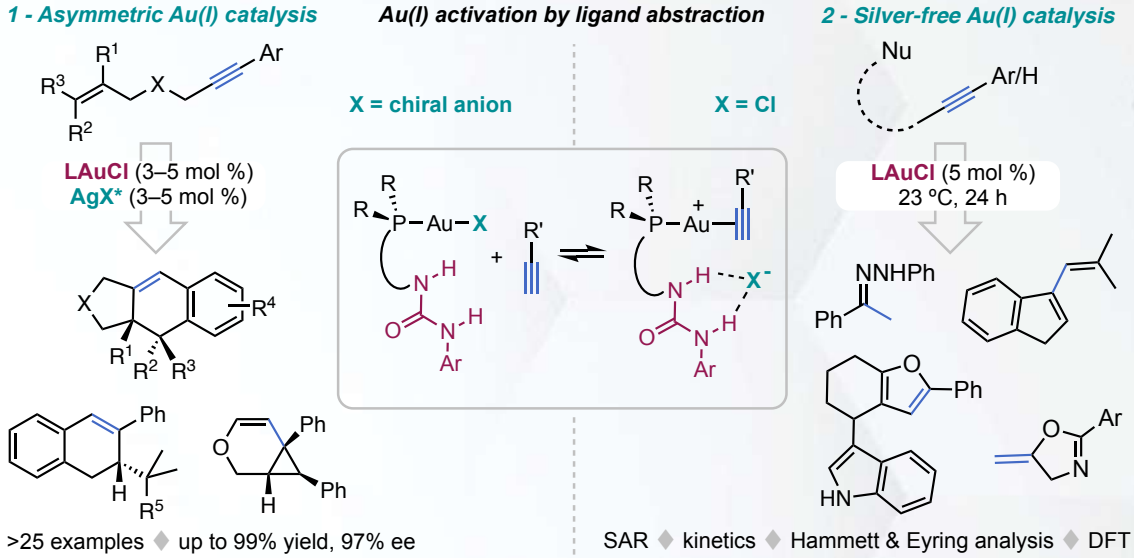
Keywords: *Gold catalysis, alkynes, bifunctional ligands*

We report on Au(I) complexes with H-bond donors tethered on phosphine ligands for carbo- and heterocyclizations of alkynes. Thanks to their H-bonding ability, these complexes contribute to the solution of two long-standing issues in gold catalysis [1]:

1 - The realization of challenging Au(I)-catalyzed enantioselective transformations of alkynes by placing the chiral information on the counterion [2]. This strategy is demonstrated for various asymmetric 1,6-enyne cycloisomerizations, enabled by a conceptually new H-bonded chiral anion approach [3] (Figure, left).

2 - The necessity of a silver co-catalyst, which has the drawback of mandating the use of an additional metal, while sometimes negatively impacting selectivity [4]. The new phosphinosquaramide and phosphinourea Au(I) chloride complexes display good activity in both intra- and intermolecular reactions [5] (Figure, right). Extensive kinetic studies, aided by DFT calculations, allow to draw the silver-free catalytic cycle.



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P17 SYNTHESIS AND CYTOTOXIC EVALUATION OF BENZYL ANILINES AS POTENTIAL ANTIMITOTIC AGENTS

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Keywords: *tubulin, microtubule, colchicine, combretastatin.*

Colchicine binding site is one of the pockets in tubulin as a target, which is a key component of the mitotic spindle. Ligands which interact in this area disrupt the dynamic polymerization of tubulin and destabilize the microtubules. This effect leads the mitosis to an arrest state and induces cell apoptosis, which can be applied for cancer treatement.[1] Combretastatins are examples of colchicine binding site ligands and combretastatin A-4 (CA4) is usually selected as reference due to its activity profile.[2]

Colchicine binding site is formed by 3 binding sub-pockets, but only two of them are occupied by the CA4 in its interaction. Trimethoxyphenyl ring (A ring) binds to the zone 2 while 3-hydroxy-4-methoxyphenyl ring (B ring) binds in the zone 1, both mainly formed by hydrophobic aminoacids.[1] These two rings are connected by an olefin bridge with *cisoid* configuration, which is necessary for the activity. Unfortunately, CA4 isomerizes to the *transoid* disposition and presents low aqueous solubility.[2]

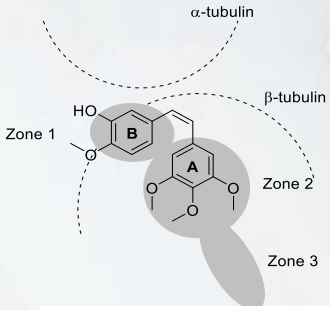

Figure 1: Zones in the colchicine binding site and

For this reason, this project is focused on exploring a methylamine group as a bridge which could improve aqueous solubility. This scaffold solves the problem of the configuration because presents free rotation. The *cisoid* disposition will be adopted in the binding site to make favourable interactions. In order to study the influence of the methylamino bridge orientation, compounds with the A ring on both sides were synthesized. Cytotoxicity against HeLa cancer cell line were performed to evaluate the effect of different patterns of methoxylated phenyls and the new methylamino bridge.

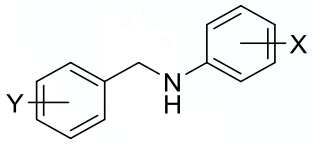

Figure 2: Common scaffold of the synthetic compounds.

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P18 COMPUTER-GUIDED SCAFFOLD HOPPING APPROACH BY INCORPORATING NITROGEN ATOMS IN THE PYRROLO[1,2-α]QUINOXALINE CORE: TOWARDS NEW ANTIDIABETIC DRUGS

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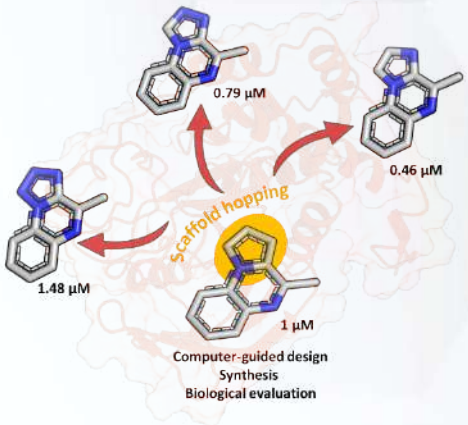
Keywords: *PTP1B, scaffold hopping, molecular modelling, heterocycle.*

Protein tyrosine phosphatase 1B (PTP1B) is a very promising target for the treatment of metabolic disorders, especially type II diabetes mellitus. Although it was validated as a promising target for this disease there is no drug in advanced clinical trials. In the present work, based on our experience generating PTP1B inhibitors, we have developed and implemented a scaffold hopping approach to vary the pyrrole ring of the pyrrolo[1,2-*a*]quinoxaline core [1]. Using a combination of docking, molecular dynamics and end-point free-energy calculations, we have rationally designed a hypothesis for new PTP1B inhibitors, supporting their recognition mechanism at a molecular level. After the design phase, we were able to easily synthesize proposed candidates and their evaluation against PTP1B was found to be in good concordance with our predictions in terms of IC_{50}. Moreover, best candidates exhibited glucose uptake increments *in cellulo* modell, thus confirming their utility for PTP1B inhibition and validating this approach for inhibitors design and molecules thus obtained.



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P19 A FIBRIN-FILAGGRIN CHIMERIC HOMOCITRULLINATED PEPTIDE AS A NOVEL ANTIGEN TO DETECT THE PRESENCE OF ANTI-CARP IN RHEUMATIC PATIENTS

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Keywords: *Peptide, homocitrulline, anti-CarP, rheumatoid arthritis, palindromic rheumatism*

Palindromic rheumatism (PR) is an intermittent form of arthritis that may progress to rheumatoid arthritis (RA) in a significant proportion of patients. The presence of the most relevant serological marker in RA and a hallmark of the disease, the anti-citrullinated protein/peptide antibodies (ACPAs) [1], has also been confirmed in PR patients [2]. However, the response against this modification is more restricted and it has less isotype usage. Other modifications in proteins that induce an immune response have also been described in RA, the most relevant being homocitrullination (carbamylation), acetylation and MAA-protein adducts (malondialdehyde-acetaldehyde-adducts) [3,4]. Specific antibodies against carbamylated peptides/proteins, known as anti-CarP, have been found in 10-20% of patients previously considered ACPA negative.

Considering this, and with the aim to further characterize the immune response in PR patients, we comparatively analysed the presence of two anti-CarP specificities in the sera of PR and RA patients (n=54). We designed and synthesized by solid phase synthesis a chimeric peptide derived from the fibrin and filaggrin proteins in its completely homocitrullinated (CFFHP) form as well as a non-homocitrullinated version as a specificity control, and used them in home-made ELISA assays to detect anti-CarP. We also worked with a protein antigen, fetal calf serum (FCS), using both the carbamylated and non-carbamylated form with the same objective. Our results confirmed the presence of anti-CarP in PR patients, nonetheless in fewer cases (24% of positivity in PR vs 64% in RA) and with a smaller proportion of isotypes as well as lower titers of antibodies [5].

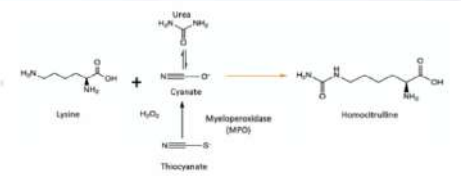

Figure 1: Illustration of protein carbamylation, a post-translational modification occurring on lysines.

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P20 BIOMASS DERIVED FURANIC PLATFORMS IN A DIVERSITY-ORIENTED SYNTHESIS STRATEGY

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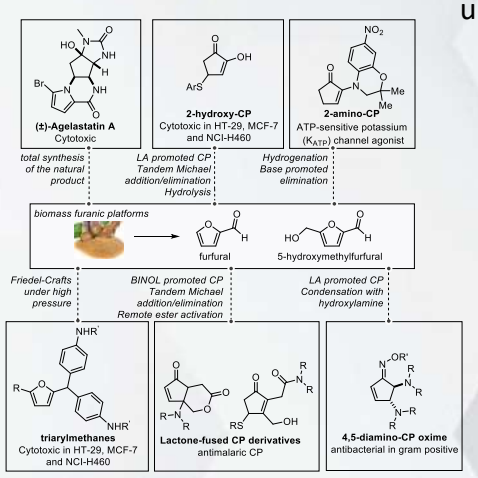
Keywords: biomass; furanic platforms; DOS; anticancer; antimicrobial

The modification of simple synthons to structurally complex scaffolds has been a cornerstone of drug discovery and is the foundation of how nature designs biological relevant compounds.[1] This diversity-oriented synthesis (DOS) strategy has emerged on drug discovery programs to increase structural diversity to discover new targets.

