

Salamanca, January 23-26

2018  
SEQT

MEETING OF THE  
SPANISH SOCIETY OF  
MEDICINAL CHEMISTRY



Salamanca, 23-26 enero

2018  
SEQT

CONGRESO DE LA  
SOCIEDAD ESPAÑOLA DE  
QUÍMICA TERAPÉUTICA





Salamanca, January 23-26



# MEETING OF THE SPANISH SOCIETY OF MEDICINAL CHEMISTRY



Dear colleagues,

The Organizing Committee welcomes you to the 18<sup>th</sup> SEQT Meeting “New perspectives in drug discovery”, which takes place in Salamanca from January 23<sup>rd</sup> to 26<sup>th</sup>, 2018.

The Meeting has been organised jointly by the Spanish Society of Medicinal Chemistry (*Sociedad Española de Química Terapéutica*, SEQT) and the University of Salamanca, continuing a long tradition established by biennial meetings in different cities at research and academic institutions throughout Spain.

About 115 scientists will meet at the Faculty of Pharmacy, located in Campus Miguel de Unamuno. More than 125 participants, among them 80 speakers, will discuss the latest advances and perspectives in drug discovery. The Meeting will cover different topics related to Medicinal Chemistry, such as drug design, new emerging targets, and novel approaches in drug discovery and development, among others.

The 18<sup>th</sup> SEQT Meeting “New perspectives in drug discovery” has been organized with the support of different companies within the field of Medicinal Chemistry: Janssen, Lilly, FAES Farma and Galchimia, together with the University of Salamanca and the European Federation for Medicinal Chemistry (EFMC). The Organizing Committee and SEQT want to acknowledge their support to this event.

This meeting is one of the many events programmed to celebrate the 800 years of the University of Salamanca, the oldest University in Spain, founded in 1218. The Organizing Committee is honoured to invite all participants to such an important celebration for our *Studii Salamantini* and our city, which was declared UNESCO World Heritage Site in 1988.

We want to give you our warmest welcome and we wish the conference to meet your expectations. We would also like you to know our eight times centenary and at the same time modern university and to enjoy our friendly and beautiful city.

We look forward to your active participation!

***The Organizing Committee***

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## COMMITTEES

### ✓ SCIENTIFIC COMMITTEE

- **Pilar Goya** (Medicinal Chemistry Institute-CSIC, Madrid, Spain)
- **Marina Gordaliza** (University of Salamanca, Salamanca, Spain)
- **Jordi Gracia** (Almirall, Barcelona, Spain)
- **Guillermo de la Cueva** (Bionand, Málaga, Spain)
- **José María Fiandor** (GlaxoSmithKline - GSK-, Tres Cantos, Spain)
- **María Jesús Pérez** (Medicinal Chemistry Institute-CSIC, Madrid, Spain)
- **Rodolfo Lavilla** (University of Barcelona, Barcelona, Spain)
- **Concepción Pérez** (University of Salamanca, Salamanca, Spain)

### ✓ ORGANIZING COMMITTEE

- **Marina Gordaliza** (University of Salamanca, Salamanca, Spain)
- **Eva María Priego** (Medicinal Chemistry Institute-CSIC, Madrid, Spain)
- **Concepción Pérez** (University of Salamanca, Salamanca, Spain)
- **Pablo Anselmo García** (University of Salamanca, Salamanca, Spain)
- **Miguel Ángel Salinero** (Fundación General USAL, Salamanca, Spain)
- **Constantino Iglesias** (University of Salamanca, Salamanca, Spain)

## SCIENTIFIC PROGRAMME

## TUESDAY, JANUARY 23<sup>rd</sup>

University of Salamanca Old Building (Patio de Escuelas, C/ Libreros)

17:00	Registration
18:00	OPENING CEREMONY ( <i>Paraninfo</i> )
18:15	<i>Opening session.</i> Chairperson: Pilar Goya Ginés Morata (CBM, CSIC-UAM, Príncipe de Asturias Prize 2007) <b><i>Cell competition: killing cells to keep you alive</i></b>
19:15	SEQT AWARDS
19:30	Welcome cocktail ( <i>Salón de Claustros</i> )

## WEDNESDAY, JANUARY 24<sup>th</sup>

Main hall, Faculty of Pharmacy (Campus Miguel de Unamuno, C/ Licenciado Méndez Nieto s/n)

<b>9:00</b>	<b>Session 1. Chairpersons: M<sup>a</sup> José Camarasa and Toni Torrens</b>	
	9:00	PL1. David K. Smith (Department of Chemistry, University of York) <b><i>Supermolecules for self-assembled medicine (Super-SAM)</i></b>
	9:45	OC1. Javier García <b><i>Pyrrolo[1,2-a]quinoxalines as new small molecules to modulate PTP1B activity by an allosteric mechanism</i></b> OC2. Sonia Martínez <b><i>Novel CDK8 inhibitors</i></b>
	10:25	FL1. Álvaro Lorente <b><i>Amide-controlled, one-pot synthesis of tri-substituted purines generates structural diversity and analogues with trypanocidal activity</i></b> FL2. José Clerigué <b><i>Alkaloid-like, benzo-fused diazabicyclic compounds as neuroprotective agents</i></b> FL3. Miryam Pastor <b><i>Promising HITs as selective MMP13 inhibitors</i></b> FL4. Sarah Mazzotta <b><i>Synthesis of new aminoglycerol derivatives as potential antibacterial agents</i></b> FL5. Bruno di Geronimo <b><i>Towards selective phosphatase inhibition: a new PTPRZ1 binding mode proposal promotes rational design of compounds that increase PTPRZ1/PTP1B selectivity</i></b> FL6. Sara del Mazo <b><i>Antimitotic amides based on combretastatin A-4</i></b> FL7. Horacio Larqué <b><i>Synthesis of falcarinol-type compounds and in vitro leishmanicidal activity</i></b> FL8. Dolores Viña <b><i>Parkinson's disease: potential therapeutic alternatives based on the coumarin scaffold</i></b>
	11:25	Coffee break
	11:45	VISIT TO THE UNIVERSITY OLD BUILDING AND LIBRARY
	14:00	Lunch: Colegio Mayor "Arzobispo Fonseca" (C/ Fonseca, 4)
<b>16:20</b>	<b>Session 2. Chairpersons: Francisco Palacios and Javier Rojo</b>	
	16:20	KN1. Ignacio García-Ribas (Takeda Pharmaceutical International Co.) <b><i>From cytotoxics to immunotherapy: shortening the long story of systemic cancer treatment</i></b>
	16:50	OC4. María Marco <b><i>Discovery of GSK3494245A as a potential antileishmanial drug</i></b>