On the other hand, biomass synthons are looked upon has the solution for sustainability issues that plague the common bulk chemicals derived from oil.[2] Therefore the transformation of biomass synthons to relevant scaffolds is of importance to develop sustainable and cheap drug products. In this work is described a reagent-based DOS strategy, focused on the creation of complex scaffolds from biomass derived furanic platforms. These novel scaffolds exhibit relevant cytotoxic activity, antibacterial activity and antimalarial activity. [3]



Acknowledgements

We thank the Fundação para a Ciência e a Tecnologia (PD/BD/143127/2019, PTDC/QUI-QOR/32008/2017 and UID/QUI/50006/2019), COMPETE Programme (SAICTPAC/0019/2015). The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951996.

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P21 DESIGN OF NOVEL CDC20 INHIBITORS USING SCAFFOLD HOPPING

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Keywords: *cancer, Cdc20, apcin, virtual screening, scaffold hopping*

Cancer is recognized as one of the main leading causes of death worldwide. Among all the processes involved in the cell cycle, mitogenic signal transduction, has turned out to be one of the most appealing research targets for oncology in recent years. The Anaphase Promoting Complex (APC/C) is in charge of cell cycle progression mainly from metaphase to anaphase and it is closely associated to cancer progression [1]. The structure of the complex was recently elucidated by cryo-EM (PDB: 5G05) [2], solving the issues regarding to its complexity and taking a closer look to the interaction between the co-receptor Cdc20 and the APC/C. It has been previously demonstrated that Cdc20 down-regulation takes place in low-grade tumors and Cdc20 over-expression is connected to glioblastomas in patients. The inhibition of Cdc20 has become a therapeutic target due to its oncogenic function [1]. 3D structure of the Cdc20-Apcin complex (PDB: 4N14) suggests that apcin blocks mitotic exit synergistically amplified by co-addition of proTAME, which blocks the APC/C-Cdc20 interactions.

In this context, we aim to identify novel potent s small molecules that could inhibit Cdc20.

For this study, the apcin molecule has been used as a structural basis for the computational design of Cdc20 antagonists. Using a fragment-based replacement scaffold hopping approach on three different moieties (highlighted in Figure 1) a library of over 86000 cores was screened. The resulting structures with the new cores were filtered upon core overlapping and glide docking scores through extra precision virtual screening. *In silico* ADME properties and the absence of promiscuous moieties (the so-called Pan Assay Interference Compounds or PAINS) were also considered in the drug design process. This allowed us to select novel promising chemotypes that will be synthesized and tested in future work.

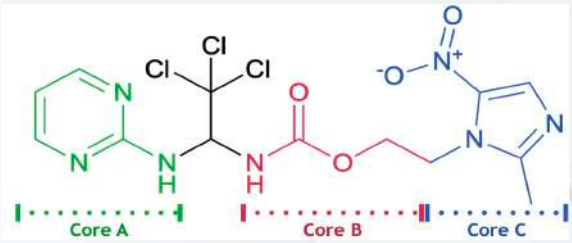

Figure 1. The three apcin cores that have been investigated through scaffold hopping techniques. Core A is represented in green, core B is in red and core C is in blue.

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P22 POLYAROMATIC N-HETEROCYCLES FROM ANILINES AND DIOLS

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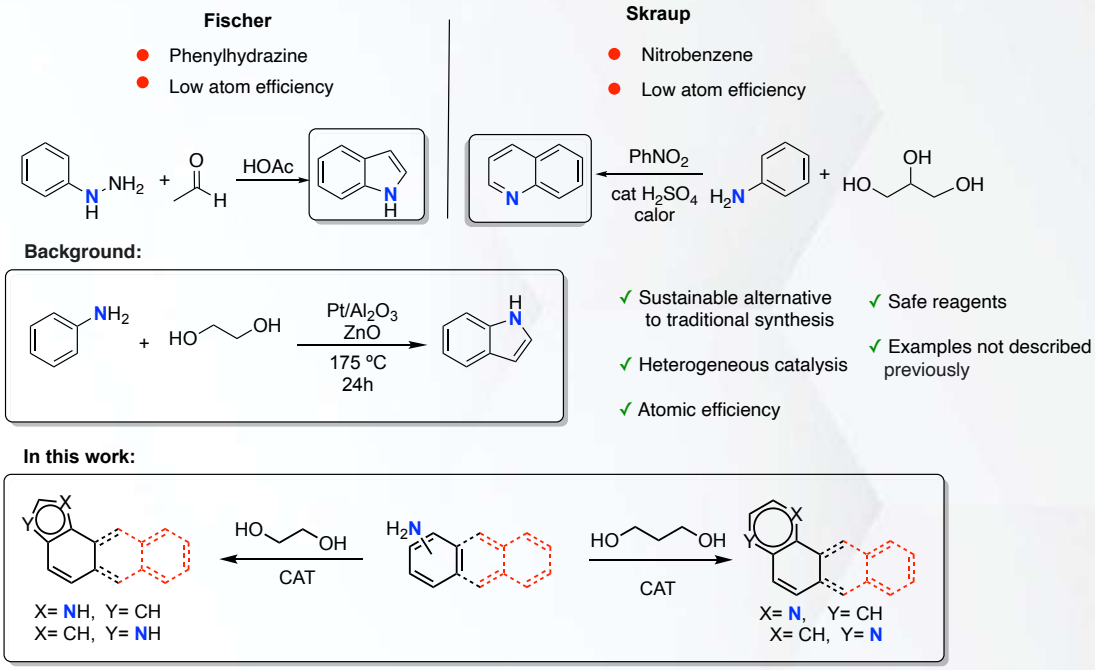
According to the Food and Drug Administration (FDA) database, approximately 60% of small molecule drugs contain at least one nitrogen heterocycle. Among these scaffolds, indoles can be found in many natural products, such as tryptophan and serotonin. On the other hand, quinoline is found in quinine, in many quinoline alkaloids, and in antimalarial drugs. In general, reported traditional protocols to obtain these compounds have important drawbacks, especially considering the principles of green chemistry. For this reason, our research group focused the obtention of these structures by means of heterogeneous catalytic hydrogen autotransfer methodology, where the only by-products of the reaction are water and hydrogen. This method allows the use of easily-accessible reagents, such as anilines and diols.

Herein we employ this green approach for the preparation of polyaromatic heterocycles which may have relevant applications as fluorescent sensors and materials science. 1- and 2-aminonaphthalene and 1- and 2-aminoanthracy have employed to obtain benzo condensated indole derivatives and even benzo quinoline derivatives.



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P23 AMINO-OPES FUNCTIONALIZED WITH CARBOHYDRATES AS BIOCOMPATIBLE PHOTOSENSITIZING AGENTS IN PDT

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Keywords: *OPEs, Photosensitizers, Photodynamic Therapy, HeLa, HaCaT, Blue light*

Photodynamic therapy (PDT) is a minimally invasive therapeutic modality that can provide selective removal of neoplastic cells by the combined effect of three non-toxic elements, a photosensitizer, light and oxygen [1].

Oligo(phenylene-ethynylene)s (OPEs) are luminescent linear oligomers with extended conjugated aromatic and ethynylenic moieties. Due to their photophysical and electronic properties, OPEs have found application as sensing or electronic organic devices [2-3]. Herein, new amino oligo(phenylene-ethynylene)s (OPEs), bearing hydrophilic sugar terminations (glucose, mannose, maltose and galactose), have been prepared, characterized and tested as photosensitizers under blue light, using two epithelial cell lines, HeLa (cervical carcinoma) and HaCaT (epidermal keratinocytes). All the compounds were able to easily cross the cell membrane and localize in intracellular organelles (Fig.1). In addition, cell death was induced after illumination with blue light, at very low concentrations (up to 3µM) and low light doses (less than 10 min). The photophysical properties of OPEs, such as high quantum yield, stability, singlet oxygen production, biocompatibility, easy cell-internalization and very good response even at low concentration, make them promising photosensitizers in the application of PDT.

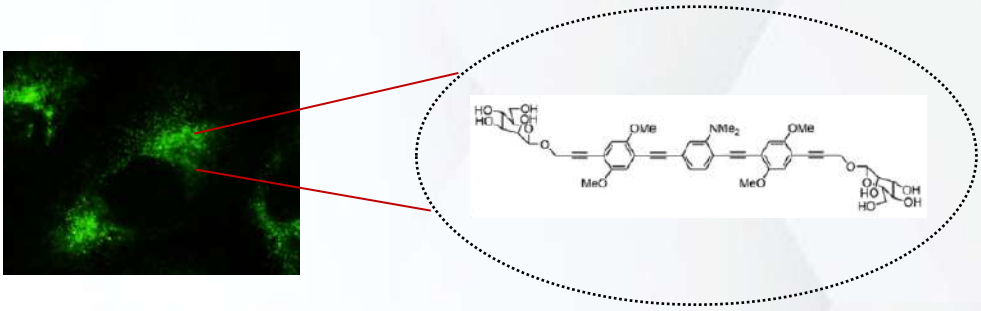

Figure 1. Fluorescence microscopy images of HaCaT cells under blue light with OPE-Mannose.

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P24 SUSTAINABLE SYNTHESIS OF NEW ANTIPROLIFERATIVE DRUGS

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Keywords: *Green Chemistry, green metrics, APIs*

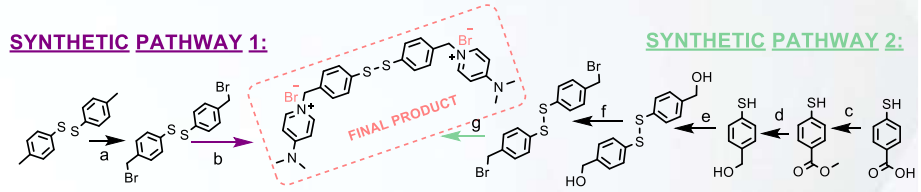
In recent years, the demanding change of chemical processes towards more environmentally benign transformations that reduce the use of hazardous reagents and solvents has become a priority to accomplish the target of sustainability. [1]

The pharmaceutical sector is one of the most polluting ones because of the use of multi-step synthesis to produce low quantities of APIs. For that reason, the establishment of new chemical pathways for the synthesis of pharmaceutical ingredients becomes a challenge, that should be addressed from the beginning applying a green by design approach.