17:10	<p>FL9. Marta Gargantilla <b><i>Exploration of the <math>\alpha\beta</math> tubulin interface at the colchicine-domain through cyclohexanedione derivatives</i></b></p> <p>FL10. Julia Revuelta <b><i>Tunable heparan sulfate glycomimetics for promote neural differentiation</i></b></p> <p>FL11. Ángela P. Hernández <b><i>New hybrids derived from podophyllic aldehyde and diterpenylhydroquinones selective to osteosarcoma cells</i></b></p> <p>FL12. Marco Leonardi <b><i>Diversity-oriented synthesis of pyrrole-related frameworks for lead discovery via high-throughput screening</i></b></p> <p>FL13. Cristina Blázquez <b><i>Synthesis and metal chelating properties of aminophenanthridinones as potential therapeutic agents for the treatment of Alzheimer's disease</i></b></p> <p>FL15. Matteo Staderini <b><i>A robust sensing system for electrochemical detection of proteases</i></b></p>
18:00	Coffee break
18:30	Session 3. Chairpersons: Rodolfo Lavilla and M <sup>a</sup> Jesús Pérez
18:30	<p>KN2. M<sup>a</sup> Ángeles Martínez-Grau (Medicinal Chemistry, DCRT Spain, Lilly, S.A.) <b><i>Discovery and optimization of the first small molecules targeting GOAT (ghrelin O-acyl transferase) inhibition in vivo</i></b></p>
19:00	<p>OC5. Oskia Bueno <b><i>Protein-ligand complex for structure-based design: impact on the affinity and antitumor activity of new tubulin ligands</i></b> RAMÓN MADROÑERO AWARD</p>
19:20	<p>FL16. Marta Barniol <b><i>Multitarget directed ligands featuring an NMDA antagonist moiety: new strategies of potential interest for the treatment of Alzheimer's disease</i></b> ESTEVE AWARD</p> <p>FL17. Alejandro Revuelto <b><i>First non-peptide dimerization inhibitors of trypanothione reductase with potent in vitro leishmanicidal activity</i></b> ALMIRALL AWARD</p> <p>FL18. Belén Martínez <b><i>Modified tryptophan derivatives as dual inhibitors against HIV and enterovirus 71 (EV71) replication</i></b> JANSSEN-CILAG AWARD</p> <p>FL19. Cristina Chamorro <b><i>iLab: drug discovery and design research in co-creation</i></b></p> <p>FL20. Begoña Verdejo <b><i>Synthesis and platinum (II) complexes of polyazacyclophane receptors as potential therapeutic agents</i></b></p> <p>FL21. Sheila Abril <b><i>Synthesis and study of new chiral melatonin-acetylcholinesterase inhibitor hybrids to treat neurodegenerative diseases</i></b></p>



<b>9:00</b>	<b>Session 4. Chairpersons: Beatriz de Pascual-Teresa and José Ignacio Andrés</b>	
	9:00	PL2. Christa Müller (PharmaCenter, Bonn Pharmaceutical Institute) <b><i>Medicinal chemistry of purinergic signalling in inflammation and cancer</i></b>
	9:45	OC6. F. Javier Rojo <b><i>Glycodendropeptides including a PRU P 3 epitope induce tolerance to peach allergy in mice</i></b> OC7. M <sup>a</sup> José Lorite <b><i>Lilly Open Innovation Drug Discovery Program (OIDD)</i></b> OC8. Rocío V. Paucar <b><i>Preclinical development of Mannich base derivatives as potent antichagasic agents</i></b>
	10:45	FL22. Asier Selas <b><i>Design, synthesis and biological evaluation of novel Top I inhibitors</i></b> FL23. Jorge Gómez-Carpintero <b><i>Design and synthesis of novel m-terphenylamine-tacrine hybrids compound as potential multitarget agents for the treatment of Alzheimer's disease</i></b> FL24. Sonia de Castro <b><i>Discovery of 1,4,4-trisubstituted piperidines as dual inhibitors of influenza and human corona viruses</i></b> FL25. Javier Recio <b><i>Synthesis and study of non-hepatotoxic acetaminophen analogs</i></b> FL26. Marta Piquero <b><i>Novel mitochondria-targeted, leishmanicidal derivatives of 4-aminostyrylquinolines</i></b> FL27. Concepción López <b><i>AOX properties and cytotoxicity of 1,5-benzodiazepin-2-ones</i></b> FL28. Myriam González <b><i>Modifying the methoxy groups of new tubulin inhibiting sulfonamides</i></b>
11:35	Coffee break	
<b>12:00</b>	<b>Session 5. Chairpersons: David K. Smith and José Fiandor</b>	
	12:00	KN3. Gabriele Costantino (Department of Food and Drugs, Università di Parma) <b><i>Non essential targets for the discovery of new potential antibacterial agents</i></b>
	12:30	OC9. Daniel Plano <b><i>As-10: Pre-clinical data of a very promising cancer drug candidate</i></b> OC10. Javier García <b><i>A positive allosteric modulator of the serotonin 5-HT<sub>2C</sub> receptor for obesity</i></b>
	13:10	FL29. Pablo Duarte <b><i>Design, synthesis and biological evaluation of new multitarget compounds for the treatment of Parkinson's disease</i></b> FL30. Regina Martínez <b><i>CK2/HADAC1 dual inhibitors: new strategy for the design of antitumoral agents</i></b>

	<p>FL31. Carolina Estarellas <b><i>Molecular dynamics simulations of AMPK mechanism of allosteric regulation by direct activators</i></b></p> <p>FL33. Juan F. González <b><i>New synthetic approach to quinoxaline di-N-oxide containing a peptide side chain with in vitro anti-leishmanial activity</i></b></p> <p>FL34. Pilar M<sup>a</sup> Luque <b><i>Design, synthesis and biological evaluation of bioisosteric inhibitors of choline kinase</i></b></p> <p>FL35. Tiziana Ginex <b><i>Natural (poly)phenols and Alzheimer's disease: theoretical elucidation of the structural determinants for covalent amyloid beta (A<math>\beta</math>) inhibition</i></b></p>
14:00	Lunch: Residencia Universitaria "Colegio de Oviedo" (Campus Miguel de Unamuno)
16:00	<b>Session 6. Chairpersons: Guillermo de la Cueva and Bárbara Noverges</b>
16:00	<p>KN4. Juan Carlos Morales (Inst. Parasitology &amp; Biomedicine "López Neira", CSIC, Granada) <b><i>From food ingredients to effective drugs?</i></b></p>
16:30	<p>OC11. Clara Herrera <b><i>Design, synthesis, and functional characterization of new photoswitchable neuromuscular ligands</i></b></p> <p>OC12. Concepción Alonso <b><i>Anticancer activity of novel phosphorylated quinolines</i></b></p>
17:10	<p>FL36. José Manuel Méndez <b><i>Triazolopyrimidine derivatives and complexes: Synergic effect of metal ions against parasitic neglected diseases</i></b></p> <p>FL37. Lucía Mayán <b><i>Curcumin-coumarin analogues: new MAO-B inhibitors with neuroprotective activity</i></b></p> <p>FL38. Raquel Álvarez <b><i>Replacement of trimethoxyphenyl ring of combretastatin analogues by pyridine moieties. Study of the biological effect</i></b></p> <p>FL39. Sofía de la Puente <b><i>Aminophenol derivatives as antibiotic alternatives</i></b></p> <p>FL40. Ricardo Escarcena <b><i>Design, synthesis and antiparasitic activity of phthalazinones</i></b></p> <p>FL41. Martín Estrada <b><i>New neurogenic and neuroprotective donepezil-flavonoid hybrids as multitarget drugs for Alzheimer's disease</i></b></p> <p>FL42. Ana Carolina Ruberte <b><i>Synthesis and biological evaluation of selenocompounds as antioxidant and antiproliferative agents</i></b></p>
18:00	Coffee break
18:30	SEQT MEETING
21:00	Conference dinner : Gran Hotel Corona Sol (C/ Víctor García de la Concha, s/n)