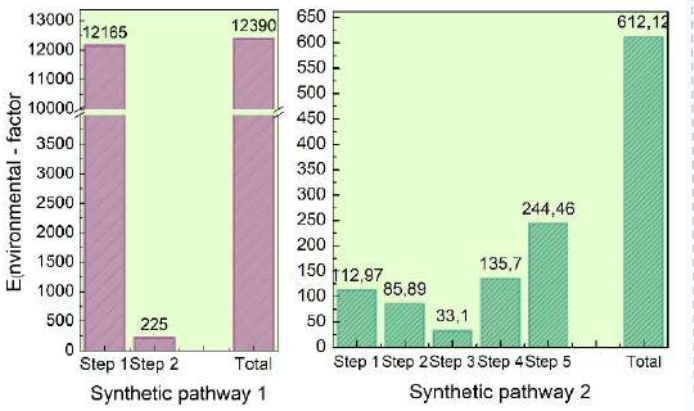
Herein we report the comparison of two synthetic pathways for the synthesis of new antiproliferative drugs that act as inhibitors of the enzyme Choline Kinase. The first one is based on a traditional retrosynthetic methodology while the second synthesis was performed taking into account the Principles of Green Chemistry.

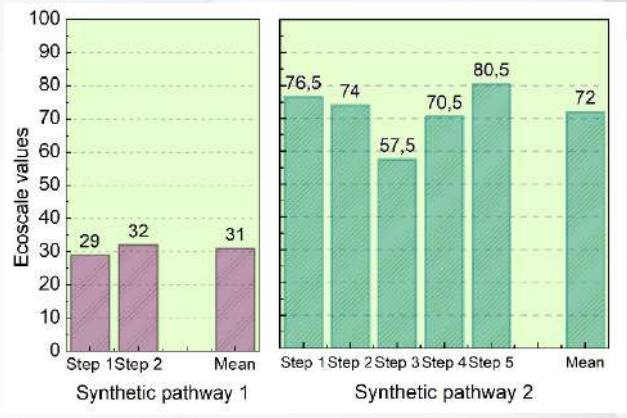
Finally, to evaluate the "greenness" of both protocols we determined the E(Environmental) factor [2] that measures the quantity of waste per unit of product and, employing the free software EcoScale, we analyzed the energy usage and hazard of reagents.

We satisfactory disclosed that synthetic pathway 2 produces 20 times less waste than synthetic pathway 1 and that there is a 40% improvement in the choice of environmentally benign reagents and reaction conditions.



a. Radical bromination and chromatographic purification.
b. Nucleophilic substitution.
c. Esterification.
d. Reduction.
e. Dimerization.
f. Nucleophilic bromination.
g. Nucleophilic substitution.





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P25 LIGAND AND STRUCTURE-BASED VIRTUAL SCREENING TOWARD IDENTIFYING NEW POTENT INHIBITORS AGAINST SGK1

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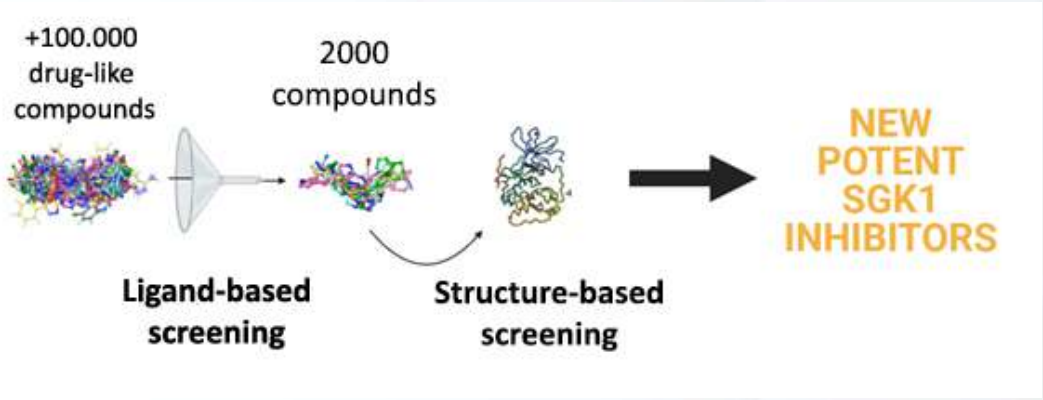
Keywords: *SGK1, Alzheimer´s disease, virtual screening*

Alzheimer´s Disease (AD) is a devastating neurodegenerative disease characterized by memory impairment and cognitive defects which are typically caused by the loss of cortical and hippocampal neurons [1]. As for other neurodegenerative disorders, there is no current effective treatment, and the etiology is far from being deciphered despite the increasing efforts over the last decades. AD main features are (i) the deposit of β-amyloid in the extracellular space and (ii) the formation of neurofibrillary tangles inside neurons due to the abnormal aggregation of tau protein [2]. Since tau hyper-phosphorylation and its consequent imbalance are clearly involved in its aggregation, protein kinases represent new targets of great interest against this disease. Among them, serum and glucocorticoid-regulated kinase 1 (SGK1) is a novel kinase that may be involved in several neurodegeneration-related pathways such as neuro-inflammation, autophagy and apoptosis [3,4]. In this work, a high-throughput virtual screening of structurally diverse compounds whitin a library of more than 100,000 drug-like ligands was performed. The successful combination of both ligand and structure-based methods led to the discovery of several potent and structurally diverse SGK1 inhibitors with IC50 values ranging from low micromolar to low nanomolar. These compounds are currently being tested in several *in vitro* AD models and preliminary results reveal that SGK1 inhibitors are able to recover the cell viability from the toxic effect of okadaic acid, a widely used AD *in vitro* model.



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P26 TOWARDS MORE POTENT SYMMETRICAL TRIAZOLE-PHENYL-THIAZOLE ANALOGUES AS DIMERIZATION DISRUPTORS OF TRYPANOTHIONE REDUCTASE

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Keywords: *Leishmania, Trypanothione reductase, Pd-catalyzed C-O cross-coupling*

Leishmaniasis is an important parasitic disease that affects 12 million people all over the world, being prevalent in tropical and subtropical areas. The research for more effective and innovative antileishmanial drugs is urgently needed. Trypanothione Reductase (TryR) is an attractive validated drug target because this enzyme is exclusive and essential for antioxidant defense of these parasites. In our group we have devised an alternative inhibition strategy by disruption of the homodimeric interface of the *Leishmania infantum* TryR (*Li*TryR).[1] Proof-of-concept of this novel approach was performed by using peptides and peptidomimetics that mimic "hot-spots" at the interface.[2] In the search of nonpeptidic *Li*TryR dimerization inhibitors,[3] we recently described efficient dimerization disruptors based on monomeric and symmetrical 1,2,3-triazole-phenyl-thiazole analogues.[4] Molecular modeling studies identified a so-far unexplored druggable binding site at the central interfacial cavity for these inhibitors. We herein report the design and synthesis of novel symmetrical triazole-based compounds of general formula **I** (Figure). Modifications at the phenyl linker were designed to target a hydrophobic subpocket at the bottom of the cavity. The key step of the synthetic route involves a palladium-catalyzed C-O cross-coupling reaction of aryl bromides with primary alcohols. Optimization conditions of this reaction will be described in detail.

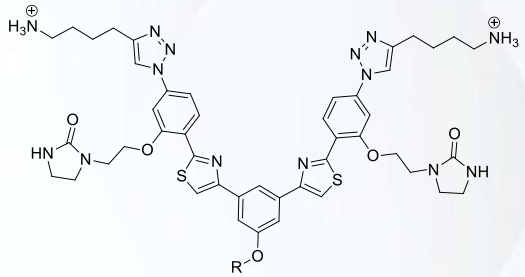

Figure. Target symmetrical triazole compounds **I**.

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P27 ORGANOPHOTOCATALYTIC LATE-STAGE OXIDATION OF *N*-METHYL ALKYLAMINES IN A GAS-LIQUID FLOW PHOTOREACTOR

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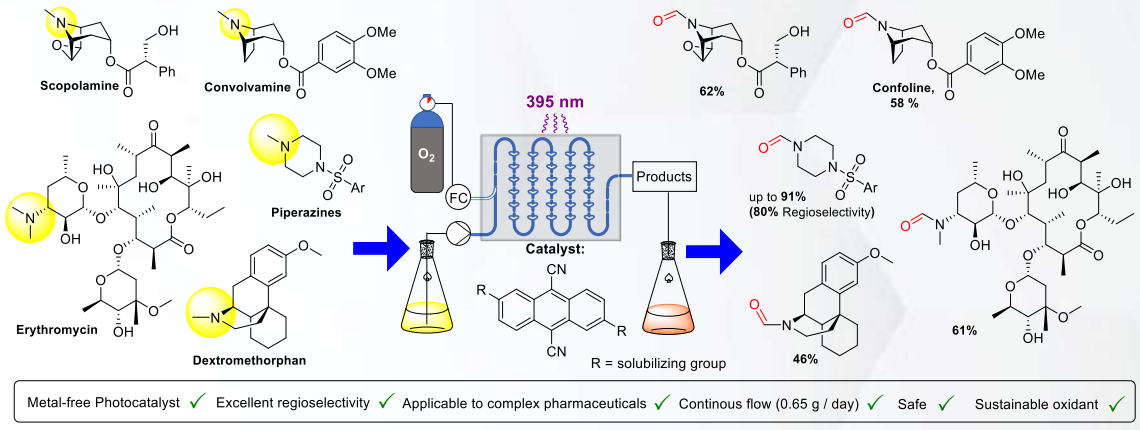
Keywords: (*Photocatalysis, Singlet Oxygen, Tropanoids, N-formyl, Flow chemistry*)

Direct access to *N*-formyl groups from tertiary amines is typically achieved by transition metal[1] or carbene reagents[2]. However, these reagents are either incompatible with redox sensitive functionalities that are ubiquitous in alkaloids and pharmaceuticals, or are used in excess. Direct use of molecular oxygen is a more benign and sustainable alternative, but issues of O_2 solubility in typical organic solvents and safety remain challenges in its applicability[3]. Herein, we report a gas-liquid flow photocatalytic selective oxidation of *N*-methyl groups of alkylamines using a novel, modified 9,10-dicyanoanthracene (DCA) organophotocatalyst. Back-pressure promoted O_2 solubility while the small (2.7 mL) continuous reacting volume at any time allowed safe handling of O_2. Electron-withdrawing and solubilizing 2,6-substituents on the catalyst benefited the chemistry by: i) increasing catalyst solubility in polar aprotic media; ii) promoting an $^1O_2$ sensitization mechanism vs. parent DCA. A range of *N*-methyl alkylamine natural products, drug molecules and API fragments were transformed into *N*-formyl products in moderate to very good yields with excellent selectivities (vs. *N*-CH_2 positions). Functional groups such as alcohols, epoxides, and esters were tolerated. Productivities of up to 0.65 g / day were achieved, and the synthesis of Confoline was demonstrated.



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P28 SYNTHESIS AND EVALUATION OF NOVEL NAPHTHALENE SULFONAMIDES ANTIMITOTIC

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Keywords: *Cancer, Tubulin, CA-4, Naphthalene, Sulfonamide*

Tubulin forms the mitotic spindle which plays a vital role in mitosis and therefore tubulin-binding drugs are promising chemotherapeutic agents. Combretastatin A-4 (CA-4), one of the best known tubulin ligands, shows potent cytotoxic effects inhibiting tubulin polymerization by binding at the colchicine site of tubulin [1].

We have synthesized a new family of naphthalene sulfonamides based on the structures of CA-4 and naphthylcombretastatin (Figure 1):

a) We replaced the B ring of CA-4 by a naphthalene, which showed good activity in previous works [1] [2];

b) The olefinic bridge was replaced by a sulfonamide bridge with different substituents on the nitrogen atom: secondary and tertiary sulfonamides are known to be inhibitors of multiple kinases or tubulin inhibitors binding to the colchicine domain [3]

c) We carried out modifications on the methoxy group substitution pattern in order to explore the structure–activity relationships (SAR) of these moieties.

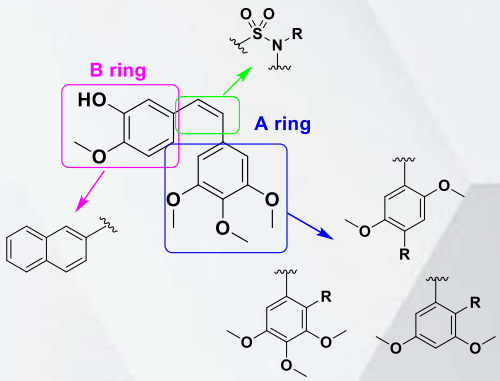

Figure 1: Structure of CA-4 and our aimed modification scheme

Cytotoxicity studies against HeLa cells were carried out using the MTT/XTT method. IC_{50} of the best molecules showed sub-micromolar values. Results of synthesis and cytotoxicity will be presented and discussed.

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P29 STRUCTURAL CHARACTERISTICS OF THE BINDING MODE OF A SERIES OF MMP13 INHIBITORS

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Keywords: MMP13, metalloproteinases, Molecular Modeling, Docking

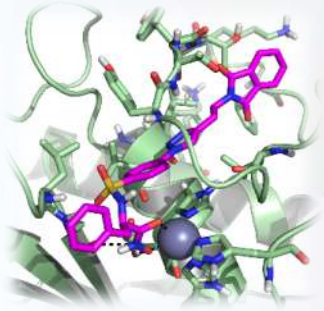
MMPs are a large family of Zn-dependent metalloenzymes that catalyze the degradation of several extracellular matrix proteins, such as gelatins, collagens and proteoglycans amongst others.[1] The implication of these family members in the development of different types of cancers, neurodegenerative, cardiovascular and inflammatory diseases has been reported, so their inhibition has reached an important relevance in Drug Discovery.[2]

The selective MMP inhibition is decisive since pan-MMP inhibitors have been associated with the development of the musculoskeletal syndrome (MSS) as a critical adverse effect.[3] To achieve selectivity, the researchers rely on the structural differences of the MMP family members, specially on the size of the S1' pocket delimited by the Ω-loop.

In fact, this difference is one of the criteria used for the classification of the MMP family: small loop (MMPs 1,7,11 and 20), medium loop (MMPs 2,8,9,12,14 and 16) and large loop (MMPs 3,10 and 13).[4]

Our research group has focused on the design and synthesis of selective MMP2 and MMP13 inhibitors as feasible candidates for cancer and osteoarthritis treatments.[4,5,6]

Here we present the most plausible binding modes of a series of benzotriazole and phthalimide based MMP13 inhibitors using Induced Fit Docking methods. With this aim, we have selected several crystal structures, which differ in their Ω-loop conformation, to explore how the plasticity of the loop affects the selectivity of the designed MMP13 inhibitors.



Acknowledgements: Financial support from RTI2018-093539-B-I00 *(MICIU/FEDER, UE) is kindly acknowledged. Laura Márquez-Cantudo thanks Universidad San Pablo CEU and Banco Santander for a Young Researcher contract.*

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P30 VIRTUAL SCREENING-BASED DISCOVERY OF A NOVEL LEAD WITH *IN VIVO* EFFICACY IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

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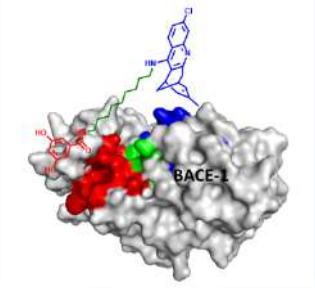
Keywords: *multitarget agents*, *BACE-1*, *virtual screening*, *SAMP8 mice*, *hybrids*

Molecular hybridization of a virtual screening hit with potential affinity for a cryptic pocket of BACE-1 [1,2], at the edge of the catalytic cleft, and the anticholinesterase huprine Y has led to the new anti-Alzheimer lead KPM150 with i) multitarget *in vitro* profile, including inhibition of human BACE-1 (arising from dual site binding), cholinesterases, and Aβ42 and tau aggregation; ii) *in vitro* brain permeability; iii) lack of neurotoxicity (HT-22 cells) and acute toxicity (zebrafish embryos); and iv) cognition-enhancing and disease-modifying effects in a mouse model of Alzheimer's disease (SAMP8 mice) after chronic oral treatment at a dose of 2 mg/kg/day.



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P31 2-(PIPERIDIN-4-YL)ACETAMIDES AS POTENT INHIBITORS OF SOLUBLE EPOXIDE HYDROLASE

J. Martín-López[1], S. Codony[1], C. Morisseau[2], M.I. Loza[3], C. Bartra[4], C. Sanfeliu[4], B.D. Hammock[2], J. Brea[3], and S. Vázquez[1]

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Keywords: *Benzohomoadamantane; DMPK properties; piperidine; soluble epoxide hydrolase; urea; amide.*

The pharmacological inhibition of soluble epoxide hydrolase (sEH) has been suggested as a potential therapy for the treatment of pain and inflammatory diseases. Numerous potent sEH inhibitors (sEHI) have been developed, mainly ureas containing highly lipophilic substituents.[1,2]

Recently, we reported a new series of benzohomoadamantane-based ureas endowed with potent inhibitory activity of the human and murine sEH.[3] However, their high melting points and very low microsomal stability prevented further development. Substitution of the urea moiety by an amide group might increase their microsomal stability, solubility and might low their melting points.

In this work, a new series of benzohomoadamantane-based amides were designed, synthetized, fully characterized and evaluated as sEHI inhibitors. Afterwards, DMPK evaluation was performed and one candidate endowed with excellent inhibitory potencies and lower melting point was selected and further evaluated *in vitro* for its anti-inflammatory properties.

This compound showed high efficacy as inhibitor of the nitric oxide pro-inflammatory pathway. Furthermore, it showed higher effectiveness than the reference compound TPPU. Overall, the results emphazise the significance of sEH as a druggable target in therapies involving inflammatory processes.

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P32 CYTOTOXIC BISCYCLOLIGNANS DERIVED FROM PODOPHYLLOTOXIN

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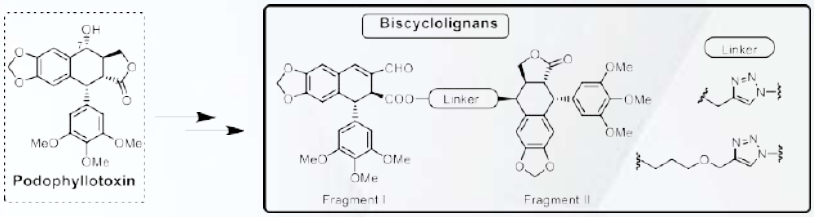
Key words: *biscyclolignans, podophyllotoxin, hybrids, cytotoxicity*

Podophyllotoxin is a natural occurring cyclolignan isolated from *Podophyllum sp*. that presents cytotoxic and antiviral properties. Chemical transformations performed on the cyclolignan skeleton led to the semisynthetic 7-*epi*-derivative etoposide, which is inclinical use as anticancer drug. Both compounds have different mechanism of action, while podophyllotoxin inhibits tubulin polymerization, etoposide, is an inhibitor of DNA-topoisomerase II [1].

Our group has been involved for several years in the chemical modifications of podophyllotoxin obtaining compounds with interesting cytotoxic results as podophyllic aldehyde, a non-lactonic derivative with improved cytotoxicity and selectivity. It sharesthe same mechanism of action as podophyllotoxin [2].

Molecular conjugation or hybridization is a useful tool widely used in Medicinal Chemistry to generate multifunctional compounds. Our group had already applied this strategy to cyclolignans [3]. Based on this strategy, now we have designed a new familyof hybrids, named biscyclolignans, that combines in a single molecule, the structure requirements to target both tubulin and Topo-II [4]. They are formed by two cyclolignan fragments, one derived from podophyllic aldehyde as tubulin polymerization inhibitor (fragment I) and the other from epipodophyllotoxin as Topo-II inhibitor (fragment II).



Both fragments were obtained from podophyllotoxin and connected through triazole linkers obtained by click chemistry. Their synthesis and evaluation of the cytotoxicityon several tumor cell lines is presented and discussed in this communication.

Acknowledgements: Financial support from Junta de Castilla y León, co-financed by Fondo Social Europeo (SA076P20) and from the University of Salamanca (PIC2-2020-13).

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P33 BINDING STUDIES OF PYRROLIDINES GLYCOMIMETIC TO POLYPEPTIDE N-ACETYLGALACTOSAMINYLTRANSFERASE 2.