<b>9:00</b>	<b>Session 7. Chairpersons: Gabriele Costantino and Víctor Segarra</b>	
	9:00	KN5. Fernanda Borges (Department of Chemistry, University of Porto) <b><i>Shifting from single to multitarget drugs. Is pharmacological promiscuity a herald for neurodegenerative diseases?</i></b>
	9:30	OC13. Patrycja Michalska <b><i>Novel multitarget Nrf2 inducers with potent antiinflammatory properties and neurogenic effect for the treatment of Alzheimer disease</i></b> OC14. Ouldouz Ghashghaei <b><i>Unexplored chemistry of isocyanides: modular access to N-heterocyclic scaffolds with applications in Medicinal Chemistry</i></b> OC15. Claire Coderch <b><i>In silico identification and in vivo characterization of small molecule therapeutic hypothermia mimetics</i></b>
	10:30	FL43. José Manuel Espejo <b><i>Design and synthesis of HA-CD44 interaction inhibitors as antiproliferative compounds</i></b> FL44. José Luis Lavandera <b><i>Citotoxicity and neuroprotective effects of N,C-diaryl-1,2,3-triazoles</i></b> FL45. Francisco Muñoz <b><i>Anion receptors based on pirazolones</i></b> FL46. M <sup>a</sup> Eugenia González <b><i>New polyamine derivatives as antiproliferative compounds</i></b> FL47. Alba Gigante <b><i>Hit selection from the GSK Tres-Cantos anti-kinetoplastid set (TCAKS) using a rapid in vivo assay</i></b> FL48. Pedro J. Labrés <b><i>Controlled release of molecules using macroscopic IRMOF-10 crystals</i></b> FL49. M <sup>a</sup> Dolores Moya <b><i>Structural modulation of salicylates reducing oxalate production in hyperoxaluric mouse hepatocytes</i></b> FL50. Francisco Javier García <b><i>Novel DDR1/2 inhibitors: from hit identification (HTS) to hit generation by drug design</i></b>
11:30	Coffee break	
<b>12:00</b>	<b>Session 8. Chairpersons: Fernanda Borges and Belén Abarca</b>	
	12:00	OC16. Alba Vicente <b><i>Design, synthesis and evaluation of sulphonamide-based microtubule disruptors causing mitotic arrest</i></b>

12:20	<p>FL51. José Carlos Menéndez <b><i>Leishmanicidal activity of 2-acylquinolines and their hydrazones</i></b></p> <p>FL52. Olmo Martín <b><i>Multiple target directed ligands derived from a rho-associated kinase (ROCK) inhibitor for the potential treatment of neurodegenerative disorders</i></b></p> <p>FL53. Olaia Martí <b><i>Tryptophan dendrons as potent HIV and enterovirus A71 entry inhibitors. SAR in the focal point</i></b></p> <p>FL54. Belén Rubio <b><i>Gold-triggered release of histone deacetylase inhibitor panobinostat from a biorthogonal precursor</i></b></p>
13:00	<p><i>Closing session.</i> Chairperson: Marina Gordaliza</p> <p>PL3. Sergio Moreno (Inst. of Functional Biology and Genomics, CSIC-USAL) <b><i>Using chemical-genomics to identify new targets for cancer and aging</i></b></p>
14:00	MEETING CLOSURE

## ABSTRACTS



## OPENING LECTURE



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Prof. Ginés Morata is an expert in Developmental Biology of the fruitfly *Drosophila*, specialty on which he has been working for over 40 years. Over the years he has been involved in several major scientific findings, including the discovery of compartments, the phenomenon of cell competition in *Drosophila*, the elucidation of the structure of the Hox gene complex, the establishment of genetic subdivisions of the *Drosophila* body, the discovery of mitogenic signalling by apoptotic cells etc. Many of his results have been published top scientific journals (*Nature*, *Cell*, *Science*, *EMBO J.*, *PNAS*) and presented in numerous lectures in scientific meetings, universities and research institutions all over the world.

The work of Prof. Morata has been recognised with a number of prizes and distinctions, including the Spanish National Prize of Research in Biology 2002, the México Prize on Science and Technology 2004, the Prince of Asturias Prize in Science and Technology 2007 and his election as a Foreign Member of the Royal Society of London 2017.

## CELL COMPETITION: KILLING CELLS TO KEEP YOU ALIVE

G. Morata

Centro de Biología Molecular, CSIC-UAM. Madrid, Spain

One of the major achievements of Evolution is the construction of the animal body. Consider for example the human body, made of approximately by  $4 \times 10^{13}$  cells and composed of different organs with stereotyped size and shape that are situated in their appropriate positions. Moreover, each of these organs contains specific cell types necessary for its particular function.

All the information to build this complex structure resides in the set of genes characteristic of each species. In humans there are about 22.000 protein-coding genes, whose functions are regulated in temporal and spatial manner to ensure the formation of the correct body size, shape and function.

But many things can go wrong in the process, and one serious problem is the continuous appearance during life of abnormal/aberrant cells, most of which are originated by somatic mutations. These aberrant cells may compromise the normal functioning or the survival of the entire organism. The mutation rate of human somatic cells is within the range  $10^{-8} - 10^{-9}$  mutations per gene/cell cycle. Taking into account the estimate above that the human body contains  $4 \times 10^{13}$  cells, simple arithmetic indicates that any human subject contains many millions of mutant cells in any moment of his/her life. Considering only oncogenic mutations, there are at least 350 genes in the human genome whose mutations have a causal effect on cancer development.

The considerations above call for a safeguard mechanism(s) in charge of the identification and elimination of aberrant/malignant cells that appear in animal tissues. We are studying this problem in the fruitfly *Drosophila*, the organism in which this cell quality control process was first identified. The process was called *cell competition* and its broad significance has become apparent in recent years.

Much of our recent work has been devoted to investigate the role of cell competition in tumour processes. In our assays we make use of oncogenic cells mutant for genes that are also present in humans and known to be associated with human cancer. We have shown that cell competition functions to recognise and subsequently eliminate oncogenic cells that appear in normal tissues. The operation involves the triggering in oncogenic cells of the intrinsic cell death program (apoptosis), which leads to their destruction.

I will be discussing these results and then the recently discovered “group protection” mechanism used by the tumour cells to successfully confront cell competition and eventually to develop an invasive tumour. I shall also be discussing the implications of these results in the understanding and treatment of human cancer.

## NOTES

## PLENARY LECTURES



## DAVID K. SMITH

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Dave Smith is Professor of Chemistry at University of York, where he carries out research into smart nanomaterials and nanomedicines, publishing ca. 150 papers, with an h-index >50. He is a passionate educator, giving outreach lectures to ca. 50,000 UK school students and developing his own YouTube chemistry channel, with over half a million views. Dave has been recognised for excellence both in research and teaching, receiving the RSC Corday Morgan Award in 2012 and an HEA National Teaching Fellowship in 2013. In 2014, he was nominated as one of the RSC's 175 diverse 'Faces of Chemistry'. Dave entered into a civil partnership with his husband Sam in 2010. They live in central York, with their adopted son, where they enjoy the vibrant and historic city, and like cooking and travelling.