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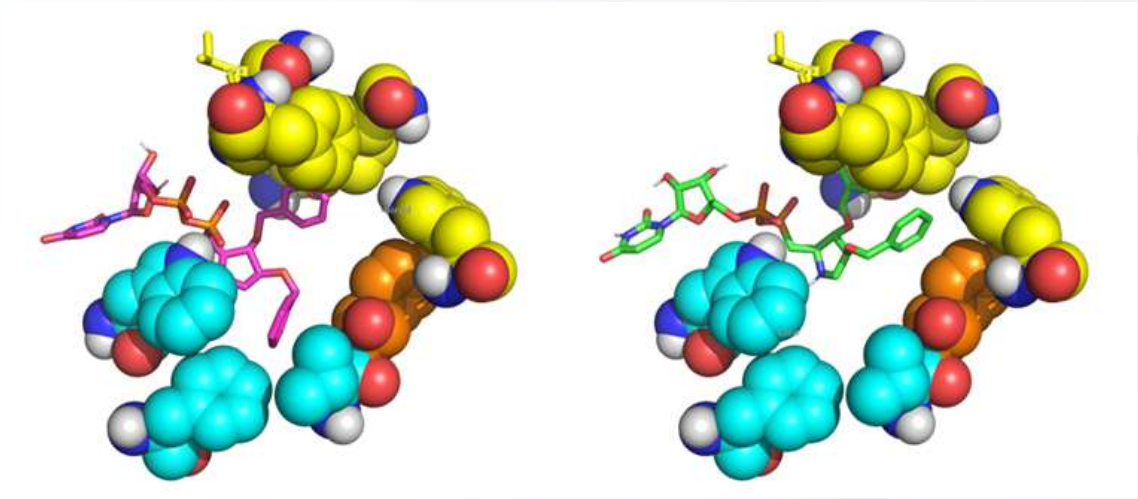
Keywords: *Glycosyltransferases, Pyrrolidines, Molecular Dynamics*

Glycosyltransferases (GTs) catalyse the biosynthesis of a new glycosidic linkage by transferring a monosaccharide from an activated sugar donor (UDP sugars) to an acceptor substrate. [1] Glycosylated compound directly exert a wide range of functions, including energy storage, maintenance of cell structural integrity, information storage and transfer, molecular recognition, cell–cell interaction, cellular regulation, immune response, virulence and chemical defence. [2] Only nine sugar donors are known to be involved in protein glycosylation in mammal organisms which is the most abundant post-translational modification in nature. Six of these sugar donors contain the uridine moiety that is in line with the existence of GTs employing UDP sugars as the most predominant in nature. Therefore, the design of inhibitors mimic UDP sugars could lead to the development of compounds with therapeutic applications. [3] In this work we will focus on the computational study of pyrrolidines as glycomimetic of the sugar donors.



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P34 MEASURING PROTEIN AGGREGATION IN LYMPHOBLASTS FROM ALS PATIENTS WITH A TURBIDOMETRIC ASSAY

C. Pérez de la Lastra[1], C. Tosat-Bitrián[1], V. Nozal[1], A. Martínez[1], A. Martín Requero[1], V. Palomo[1].

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Keywords: *ALS, Turbidimetry, lymphoblasts, drug candidates.*

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease characterized by the degeneration of upper motor neurons in the brain and lower motor neurons in the spinal cord, which are responsible for voluntary muscle movement. Due to the heterogeneity of the disease and the lack of biomarkers the diagnosis of the patients and pharmacological response is intricate. [1, 2]

Current experimental models do not reflect on this diversity, therefore a model consisting of samples extracted from patients is essential to characterize the pathology. Considering the degeneration in ALS is multisystem, an analysis of lymphoblasts from blood samples is proposed. [3, 4]

Here we have studied protein aggregation in healthy controls, sporadic and familiar patients, characterizing the pathological aggregation. We are observing that the proteinopathy aspect of sporadic ALS is manifested in this model. By turbidimetry measurements of protein extracts, a difference in the total amount of protein aggregation comparing patients with healthy controls is shown. Moreover, this methodology enables a rapid evaluation of promising drug candidates, and we show here how some of them are able to rescue the pathologic aggregation of the patients.

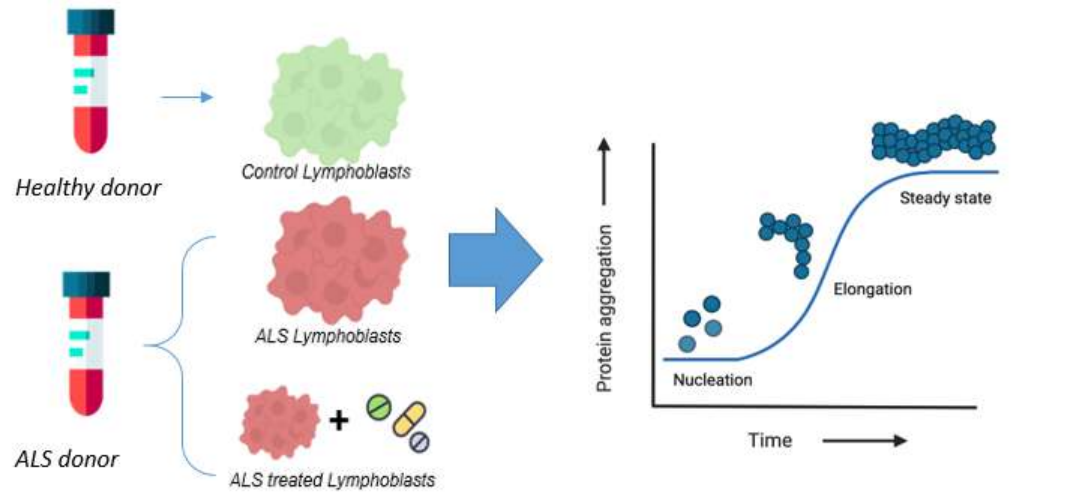

Figure 1. Scheme representing our project methodology and the process of protein aggregation over time with our lymphoblastic lines

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P35 PHOTOCHROMIC LIGANDS FOR IN VIVO MODULATION OF ADRENERGIC NEUROTRANSMISSION

D. Prischich[1,2], A. M. J. Gomila[1,2], S. Milla-Navarro[3], G. Sangüesa[4,5], R. Diez-Alarcia[6,7], B. Preda[1], C. Matera[1,2], M. Batlle[4,5], L. Ramírez[3], E. Giralt[8,9], J. Hernando[10], E. Guasch[4,5], J. J. Meana[6,7], P. de la Villa[3,11], P. Gorostiza[1,2,12]

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Keywords: *adrenergic receptors, azoheteroarenes, neurotransmitters, photochromism, photopharmacology*

Adrenoceptors are ubiquitous and regulate most vital functions in the human body, including heart and respiratory rate, digestion, smooth-muscle contraction, gland secretion, and pupil diameter among others. In addition, adrenergic neurons firing from the locus coeruleus towards different areas of the central nervous system mediate alertness, responses to acute stress and danger, pain modulation, arousal, sleep-wake cycles, as well as neuroplasticity and cognitive behaviour. Despite the physiological relevance of adrenergic neurotransmission, molecular methods to precisely modulate the activity of endogenous adrenoceptor and to functionally dissect their pathways *in vivo* are not available. Here we present a set of photochromic ligands, that we call adrenoswitches, to switch on and off adrenoceptor activity with high spatio-temporal resolution. Using a non canonical azologization approach, we have designed novel arylazoheteroarene units that we have characterized *in vitro* and in two animal models (zebrafish locomotion and pupillary reflex in mice). The drug-like properties of these molecules, their efficacy and absence of acute toxicity in zebrafish larvae, and most remarkably the fact that specific adrenergic photomodulation was readily and reversibly achieved in the mammalian eye by topical application without formulation, all indicate that adrenoswitches could be a disruptive tool to dissect physiological adrenergic signaling and to develop safe and effective therapies. For example, photocontrol of adrenoceptors at specific locations might allow to single out individual adrenergic projections from the locus coeruleus, or to selectively decouple pupil tone from environmental illumination.

P36 NEW DIARYLUREAS AS INDUCTORS OF FIBROBLAST GROWTH FACTOR 21 EXPRESSION FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS

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Keywords: *Diarylureas, FGF21, HRI, glucose intolerance, hepatic steatosis, proof of concept, T2DM.*

Type 2 Diabetes Mellitus (T2DM) has reached epidemic proportions. Unfortunately, current drugs are suboptimal and more effective therapies are required. Lately, the anti-diabetic hormone fibroblast growth factor 21 (FGF21) has been considered as an emerging therapeutic strategy for treating T2DM. This has led to the development of FGF21 long-acting analogs.[1] However, these compounds require subcutaneous injection and have shown some serious side effects. Therefore, there is a need for orally available approaches to enhance FGF21 native production.

We have previously demonstrated that activation of the Heme-Regulated eIF2α kinase (HRI) by intraperitoneal administration of some known *N,N'*-diarylureas increases FGF21 levels in liver, resulting in an improvement of glucose intolerance and hepatic steatosis in mice fed a high-fat diet (HFD).[2] These findings encouraged us to design and synthesize new *N,N'*-diarylureas suitable for oral administration, which have been evaluated in a human hepatocyte cell line in culture.[3] Further *in vitro* profiling and pharmacokinetics allowed us to select a candidate for *in vivo* efficacy studies. Overall, we demonstrated that our lead compound improves glucose intolerance, hepatic steatosis and hypertriglyceridemia in mice fed a HFD following oral administration.[4]

These results suggest that orally bioavailable HRI activators induce FGF21 production and may be of clinical interest for the treatment of T2DM.

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P37 HIGH YIELD SYNTHESIS OF TRANS-AZOXYBENZENE VERSUS 2-ISOPROPOXY-4-NITROBENZOIC 3 ACID

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Keywords: Azoxybenzene; ^{15}N NMR spectroscopy; infrared spectroscopy; 2-isopropoxy-4-nitrobenzoic acid; GIAO

During our project dedicated to the design of new dicationic compounds targeting kinetoplastid parasites, the synthesis of 2-isopropoxy-4-nitrobenzoic acid (**1**) was required. Our attempts to obtain **1** following the two-step synthesis reported earlier by Adler & Hamilton (*J. Org. Chem*. **2011**, 76, 7040) [1] from 2-hydroxy-4-nitrobenzoic acid, using iodopropane/K_2CO_3 and subsequent hydrolysis of the isopropyl 2-isopropoxy-4-nitrobenzoate intermediate with 45% NaOH/THF-EtOH at 80 °C were unsuccessful. (*Z*)-1,2-bis(4-carboxy-3-isopropoxyphenyl)diazene-1-oxide derivative (**3**), which was isolated as main product (92%) of the reaction, was characterized by IR, ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy. The ^{15}N chemical shifts were consistent with the trans-configuration for this azoxybenzene derivative. Hence, this synthetic protocol may be useful for the gram scale synthesis of 2-alkoxy-trans-azoxybenzene derivatives. As an alternative, synthesis of **1** acid was accomplished in high yield (82%) working at room temperature and using lithium hydroxide instead of concentrate NaOH.