# SUPERMOLECULES FOR SELF-ASSEMBLED MEDICINE (SUPER-SAM)

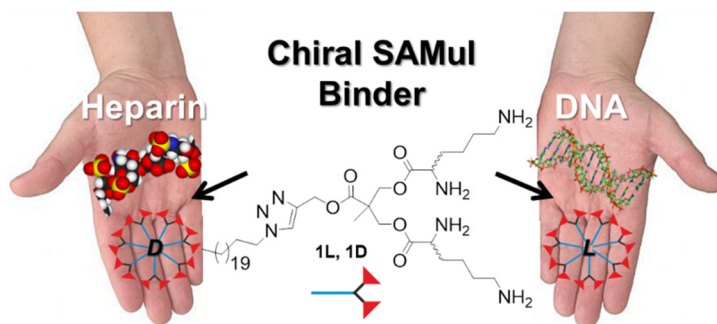
D. K. Smith

Department of Chemistry, University of York, Heslington, York, Yo10 5DD, UK.

Email: david.smith@york.ac.uk

**Keywords:** DNA, heparin, multivalency, polyanions, self-assembly

Polyanions dominate biology[1] and play vital roles in medicinal processes – for example, DNA is essential in gene delivery, while heparin controls blood coagulation. Binding such anions is therefore of great biomedical relevance. Multivalency is a molecular recognition strategy well-known to enhance binding of nanoscale biological targets.[2] Using a supramolecular approach to create self-assembling multivalent (SAMul) ligand displays avoids time-consuming synthesis whilst retaining high-affinity binding.[3] SAMul systems use low-molecular-weight species, which are highly tunable based on the information programmed into their structures by organic synthesis. Furthermore, disassembly of SAMul systems switches off their activity, limiting problems associated with biopersistence. This talk will explore SAMul binding and the ways it can be used with different anionic targets.[4] Surprising levels of selectivity can be achieved.[5] It will be demonstrated that the SAMul approach is capable of intervention in biomedically important processes such as coagulation control.[6]



## References

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- [2] Fasting C, Schalley CA, Weber M, Seitz O, Hecht S, Kokschi B, Dornedde J, Graf C, Knapp E.-W., Haag R, Angew. Chem. Int. Ed., 2012, 51, 10472.
- [3] Barnard A, Smith DK, Angew. Chem. Int. Ed. 2012, 51, 6572
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- [6] Bromfield SM, Posocco P, Chan CW, Calderon M, Guimond SE, Turnbull JE, Prici S, Smith DK, Chem. Sci. 2014, 5, 1484.



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Christa Müller studied pharmacy at the University of Tübingen, Germany, and received her Ph.D. in Pharmaceutical/Medicinal Chemistry from the same university. After a postdoctoral stay with John W. Daly (1989-1990 and 1992) at the Laboratory of Bioorganic Chemistry, National Institutes of Health, in Bethesda, Maryland, USA, she completed her habilitation thesis at the University of Tübingen in 1994, and became Associate Professor of Pharmaceutical Chemistry at Würzburg University in the same year. Since 1998 she is full professor of Pharmaceutical Chemistry at Bonn University. She is a co-founder of the Pharma-Center Bonn ([www.pharmazentrum.uni-bonn.de](http://www.pharmazentrum.uni-bonn.de)), and has >350 publications in the field of medicinal chemistry and pharmacology (Hirsch index: 48).

Her scientific interests are focused on the medicinal chemistry and molecular pharmacology of purine-binding membrane proteins (purine receptors, ectonucleotidases) and orphan G protein-coupled receptors. Disease indications include neurodegenerative and inflammatory diseases, cancer, and rare diseases. Her activities are ranging from basic research to collaborative drug development projects with pharma industry partners.

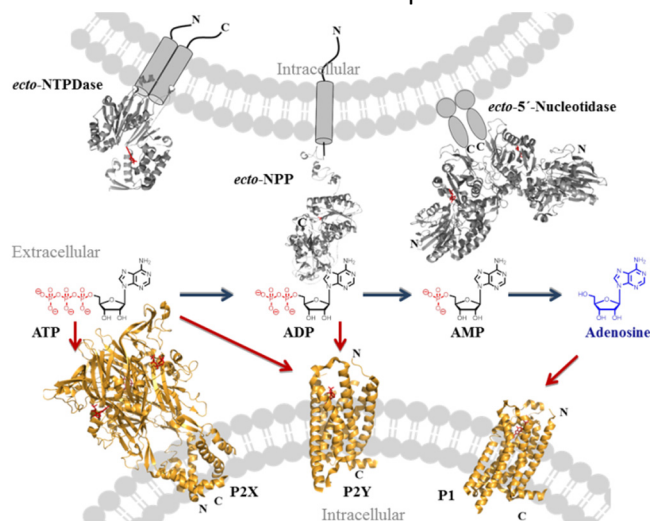
# MEDICINAL CHEMISTRY OF PURINERGIC SIGNALLING IN INFLAMMATION AND CANCER

C.E. Müller

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**Keywords:** Adenosine, ATP, GPCRs, Membrane Proteins, Nucleotides, Nucleotides

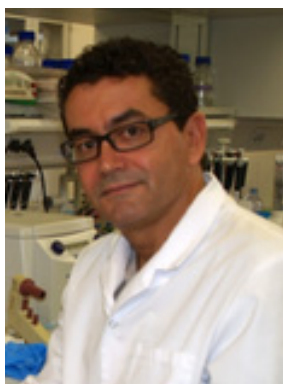
Nucleosides and nucleotides are important extracellular signalling molecules which activate different classes of cell membrane receptors, the co-called purine/pyrimidine P1 and P2 receptors. P1 (or adenosine) and P2Y receptors are G protein-coupled receptors (GPCRs), while P2X receptors are ligand-gated ion channels (see Figure) [1,2]. The concentrations of extracellular nucleosides and nucleotides are tightly regulated by ecto-enzymes, mainly by ectonucleotidases including ecto-nucleoside triphosphate diphosphohydrolases (ecto-NTPDases, CD39), ecto-nucleotide pyrophosphatases (ecto-NPPs) and ecto-5'-nucleotidase (CD73). Nucleoside and nucleotide signalling plays a major role in all parts of the body especially under pathological conditions, e.g. in inflammation, pain, immune reactions and cancer. While nucleotides such as ATP are pro-inflammatory and increase pain sensation, adenosine is strongly immunosuppressant and involved in the immune escape of cancer cells.



Our group has focused (i) on the development and characterization of tool compounds and drugs for purine/pyrimidine receptors and ectonucleotidases, and (ii) on studies directed towards gaining structural information regarding protein-ligand interactions. Recent examples include antagonists for P2Y receptors [3], allosteric modulators for P2X receptors, structural studies on A<sub>2A</sub> and A<sub>2B</sub> adenosine receptors, and inhibitors of ectonucleotidases [4-6].

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Sergio Moreno carried out his PhD studies at the University of Salamanca (Microbiology Dept., 1982-1986) and a postdoctoral stay at Paul Nurse laboratory (1986-1993) working on cell cycle regulation. In 1993, he became research scientist at CSIC and started his own research group to work on the molecular mechanisms regulating cell cycle exit. Particularly, they focused on the function of two proteins, Rum1 and Ste9, and they characterized the role of *puc1*, *cig1* and *cig2* cyclins in the cell cycle. During this time, they participated in an EU funded project for sequencing *S. pombe* genome.