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P38 TRIFUNCTIONAL NANOPARTICLE DESIGN TO RESCUE NEUROSYSTEM FAILURE CAUSED BY PROTEIN AGGREGATION (TRINADES)

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Keywords: *artificial proteases, Alzheimer's disease, protein aggregation*

Alzheimer's disease (AD) is the most prevalent form of dementia, with 50 million people affected around the world.[1] Aβ is one of the proteins involved in AD, which can misfold and form plaques that collect between neurons and disrupt cell function. To this day, an effective treatment against Aβ deposition has yet to be found.

With this challenge in mind, a trifunctional nanoparticle was designed to prevent the toxic effect of Aβ aggregation. Each nanoparticle is equipped with three elements: a selector, which binds to small neurotoxic Aβ oligomers; a breaker, which disrupts the existing β-sheet by dissociating its hydrogen bonds; an artificial protease, which cuts the absorbed protein molecules into smaller fragments, regenerating the original trifunctional state and therefore making the cycle catalytic.

With this approach, the trifunctional nanoparticle is turned into a **disaggregation nanomachine**, which may completely abolish the aggregation propensity of Aβ and rescue cell viability.

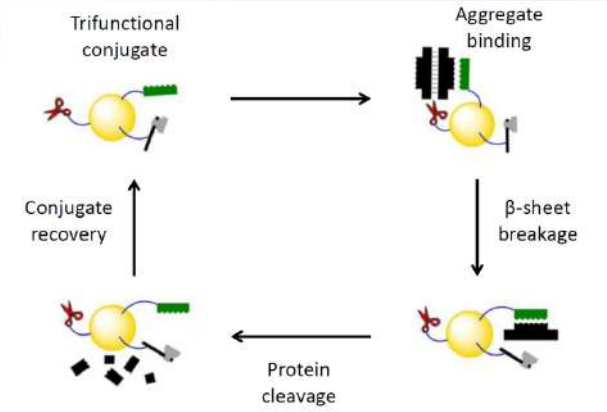

Figure 1. Aβ disaggregation machine.

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P39 SYNTHESIS OF 1,5-DISUBSTITUTED TRIAZOLE CERAMIDE ANALOGS AS POTENRIAL DES1 INHIBITORS

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Keywords: *sphingolipid ● ceramide ● GT11 ● Des1 ● triazole*

The view on dihydroceramides (dhCer), generally regarded to be innocuous, changed after the revelation that they might have regulatory roles in biology.[1] In this scenario, dihydroceramide desaturase 1 (Des1) stands out as a new therapeutic target as its inhibition would cause an accumulation of dhCer, leading to anti-cancerogenic effects.[2] GT11 is the first, and still the most effective, sphingolipid analogue Des1 inhibitor reported to date (Figure 1). The limited amount of Des1 inhibitors described until now, as well as the lack of a crystalline structure of the enzyme difficult the understanding of its inhibition mechanism. For this reason, the synthesis of new inhibitors could shed light on this area as well as in the biological pathways of action of dhCer.

We will present, in this communication, the syntheses of three ceramide analogues (Figure 1) and their biological evaluation as Des1 inhibitors. These analogues maintain all the structural requirements described until the date for the inhibition of Des1 [3] but incorporating the 1,5-disubstituted triazole unit in place of the of the ceramide double bond. This modification is envisioned to mimic the geometry of the cyclopropene moiety in GT11, although the heterocycle might as well stablish additional interactions with the enzyme active site.

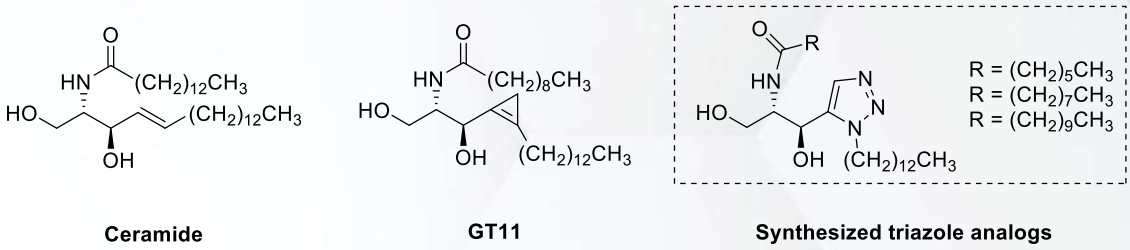

Figure 1. Structure of Ceramide, GT11 and triazole analogs synthesized.

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P40 BICYCLIC α-IMINOPHOSPHONATES: NEUROPROTECTIVE PROPERTIES OF A FAMILY OF NEW IMIDAZOLINE I_2 RECEPTOR LIGANDS

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Keywords: *I_2 receptors, bicyclic α-iminophosphonates, SAMP8, neuroprotection.*

I_2 receptors (I_2-IR) are widely distributed in the central nervous system. Their levels in neurodegeratives disorders, like Alzheimer Disease (AD), are elevated. I_2-IR structure remains unknown, the discovery of better and more selective I_2-IR ligands is necessary to build a comprehensive understanding of the pharmacological and molecular implications of I_2-IR. Recently, we described a new imidazoline-structure family which showed high affinity and selectivity for I_2-IR.[1] Further studies with a murine model of neurodegeneration, senescence-accelerated prone mouse (SAMP8), revealed beneficial effects in behaviour and cognition.[2]

Herein, we report a novel non-imidazoline-structure of bicyclic α-iminophosphonates family with high affinities for human brain I_2-IR. *In vivo* studies in 5X-FAD mice and SAMP8 mice showed an improvement in behaviour and cognition, a reduction of AD and of neuroinflammation markers for the mice treated with our lead compound **B06**. Furthermore, molecular analysis of SAMP8 mice treated with **B06** leaded us to describe the putative molecular mechanism. After evaluation of several pathways associated with neurodegeneration, we demonstrated CaN pathway as a critical role of the neuroprotective effects of I_2-IR ligands on SAMP8 mice model. In addition, we calculated DMPK and physicochemical properties in order to rule out warnings for the novel bicyclic α-iminophosphonates family. Drug metabolism and safety studies and in vivo pharmacokinetics for lead compound **B06** were as well performed.[3]

In summary, this highlights that the modulation of I_2-IR by bicyclic α-iminophosphonates may open a new therapeutic venue for unmet neurodegenerative conditions.

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P41 DESIGN AND SYNTHESIS OF MANNICH BASE-TYPE DERIVATIVES CONTAINING IMIDAZOLE AND BENZIMIDAZOLE AS LEAD COMPOUNDS FOR DRUG DISCOVERY IN CHAGAS DISEASE

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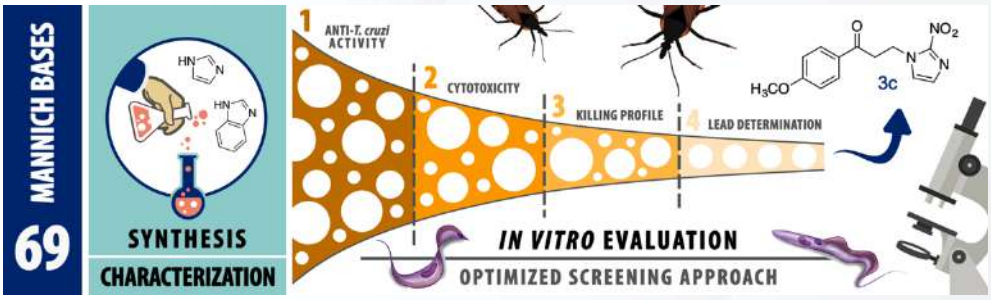
KEYWORDS: *Mannich bases, imidazole, benzimidazole, Chagas disease, neglected tropical diseases, Trypanosoma cruzi.*

ABSTRACT

The protozoan parasite *Trypanosoma cruzi* is the causative agent of Chagas Disease, the most important parasitic infection in Latin America. The only treatments currently available are nitro-derivative drugs that are characterised by high toxicity and limited efficacy. Therefore, there is an urgent need for more effective, less toxic therapeutic agents. We have previously identified the potential for Mannich [1,2] base derivatives as novel inhibitors of this parasite. To further explore this family of compounds, we synthesized a panel of 69 new analogues, based on multi-parametric structure-activity relationships, which allowed optimization of both anti-parasitic activity, physicochemical parameters and ADME properties. Additionally, we optimized our *in vitro* screening approaches against all three developmental forms of the parasite, allowing us to discard the least effective and trypanostatic derivatives at an early stage. We ultimately identified derivative **3c**, which demonstrated excellent trypanocidal properties; both its druggability and low-cost production make this compound a promising candidate for the preclinical, *in vivo* assays of the Chagas disease drug-discovery pipeline.



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P42 GRAFTING TEMPORIN L PEPTIDE: OLD TACTICS FOR NEW ANTIMICROBIAL WEAPONS

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Keywords: *Antimicrobial peptides (AMPs), Temporin L, cyclic peptides*

Antimicrobial peptides (AMPs) represent a valid chance to overcome and control the antibiotic resistance, since they act by a different mechanism of action from conventional antibiotics. Among AMPs the frog skin temporins are encouraging candidates in the development of novel antimicrobial agents.[1]

Previous solution state NMR studies revealed that Temporin L and synthetic analogues show a high helical content (>70%) responsible for their strong hemolytic activity, correlated to a "barrel stave" mechanism. [2] Moreover, they display an helical structure at C-terminus in SDS micelles which is crucial for their antibacterial activity.[3] Herein, we designed a library of constrained α-helical macrocyclic peptides analogues of Temporin L by incorporation of lactam, triazole, hydrocarbon, and disulfide bridge, to stabilize the helical conformation at the C-terminus and to investigate the impact of α-helical content on antimicrobial activity while preserving low hemolytic activities. The antimicrobial activities of all compounds were evaluated both on Gram-positive and Gram-negative strains, while the cytotoxicity and antibiofilm activities were evaluated only for the most active compounds. Helical contents of the most promising peptides were predicted by using CD spectra. The mechanism of action was investigated by performing fluorescence assays, and finally the proteases stability, due to the structural constrains, was assessed during human serum biostability assay.

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P43 IDENTIFICATION OF NOVEL HEPARANASE INHIBITORS USING VIRTUAL SCREENING

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Keywords: *heparanase, inhibitors, virtual screening, docking*

Heparanase is the only known mammalian endo-β-D-glucuronidase, it cleaves heparan sulphate (HS) side chains of heparin sulphate proteoglycans (HSPG), composed of repeating polysulfated disaccharide units of glucosamine and hexuronic acid residues. Heparanase controls the availability of growth factors, chemokines, lipoproteins and other bioactive molecules that interact with HS by degrading HS into smaller fractions and thus allowing the release of bioactive saccharide fragments that end up activating a plethora of signaling processes [1]. When overexpressed, heparanase has been correlated with tumor survival and metastasis as well as several diseases presenting chronic inflammation, COVID-19 being the latest of these diseases in which an overexpression of heparanase has been reported [2,3]. Thus, the search for molecules that could potentially inhibit this target has become increasingly relevant [1].

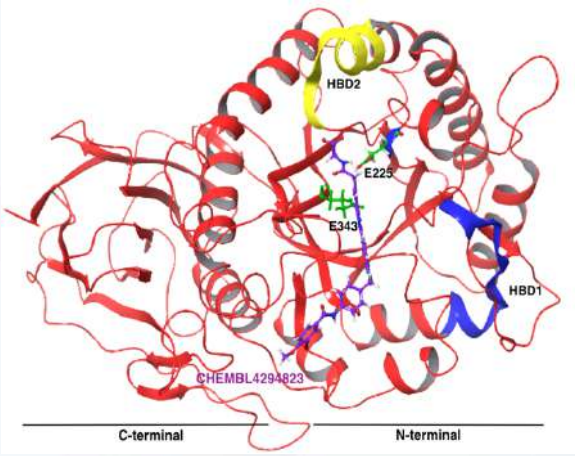

Figure 2. 3D structure of human heparanase (potential ligand CHEMBL4294823 included in purple). Catalytic residues Glu225 and Glu343 are highlighted in green. Heparin Binding Domain 1 can be seen in blue, and HBD-2 can be seen in yellow.

In this study, a 3D model of the human heparanase [4] based on the previously solved crystal (PDB: 5E9C) was firstly used to dock reported heparanase ligands. Key structural features were analyzed from the over 50 inhibitors selecting the most promising chemotypes, CHEMBL371702 and CHEMBL324065, as hits for further investigations. Chemical databases of compounds with structural similarity to each of these ligands (Tanimoto: 80%) were retrieved from PubChem. These two libraries of over 2500 molecules were virtually screened in other to identify more potent heparanase inhibitors. Extra precision Glide docking was performed for the top ranked molecules. Docking energies along with *drug-like* properties and lack of promiscuous moieties allowed us to select three promising hits that will be experimentally tested in the future.

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P44 NEW COMPOUNDS THAT INTERACT WITH TUBULIN AT THE COLCHICINE SITE

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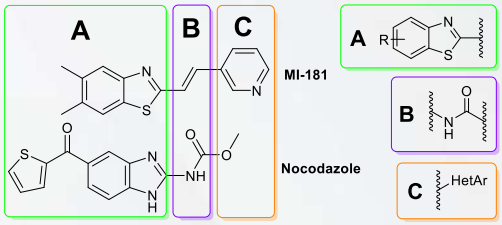
Keywords: tubulin, antimitotic, antitumoral, colchicine, MI-181, nocodazole, cancer

Tubulin is a frequently used target for the design of new antimitotic drugs. Tubulin binding drugs alter tubulin polymerization and depolymerization microtubule equilibrium, giving rise to antitumor, antiparasitic or herbicidal activities.

At least seven drugs binding sites are known for tubulin. The colchicine site is located at the interface between the α/β subunits, mainly formed by β-tubulin residues. The compounds that bind here cause the disruption of mitosis, leading to cell apoptosis. Combretastatin A-4 is a typical representative of colchicine site ligands. Other ligands with different binding modes have recently appeared that have stimulated the design of alternative scaffolds.

The main objective of the work is to find non-classical ligands that bind to the colchicine site and act as antitumor agents, taking as a reference the compounds MI-181 an nocodazole. To this ends, synthesis of compounds that contain a benzothiazole ring and an heteroaromatic ring connected by an amide bridge had been prepared.



After synthesis and purification, the antiproliferative activity against HeLa cell line has been evaluated and SAR studies have been carried out.

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P45 STYRYLQUINOLINE DERIVATIVES WITH EMBEDDED DICARBONYL BORON COMPLEXES AS POTENTIAL MULTITARGET THERANOSTIC COMPOUNDS AGAINST ALZHEIMER´S DISEASE

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Keywords: *Multitarget, Theranostic, Alzheimer´s Disease, Styrylquinoline.*

Neurodegenerative diseases are some of the most prevalent maladies worldwide. Even if they are caused by different types of disorders, protein misfolding is commonly found in several of them. Alterations in protein structure lead to activity failures, producing dysfunctions and anomalies. One of the most important neurodegenerative disease is Alzheimer´s Disease (AD), and since its development is directly correlated to ageing, it is expected to affect a rising amount of people in the future [1]. Even if its aetiology remains incompletely understood, it is known that protein misfolding plays a key role in it. These processes involve deposition of amyloid beta-peptide and hyperphosphorylated tau protein, but are not the only alterations present; oxidative stress, neuroinflammation, mitochondrial dysfunction and an imbalanced glutamatergic and cholinergic tone are known to have influence in the development of AD. Currently, there is no treatment for AD. Some drugs achieve a temporary amelioration of symptoms, but none of them addresses the cause nor cures the disease. For this reason, new alternatives are needed for the treatment of AD. One approach includes multitarget directed ligands which bind to different targets and regulate several pathways at the same time. This approach is particularly interesting for multifactorial diseases like AD. Additionally, theranostic compounds provide therapy and diagnostic information simultaneously. This allows assessment of the molecule activity, the organism response and the pharmacokinetics, and makes these compounds promising for personalized medicine.

Due to all of this, our research group is interested in combining both characteristics in new multitarget theranostic compounds against AD. On the basis of a common scaffold of styrylquinoline for its promising properties disclosed in our group [2], a novel family of molecules were found to exhibit remarkable properties, including inhibition of tau protein aggregation, neuroprotective and antioxidant activity [3]. Furthermore, beta amyloid detection was possible due to their fluorescence emission in the near-infrared range. In continuation of the push and pull strategy that worked in previous attempts, we describe the synthesis and characterization of new styrylquinoline derivatives bearing dicarbonyl moieities at quinoline C-6 position as well as their boron complexes.

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P46 PHOSPHORYLATED QUINOLINE DERIVATIVES AS TOP1 INHIBITORS

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Keywords: *TOP1 inhibition, Phosphorylated Quinolines, Antiproliferative, Antileishmanial*

The DNA damage induced by the inhibition of human nuclear topoisomerase I (hTOP1) has made this enzyme a broadly explored molecular target for cancer therapy, due to a detrimental effect on cellular survival after topoisomerase I (TOP1) poisoning [1]. Camptothecin (CPT) derivatives topotecan and irinotecan are hTOP1 inhibitors currently approved for antitumor treatment, and some other analogues are under clinical investigation. Nonetheless, the requirement to overcome several drawbacks of CPT analogues (such as structure instability in physiologic conditions, cancer cell resistance and toxic side effects) has opened the door to explore new families of hTOP1 inhibitors [2]. More recently, in an attempt of develop new drugs and strategies against infectious diseases related to cell proliferation, leishmanial TOP1 (LTOP1) has also been successfully screened as a druggable target for visceral leishmaniasis [3].

Quinoline scaffolds are structures of particular relevance in drugs with TOP1 inhibition-based mode of action [4]. Concerning this, our group has focused on the design and preparation of heterocyclic compounds as TOP1 inhibitors, including families of compounds with phosphorated moieties. Following with our previous work in the development of new TOP1 inhibitors, herein we report the synthesis and screening of small phosphorylated quinoline derivatives as TOP1 inhibitors (hTOP1 and LTOP1) with antiproliferative and/or antileishmanial activity.

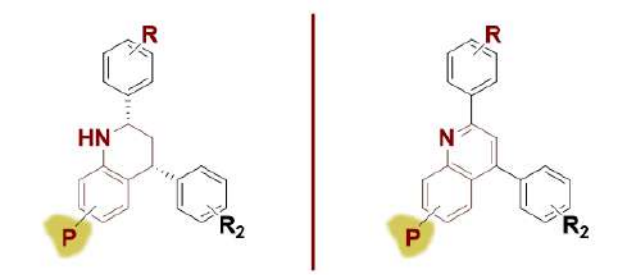

Figure 1. *General structures of phosphorylated quinoline derivatives*

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P47 BIOSENSORS AND CELLULAR MODELS DERIVED FROM PATIENTS: TOWARDS MOLECULAR CHARACTERIZATION AND PERSONALIZED MEDICINE

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Keywords: ALS, Drug Discovery, Quantum Dots, Personalized medicine

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by motor neuron (MN) death that yields in progressive paralysis. Currently, drug development is hampered due to the heterogeneity of the disease and the lack of knowledge of the mechanism triggering selective MN death.[1]

Molecular profiling is an innovative powerful technology for unravelling complex molecular pathways that underlie physiological and pathological processes. Quantum dots (QDs) are luminescent nanoparticles with a high potential to become promising tools to detect molecular mechanisms at the subcellular level enabling multiplexing applications.[2] Currently, a wide-number of QDs linked to different biomolecules of interest, including antibodies, are commercially available, enhancing their use as fluorescent probes.[3] Using this technology, different ALS targets will be analyzed at the single-cell level in human cell models such as immortalized lymphocytes derived from ALS patients.

The scientific aim of this project is to explore molecular changes in key protein targets upon pharmacological treatment to help select therapeutic candidates with a molecular pathology modulation. Our group holds already promising therapeutic candidates from the treatment of ALS, such as IGS2.7, a CK-1 inhibitor that has reached preclinical phases. The molecular modulation of IGS2.7, has been studied using these tools, alone and in combination with Riluzol, the only drug approved by the EMA for ALS treatment, showing promising results.

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P48 SYNTHESIS AND BIOLOGICAL EVALUATION OF PHOSPHORYLATED NOVEL INDENOQUINOLINES AS TOPI INHIBITORS

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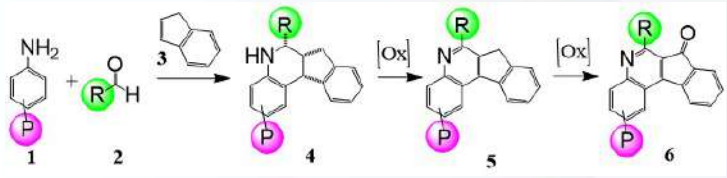
Keywords: *Phosphorylated quinolines, TopI inhibitors, Antiproliferative effect*

TopI inhibitors, such as camptothecin, have several limitations that make necessary to look for new compounds that act against this target [1]. Quasi-flat-*N*-containing heterocycles as quinolines could behave as TopI inhibitors and overcome some of these limitations. In an attempt to find new compounds with improved anticancer activity, we considered that incorporation of phosphorus substituents in the heterocyclic ring of quinolines would be interesting because organophosphorus derivatives regulate important biological functions [2]. Thus, we have been working on the synthesis of hybrid molecules containing several phosphine derivatives [3]. Following this approach, herein we propose the synthesis of novel phosphonate substituted indenoquinolines.