In 2001, he spent a year in Dr. Julie Ahring group (Cambridge University) in order to work with *Caenorhabditis elegans*. They have carried out joint projects focused on the dissection of the phagocytosis of apoptotic bodies pathway. Since 2002, a close collaboration has been established with the pharmaceutical company PharmaMar for the study of the mechanism of action of several antitumor agents, such as Yondelis, used for the treatment of soft tissue sarcoma and ovarian cancer. Further scientific collaborations have allowed the generation of a knockout mouse for the *Cdh1/Fzr1* gene, as well as studies on the neuronal differentiation and survival and on the meiosis in mice.

His group is currently working on two research areas: first, the coordination between cell growth and division in order to accomplish cell size homeostasis, regulated through the TORC1-*greatwall*-endosulfine-PP2A pathway; and second, the role of APC/C-Cdh1 in genome stability, cancer and ageing.



## USING CHEMICAL-GENOMICS TO IDENTIFY NEW TARGETS FOR CANCER AND AGING

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**Keywords:** *cancer, aging, ATR, Wee1, mTOR, Rapamycin, AMPK, Metformin*

The identification of the mechanism of action (MoA) of specific compounds is critical for drug discovery and for the development of more selective and less toxic drugs. Mutants that render cells hypersensitive to a drug identify pathways that protects the cell against the toxic effects of the drug, whereas those that render cells resistant to a drug identify pathways required for drug uptake, drug metabolism or drug target modification; and thereby provide clues for both gene and compound function. Hence, chemical-genomic data is a powerful system for linking compounds to their target pathway. Moreover, compounds that show similar chemical-genomic profiles often reflect a common biological target or mode-of-action.

A major break-through in chemical-genomics has been the generation of complete collections of yeast deletion strains. Crossing these mutants to identify synthetic lethal interactions and growth of these mutant collections in the presence of a chemical compound allows the quantitative measure of the relative “fitness” of every mutant strain, and has been widely used to identify drug-susceptible strains and, thus, gene products that play a role in specific drug-inhibitory mechanism.

Using these approaches a number of pathways have been identified as potential targets for anti-cancer treatment and anti-aging therapies. For instance, inhibitors of checkpoint kinases ATR, Chk1, and Wee1 are currently being tested in preclinical and clinical trials. In this presentation, I will review the basic principles behind the use of such inhibitors as anticancer agents. On the other hand, inhibitors of mTOR (Rapamycin) or activators of AMPK (Metformin) are promising candidates to extend healthy lifespan.

## NOTES

## KEYNOTE LECTURES



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Ignacio García Ribas holds a PhD from the Universidad Autónoma of Madrid. He is specialist in medical oncology. He is been working for the last 15 years in clinical research at the pharmaceutical industry. His main interest is the early assessment of oncological drugs at the transition from the preclinical stage to the first studies in cancer patients. He has carried out this work first at Lilly, then at Sanofi and currently in the Takeda Oncology Early Development Group.

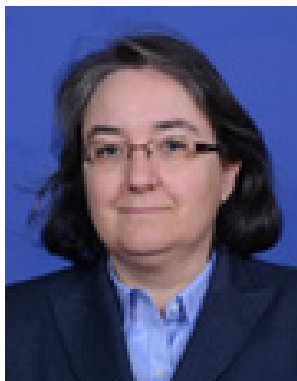
## FROM CYTOTOXICS TO IMMUNOTHERAPY: SHORTENING THE LONG STORY OF SYSTEMIC CANCER TREATMENT

I. García Ribas

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Drug development in oncology has changed dramatically in the past 20 years from the discovery of new treatments based on phenotypic screening of chemicals to the rational construction of molecules targeting relevant proteins to the oncogenic process. There have been important advances in medicinal chemistry that allowed the creation of small molecules with good pharmacological properties while retaining target specificity. In this search for specificity, numerous monoclonal antibodies have been developed but targeting is limited to cell surface molecules or to carry cytotoxics that are delivered with the antibody-drug conjugate (ADC) concept. Reaching intracellular targets is still dependent on small molecules with the right biodistribution properties. Advances in molecular oncology are clearly preceding any major progress in the outcome of patients with metastatic cancer. Understanding tumors, not only from the cancer cell perspective but also the interplay with other biological processes like angiogenesis or immunity, has been critical to significantly increase the number of patients that can be considered cured. The combination of chemotherapy, targeted agents, radiotherapy, surgery and early detection only achieved incremental benefits in survival but very few metastatic patients could be considered as cured. In the past 10 years immunotherapy showed consistently that long term remissions in patients with metastases are achievable with a relatively simple targeting of the PD-1/PD-L1 axis. Interestingly the principle of immune system activation against cancer works independently of the organ of origin of the cancer. Although cancer immunotherapy is the most remarkable advancement in oncology since the discovery of cisplatin, it is still a long way to go before we can achieve the cure of the majority of patients with metastatic disease.





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Maria Angeles received her doctorate in Organic Chemistry from Universidad Complutense in 1994 and the “National Award for Young Investigators” (Royal Spanish Society of Chemistry) in 1995. After two years of postdoctoral work with Prof. Dennis Curran at the University of Pittsburgh, she became Associate Professor at Universidad Complutense where she was the advisor of 4 Master theses. Maria Angeles joined Lilly in 1998 as Research Scientist at the Spanish site, and held several positions with scientific and managerial responsibilities throughout the years. In 2001 she was assigned to Lilly Indianapolis for three years to acquire a deep therapeutic expertise and establish cross-functional relationships. In 2013 she became Senior Research Advisor focussing on Lead Generation and Lead Optimization projects. As medicinal chemist she has been recognized for her scientific leadership, highly effective coaching, and technical contributions to twelve clinical candidates in the areas of Neuroscience, Obesity and Diabetes. In 2017 she has accepted the role of Coordinator of External Innovation in Europe in addition to her scientific responsibilities.

## DISCOVERY AND OPTIMIZATION OF THE FIRST SMALL MOLECULES TARGETING GOAT (GHRELIN O-ACYL TRANSFERASE) INHIBITION *IN VIVO*

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**Keywords:** *GOAT Inhibition, Unacylated ghrelin, Acylated ghrelin*

Ghrelin is a potent orexigenic peptide that is secreted in the gut and activates the growth hormone secretagogue receptor (GHSR1a) in the brain. Ghrelin O-Acyl Transferase (GOAT) is the only known enzyme that catalyzes the conversion of unacylated ghrelin (UAG) into acylated ghrelin (AG), its active form, by transferring *n*-octanoic acid to the third serine residue of ghrelin peptide. GOAT is co-localized with ghrelin in the stomach enabling the production of active ghrelin.

The recent identification and characterization of GOAT introduces a novel approach to attenuate indirectly the ghrelin receptor system,<sup>1,2</sup> one of the most important mechanisms regulating feeding and energy balance. Despite the potential therapeutic benefits of inhibiting GOAT, only a few examples of peptide-based inhibitors or non-optimized small molecules have been reported. The effects of AG and UAG infusion on glucose and insulin levels have been assessed in clinical studies but the lack of orally available GOAT inhibitors has precluded the pharmacological intervention to modify the AG/UAG ratio.

Lacking of computational tools for structure-based drug design, we focused our efforts on screening strategies using enzymatic and cellular assays. A few fragments and small molecules with common structural features were chosen as starting points to expand the chemical space. Several SAR iterations evolved to identify very attractive small molecules as high quality chemical probes for *in vivo* evaluation.

In this presentation we will describe the synthesis, SAR expansion and the small modifications that improved GOAT inhibition *in vitro* and *in vivo*. Medicinal chemistry optimization based on potency and PK profile refinement led to the identification of a few potent and selective GOAT inhibitors that were suitable preclinical tools. The advanced compounds showed robust reduction of plasma acylghrelin in a mouse PD model, and were considered tools of key value to identify a clinical candidate that could validate the GOAT inhibition hypothesis in humans.

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## GABRIELE COSTANTINO

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Gabriele Costantino graduated in Chemistry at University of Perugia (Italy) in 1992. In 1994 he was appointed as research assistant at the Dipartimento di Chimica e Tecnologia del Farmaco of the University of Perugia. In 1998 Gabriele became associate professor of medicinal chemistry at the same Institution. Since January 2007 he is full professor of Medicinal Chemistry at University of Parma.

During his career, Gabriele has been visiting scientist at Searle R&D (Skokie, IL, USA) and at the Departamento de Quimica Organica of University of Barcelona (Spain). Gabriele has been visiting professor at the Institute of Organic Chemistry of Goethe University of Frankfurt AM (Germany). Gabriele has been awarded in 2003 with the Farmaindustria/SCI prize as best young researcher in medicinal chemistry, and with the XVI Friederich Merz Fellowship for his research on molecular modeling of glutamate receptors. His research interests cover the design and synthesis of modulators of metabolic pathways and of antibacterial agents.

Gabriele is the coordinator of INTEGRATE, a Marie Sklodowska-Curie ETN project, funded under the H2020 framework, finalized at the design and synthesis of chemical probes for new antibacterial targets. Author of more than 130 scientific papers, Gabriele has been coordinator of the PhD program in medicinal chemistry at University of Parma from 2007 to 2011. Gabriele is Director of the Department of Food and Drug (90 faculty members and more than 3000 students) at University of Parma.

He is President of the Division of Medicinal Chemistry of the Italian Chemical Society and he has been member of the Executive Committee of the EFMC.

## NON ESSENTIAL TARGETS FOR THE DISCOVERY OF NEW POTENTIAL ANTIBACTERIAL AGENTS

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The urgent need for new effective antibacterials is at the basis of the continuous quest for new bacterial targets less prone to develop resistance. In this context, we have embarked ourselves in a research project aimed at assessing the druggability of so-called 'non essential' targets in bacteria. These non essential targets are not intrinsically vital for the bacteria, but cooperate to increase the fitness of the bacterium to challenging conditions such as those produced by antibacterials, by pH, by oxidative stress. Interfering with these targets is expected to increase the efficiency of the host immune system activation and promote the action of other antibacterial agents with reduced susceptibility to resistance.

We have thus selected two biochemical pathways whose inhibition is reported to affect the fitness of bacteria. The first one is the so-called reductive sulfur assimilation pathway, while the other one is carbonic anhydrase. In this communication we report our recent results in the identification of very potent inhibitor of O-Acetyl Serine Sulphydrylase (OASS-A/B or CysK/M), a key enzyme in the sulfur assimilation pathway in bacteria which catalyses the conversion of O-Acetyl Serine (OAS) into cysteine, required for the fitness of bacteria against oxidative stress induced by antibiotics, host immune system activation, or radiation. In a different approach, we have also developed a new series of structurally new inhibitors of bacterial carbonic anhydrase, which may have have therapeutic relevance for those bacteria for which the buffering of extracellular pH is crucial for survival.

The significance of the inhibition of these two targets for the discovery of new antibacterials will be discussed.



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Juan Carlos Morales Sánchez holds a PhD in Chemistry (Univ. Autónoma de Madrid, 1996). His research education started at the Universities of East Anglia (1991), Alcalá (1992), Sheffield (1995), Rochester (1997-1998), Stanford (1999) and the Institute of Organic Chemistry-CSIC (1993-1996) and Institute of Advanced Chemistry of Catalunya-CSIC (2000), where he worked in supramolecular chemistry and molecular interactions, carbohydrate chemistry and nucleic acids chemistry. He began his professional career as Head of Chemistry in *Puleva Biotech* (2000-2006) where he worked on new antioxidants, carbohydrates and fats for functional foods.

Dr. Morales returned to public research at the Institute of Chemical Research (CSIC-University of Seville) and became staff scientist in 2008. In 2014 he moved to the Institute of Parasitology and Biomedicine López Neyra-CSIC. He is the author of more than 70 publications and 11 patents. His research group develops three research lines: a) design and synthesis of phenolic derivatives with potential application in inflammatory-based diseases; b) DNA-carbohydrate conjugates as tools to study molecular interactions and c) carbohydrate G-quadruplex DNA ligands as potential chemotherapy drugs.

## FROM FOOD INGREDIENTS TO EFFECTIVE DRUGS?

J. C. Morales

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**Keywords:** *G-quadruplex, carbohydrate, antitumor drug, resveratrol, prodrug, neurodegeneration*

The functional food research field has demonstrated that some food ingredients possess interesting biological properties which can be beneficial for the prevention or treatment of different pathologies. Chemists are taking these food ingredients as starting scaffolds to improve their bioactivity and take them to the clinic. For example, resveratrol prodrugs have been reported as drugs for the treatment of inflammatory bowel diseases.<sup>[1]</sup> New resveratrol derivatives will be discussed as potential treatment for neurodegenerative diseases.

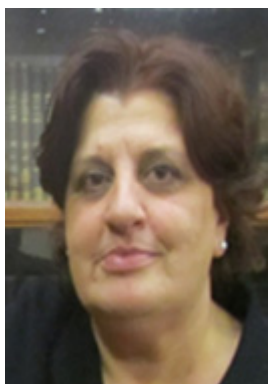
At the same time, other ingredients such as carbohydrates are being used as vectors to direct different drugs to their targets. Glucose modified G-quadruplex ligands will be presented as potential antitumoral drugs.<sup>[2]</sup>

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## FERNANDA BORGES

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Fernanda Borges is Associate Professor of the Department of Chemistry and Biochemistry of Faculty of Sciences of University of Porto and senior researcher of CIQUP. She received her MSc and PhD (Pharmaceutical Chemistry) in Pharmacy from the Faculty of Pharmacy, University of Porto, Portugal. Her current research is focused on medicinal chemistry, namely in the design and development of new chemical entities to be used in the prevention/therapy of neurodegenerative diseases. She authored more than 270 publications in peer reviewed journals, 12 international book chapters, and 4 patents.