In medicinal chemistry, it is important to find an efficient methodology to prepare molecules with high diversity, so multicomponent reactions (MCR) can be a good strategy. By means of the multicomponent Povarov reaction [4], tetrahydroquinolines **4** can be synthesized in a regioselective and diastereoselective way from anilines **1**, aromatic aldehydes **2** and indene **3** (**Scheme 1**). Furthermore, by dehydrogenation and oxidation the corresponding quinolines **5-6** are obtained.



Scheme 1. Synthesis of phosphorylated indenoquinoline derivatives.

In this way, we have obtained a new family of heterocyclic compounds and have determined the inhibition against human topoisomerase I enzyme and cytotoxicity in different cancer cell lines.

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P49 FROM THE DESIGN TO THE *IN VIVO* EVALUATION OF NOVEL NMDA RECEPTOR ANTAGONISTS

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Keywords: *NMDAR antagonists, Alzheimer's Disease, SAMP8, in vivo study*

N-methyl-*D*-aspartate receptors (NMDAR) modulate the survival of the neurons. However, excessive NMDAR activity causes excitotoxicity and promotes cell death, underlying a potential mechanism of neurodegeneration that occurred in Alzheimer's Disease (AD). Despite years of intensive efforts by scientists to develop new safe and effective treatments for AD, memantine is the only NMDA uncompetitive receptor antagonist that has been approved for the treatment of this fatal disease.[1]

Due to this reason, our research group has designed, synthesized, and carried out the pharmacological and electrophysiological evaluation of a variety of new NMDAR antagonists bearing an amine polycyclic scaffold. All the compounds exhibited comparable potency and an electrophysiological profile similar to that of memantine.[2] Based on these studies, we determined the ideal candidate for further *in vitro* profiling. Compound **1** was selected as the best candidate for *in vivo* proof-of-concept in the SAMP8 mice model because of its excellent *in vitro* profile. The oral administration of compound **1** led to better cognitive performance and a neuroprotective effect through specific pathways.[3]

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P50 AIE-DOTS BASED ON POLY(PHENYLENEVINYLENE) FOR CONTROLLED DRUG RELEASE

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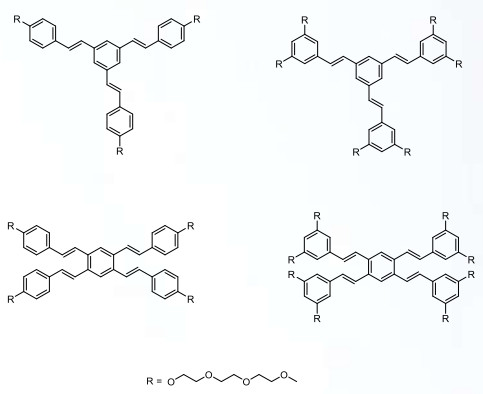
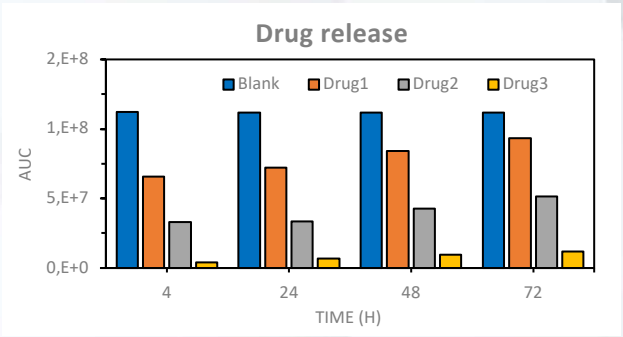
Keywords: (*fluorophores, PPV, AIE-dots, micelles, aggregation, drug-delivery*)

During last decade, π-conjugated systems have developed great interest in many fields due to singular optical properties. Moreover, aggregation induced emission (AIE) have gained importance as switchable systems for different applications [1] and micelles are usually formed by self-assembly of molecules that have both hydrophilic and hydrophobic moieties. [2] The possibility of encapsulating active compounds into micellar aggregates and be able to solve toxicity issues, [3] allows them to be used for drug delivery purposes.

In this work, we present the four amphiphilic fluorophores with a poly(phenylenevinylene) *(PPV)* core and oligo(ethylene oxide) terminal chains. Therefore, these compounds tend to aggregate to form micelles by self-assembly above the critical micelle concentration (CMC) forming fluorescent nanoparticles which are called AIEdots. A complete study of the optical properties has been carried out on both compounds and AIEdots. In addition, AIEdots can be loaded with polo-like kinase 1(PLK1) inhibitor (BI2536) for study drug storage and controlled release as a candidate for drug delivery system.





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P51 PREDICTION OF N-OCTANOL/WATER PARTITION COEFFICIENTS AND ACIDITY CONSTANTS (PKA) IN THE SAMPL7 BLIND CHALLENGE WITH THE IEFPCM-MST MODEL

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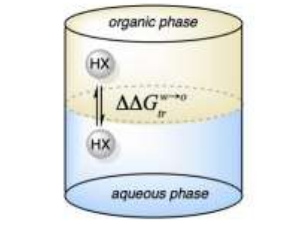
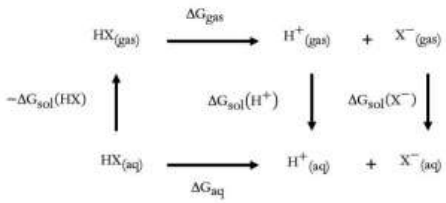
Keywords: *Water-octanol log P – pK_a – MST model – SAMPL Challenges*

Lipophilicity and ionization, respectively represented by n-octanol/water partition coefficient (log *P*) and the negative logarithm of the acid dissociation constant (pK_a) are properties that play a fundamental role to understand the biological activity of drugs, For this reason, the availability of computational tools able to provide accurate estimates of both is valuable to have useful guides in the search of hit compounds and the drug development process. [1]



$$\log P = -\frac{\Delta\Delta G_{tr}^{w\to o}}{RT\ln 10} = -\frac{\Delta G^{o} - \Delta G^{w}}{RT\ln 10}$$



$$\Delta G_{aq} = \Delta G_{gas} + \Delta G_{sol}(H^+) + \Delta G_{sol}(X^-) - \Delta G_{sol}(HX)$$

$$\Delta G_{aq} = -RT\ln K_a$$

In this work, the IEFPCM/MST solvation model, previously used in other studies is used to predict the log *P* and pK_a [2] for a group of sulfonamide-containing compounds provided by Carlo Ballatore group in the framework of the SAMPL7 challenge. [3] The performance of our method exhibited a root-mean square error of 1.03 and 1.32 units, for log *P* and pK_a respectively, which translated in both cases in the second best Quantum Mechanics (QM) based method of the challenge.

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P52 EFFECTS OF EDELFOSINE IN GASTRIC CANCER: FREE DRUG VS. NANOPARTICLE FORMULATIONS

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Keywords: *gastric cancer, cell death, autophagy, alkyl phospholipid analogs*

Although its incidence and mortality have declined over the last decade, gastric cancer (GC) is still one of the most frequently diagnosed neoplasms and the third leading cause of cancer death worldwide [1]. Therefore, there is an urgent need to find new therapeutic approaches that improve GC clinical outcomes.

The ether phospholipid edelfosine (EDLF), considered as the lead compound of a promising family of anticancer drugs collectively named alkyl phospholipid analogs, induces apoptosis in a wide range of cancer cells, whereas non-tumor cells are scarcely affected [2]. EDLF encapsulation in nanoparticles could be an appealing strategy for gastric cancer therapy to increase drug bioavailability, improve its pharmacokinetics, and reduce off-target side effects *in vivo*.

We have measured the uptake and studied the mechanism of action of EDLF in GC cell lines. The comparison of its antitumor activity to that of other alkyl phospholipid analogs assesses this drug as the most potent derivative in this type of cancer. Here, we present the preparation of two EDLF-containing nanoparticles: solid lipid nanoparticles, where EDLF is embedded in the inner lipid core surrounded by a surfactant, and superparamagnetic iron oxide nanoparticles, composed of an iron oxide core and EDLF exposed on the surface. We have studied their effects on two gastric cancer cell lines (AGS and SNU-1), compared to the activity of the free drug. Our results suggest that EDLF loaded in NPs could be a promising new approach for gastric cancer treatment.

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Acknowledgments

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P53 UNVEILING ML-276 INHIBITOR BINDING MODE AGAINST PLASMODIUM FALCIPARUM GLUCOSE-6-PHOSPHATE DEHYDROGENASE

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Keywords: *homology modeling, molecular dynamics, Malaria, drug target, inhibitors*

The bifunctional enzyme glucose-6-phosphate dehydrogenase-6-phosphogluconolactonase (*Pf*GluPho) is essential for the development of *Plasmodium falciparum* inside the human body, since it is involved in the first reaction of the pentose phosphate pathway (PPP), being the major source of NADPH for its use in other metabolic pathways. Additionally, the structure of this enzyme differs from its homolog in humans, suggesting that it could be a potential target for the development of new antimalarial drugs.

In a previous work, an homology model of the *P. falciparum* glucose-6-phosphate dehydrogenase (*Pf*G6PD) domain was designed and validated, using different substrate analogues.[1] Starting with this model, aiming to discover a coherent binding mode in the PfG6PD model, explaining different activities on different enzyme forms, we performed different molecular dynamics (MD) simulations of ML276,[2] described as a competitive inhibitor of glucose-6-phosphate (G6P), as well as some for some derivatives of this compound. The MD simulations were performed in two different species: *P. falciparum* and *P. vivax*. Recent data in bibliography, indicated a decrease in the potency of previously commented compounds against *P. vivax* form, suggesting some differences in the binding site of the inhibitors.[3] Due to the high structure similarity of both parasites enzymes, we constructed an homology model of the *P. vivax* using *Pf*G6PD model as template, in order to assess similar systems.

Performance of different MD simulations of the derivates, have permitted to found a new putative binding mode that explains the differences between the enzymes of parasites species, its human homolog and ML-276 analogues.

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