## SHIFTING FROM SINGLE TO MULTITARGET DRUGS. IS PHARMACOLOGICAL PROMISCUITY A HERALD FOR NEURODEGENERATIVE DISEASES?

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**Keywords:** *single target, multitarget, neurodegenerative diseases*

For some time, drug discovery players have been questioning the success of the reductionist philosophy to ameliorate disease states with multifactorial and polygenic nature. Consequently, it is intuitive that by targeting different regions or modules of the disease network a better regulation of the system can be achieved. The multi-target approach, where a single chemical entity may be able to modulate simultaneously multiple targets, seems to be of particular interest in areas that involve multiple pathogenic factors, like neurodegenerative diseases, cancer and infectious diseases. One of the main limitations of this approach is the ability to define the set of targets that are causative of a particular disease state and design compounds that will hit the key targets with a desirable ratio of potencies. This is certainly a daunting challenge but given the current unmet medical needs, and the possible gains, such a venture is worthwhile. Yet, the collaboration among all the stakeholders, such as research foundations, academic institutions, physicians, and pharmaceutical industry, and the establishment of international drug discovery networks are paramount for the success. In this context, our research group have been focused in the discovery of new chemical entities based on the benzopyrane and cinnamic scaffolds as therapeutic agents for neurodegenerative diseases. The data on one target to multitarget drug discovery processes will be briefly depicted.

Funded by FEDER funds through the Operational Programme Competitiveness Factors -COMPETE and national funds by FCT – Foundation for Science and Technology- under research grants (PEst-C/QUI/UI0081/2013, NORTE-01-0145-FEDER-000028 and PTDC/DTP-FTO/2433/2014). COST action CA15135 (Multitarget Paradigm for Innovative Ligand Identification in the Drug Discovery Process) support is also acknowledged.

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## NOTES

## ORAL COMMUNICATIONS

## PYRROLO[1,2-*a*]QUINOXALINES AS NEW SMALL MOLECULES TO MODULATE PTP1B ACTIVITY BY AN ALLOSTERIC MECHANISM

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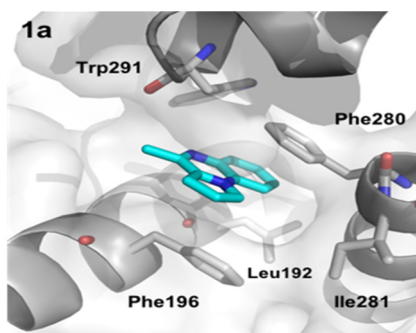
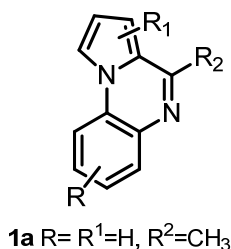
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**Keywords:** *Diabetes Mellitus, Chronic Kidney Disease, PTP1B*

According to the GDB2013 study, Chronic Kidney Disease (CKD) is the non-transmissible global cause of death that increased the most within the past 20 years. One of the main risk factors of CDK is the Diabetes Mellitus type II (DM II). Protein Tyrosine Phosphatase 1B (PTP1B) has been validated as a promising target for DM II with several inhibitors under development or in clinical trials. However, active site-specific PTP1B inhibitors failed in clinical trials. Targeting the highly conserved and highly positively charged active site has led to the discovery of highly negatively charged phosphotyrosine mimetics lacking of bioavailability and selectivity [1]. Then, allosteric inhibition has emerged as a new strategy for PTP1B inhibition. Our research group has recently discovered a new family of pyrrolo[1,2-*a*]quinoxalines with in vitro inhibitory activity against PTP1B and we have identified an allosteric inhibitor scaffold of this family [2]. In this communication, we report a series of new pyrrolo[1,2-*a*]quinoxalines and its biological activity. Moreover, we have studied the inhibition mechanism by means of docking and molecular dynamics techniques.



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## NOVEL CDK8 INHIBITORS

S. Martínez González, A. I. Hernández, C. Gómez de la Oliva, V. Rivero, R. C. Riesco, O. Renner, E. Gómez Casero, M. I. Albarrán, E. Aguirre, B. Barrera, A. Cebriá, A. Amezcuita, J. García, E. Hernandez, C. Blanco-Aparicio, J. Pastor

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**Keywords:** *CDK8 inhibitors, drug discovery, cancer.*

CDK8 kinase and its paralog CDK19 are components of the Mediator complex forming its key regulatory subunit, which itself regulates the transcriptional activity of RNA polymerase II. Several studies have shown that CDK8 modulates the transcriptional output from distinct transcription factors such as Wnt/ $\beta$ -catenin, Notch, p53 and TGF- $\beta$ , all of them with oncogenic potential. Moreover, both kinases restrain increased activation of key Super-Enhancers associated genes with tumor suppressor function in AML cells. Activities of CDK8/CDK19 have been implicated in sustained proliferation and viability of cancer cell lines. Importantly, recent reports support the potential of CDK8 inhibitors (CDK8-is) to treat Wnt dependent colorectal cancers and AML. Moreover, CDK8 has been involved in the restriction of the activity of Natural Killer (NK) cells, therefore its inhibition may have an activation role of NK cells, positioning CDK8-is as an anti-cancer therapy which present an additional immunotherapeutic potential.[1]

Here, we would like to present in detail the discovery and preclinical characterization of our novel CDK8 inhibitors as potential therapy to treat cancer.

The CNIO's CDK8 project started with a HTS campaign complemented with the application of Hit Generation strategies. Several chemical series of CDK8-is were identified. After profiling of representatives from each series and multifactorial prioritization we selected a series of tricyclic CDK8-is for further HtL and LO phases. We have generated SAR/SPR data regarding primary activity, selectivity, *in vitro* ADMET and *in vivo* PK. The x-ray structures of CDK8-CyC co-crystallized with selected CNIO CDK8-is have been generated, demonstrating a type I binding mode, essential to achieve potent cellular activity. The multi-factorial profiling has allowed the identification of ETP-827 and ETP-193 as our first orally bioavailable CDK8-is leads. We have generated antiproliferation data in a panel of +40 tumoral cell lines, providing cell line sensitivity to our CDK8-i. Selected sensitive cell lines have been used to further profile our leads in comparison with published competitors. Interestingly, our advanced CDK8-is leads inhibit also a secondary target which seems to be a positive differentiating factor versus competitors lacking such activity. Finally, ETP-827 and ETP-193 have been studied in *in vivo* PK-PD and efficacy experiments in an AML tumor model yielding positive results. The series has been protected with a patent application.

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## DISCOVERY OF GSK3494245A AS A POTENTIAL ANTILEISHMANIAL DRUG

M. Marco<sup>a</sup> on behalf of the Dundee Drug Discovery Unit<sup>b</sup>- GSK team

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<sup>b</sup>Drug Discovery Unit, Dundee University, Dundee, UK.

**Keywords:** *Visceral Leishmaniasis, preclinical candidate, proteasome inhibitor, partnership*

GSK Kinetoplastid DPU and University of Dundee with support from the Wellcome Trust have formed a five-year partnership to conduct drug discovery within kinetoplastid diseases (Visceral Leishmaniasis and Chagas disease). Current standard of care for VL suffers from multiple issues (such as lack of efficacy, safety, drug resistance, stability, cost and the majority lack an oral dosing option) and as a community there is a limited pipeline for VL [1].

The University of Dundee-GSK partnership has made significant progress, ES09 series being the second Lead Optimization program for Visceral Leishmaniasis (VL) identified through phenotypic screening.

This presentation will concentrate on the lead optimisation and progression of this series, focusing on key learnings around the following topics:

- 1) Building a fully integrated partnership between industry and academia
- 2) Working within phenotypic screening setting and very limited PK/PD knowledge.
- 3) Using scaffold hopping technique to improve the overall physicochemical profile of the original series that has offered a wide range of sub series to investigate.
- 4) Describing our pragmatic target deconvolution studies, where the proteasome has been identified as the mode of action for this series.

As a result of our Lead Optimization efforts, GSK3494245A was selected as a preclinical candidate for the potential treatment of VL.

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## PROTEIN-LIGAND COMPLEX FOR STRUCTURE-BASED DESIGN: IMPACT ON THE AFFINITY AND ANTITUMOR ACTIVITY OF NEW TUBULIN LIGANDS

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**Keywords:** *tubulin, drug design, high affinity, antitumor activity*

Microtubules, made of  $\alpha\beta$ -tubulin heterodimers, are the key components of the cytoskeleton and play a crucial role in many cellular processes, such as cell motility, morphogenesis and mitosis.[1] Interference with microtubule dynamics induces cell cycle arrest during mitosis and triggers cell death. Compounds that interact with tubulin, especially those binding at the colchicine domain, have been deeply investigated as anticancer drugs due to their dual mechanism of action as antimetotics and as vascular disrupting agents.[2,3] Our research group has recently described a new family of colchicine-domain binders, based on a cyclohexanedione skeleton, with potent antiproliferative activity against tumor and endothelial cells.[4] Moreover, to gain insight into the binding mode of these cyclohexanediones, we have determined the crystal structure of  $\alpha\beta$ -tubulin in complex with our hit compound (TUB075). Based on this detailed information and by applying the affinity maps program cGRILL, a structure-based synthesis of new cyclohexanedione derivatives has been accomplished with the objective of improving their affinity for tubulin and their antitumor activity. Following this approach, we have obtained new compounds with potent antiproliferative activity against tumor and endothelial cells ( $IC_{50}$ =8-31 nM) and with the highest  $K_b$  value reported for compounds binding at the colchicine site in tubulin. Additional studies have shown that they arrest cell cycle at G2/M and disrupt a network of endothelial cells. Moreover they keep antiproliferative activity against cell lines overexpressing P-gp, further supporting the potential of these compounds. **Acknowledgements:** The financial support of the Spanish MINECO (SAF2012-39760-C02-01 and SAF 2015-64629-C2-1-R), Comunidad de Madrid (BIPEDD2; ref P2010/BMD-2457) and the COST action CM1407 (to M.J. P.P., S.L., M.O.S. and J.F.D.) is sincerely acknowledged.

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## GLYCODENDROPEPTIDES INCLUDING A PRU P 3 EPITOPE INDUCE TOLERANCE TO PEACH ALLERGY IN MICE

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**Keywords:** *Allergy, Glycodendropeptides, Immunotherapy, Mannose, Pru p 3*

Allergen specific immunotherapy (IT) is probably the only long term treatment for allergic diseases because it induces tolerance. It is known that mannosylation of peptides or proteins induces a receptor dependent internalization process in dendritic cells together with a T-cell stimulation.[1] Based on this fact, our group has developed a synthetic strategy to combine in a well-defined structure mannosyl glycodendrons with peptide epitopes creating new glycodendropeptides.[2] The idea is to develop synthetic tools capable to modulate the immune system inducing tolerance against allergens. We have selected Pru p 3, a Lipid Transfer Protein (LTP) considered as the main allergen in some food allergy processes, especially in peach allergy. We have developed a Pru p 3-mono (D1) and tetravalent (D4) structures functionalized with a mannosyl glycodendron. The immunological responses were analyzed in vitro/in vitro by studying changes in body temperature, the monocyte-derived-Dendritic cells (moDC) maturation and lymphocyte proliferation, using a LTP-peach anaphylactic mice model.[3] Preliminary results are very promising and demonstrate that this approach can be considered as a new therapeutic strategy in different allergy diseases.

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## LILLY OPEN INNOVATION DRUG DISCOVERY PROGRAM (OIDD)

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**Keywords:** *Open Innovation, Collaboration, Drug discovery, Chemical diversity*

The Lilly Open Innovation Drug Discovery program (OIDD) was created to engage external investigators in a hypothesis-driven approach to early drug discovery. Program participants have the opportunity to contribute to the discovery of novel therapeutics that will improve patients' lives, and benefit by having access to cutting-edge research tools and data that can help them advance their own scientific work. The OIDD program is directed to investigators in academic/research institutions and small biotechs. Many of them encountered barriers to evaluate the therapeutic potential of their compounds and the OIDD platform was designed to minimize obstacles by offering:

- In-kind access to a panel of proprietary biological assays in the areas of Diabetes, Oncology, Pain, Neurodegeneration and Immunology, plus certain neglected and tropical diseases in collaboration with global leaders in the area,
- A variety of in silico tools to prioritize molecules with desirable drug-like properties,
- Opportunity to prepare compounds remotely in our Automated Synthesis Lab (ASL),
- Opportunity to have chemical samples selected for purchase through an algorithm applied to the molecular descriptor profile.

Affiliation is established at the institution level via a universal agreement that protects participant's intellectual contributions. Once the agreement is signed, investigators may create a user account that manage chemical structure selection, sample transfers, and biological data in a secure manner. The OIDD program is supported by a secure web-based interface that protects the confidentiality of proprietary information such as chemical structures. All Lilly-generated data is owned by the participating investigator and/or institution, and results are used to initiate collaboration discussions based on promising results and mutual interest of both parties. Otherwise, the investigator is free to publish and/or use the biological results in grant proposals.

This communication will describe the scientific rationale behind OIDD, the business model, operational details and metrics illustrating the performance of the program. Detailed information can be found online (<https://openinnovation.lilly.com/dd/>). The website provides details about the process, our offerings, sample logistics, biological screening and user account management. Our universal agreement is also available online. If you have questions, please feel free to contact openinnovation@lilly.com



## PRECLINICAL DEVELOPMENT OF MANNICH BASE DERIVATIVES AS POTENT ANTICHAGASIC AGENTS

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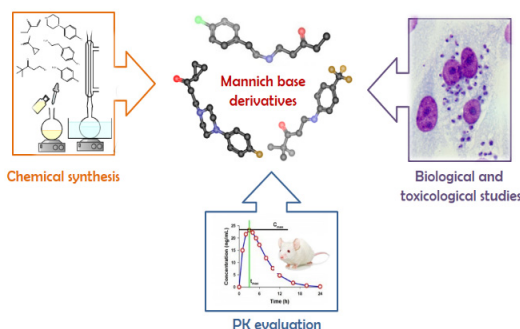
**Keywords:** Chagas disease, *Trypanosoma cruzi*, Mannich base derivatives, antichagasic agents

Chagas disease (CD) is a neglected tropical disease caused by the parasite *Trypanosoma cruzi*<sup>1</sup>. About 6-7 million people are infected worldwide<sup>1</sup>. Benznidazole and Nifurtimox are the only available drugs for CD but the problems of those are related to their variable antiparasitic activity, the undesired side effects or long treatment duration among others<sup>2</sup>. So, there is a great need for developing new effective and safe drugs for the treatment of CD.

Considering the above, twenty new derivatives were synthesized and tested in three different forms in three different *T. cruzi* strains. The cytotoxicity was also determined to establish their selectivity index (SI). The lead compound showed *in vitro* SI ranging from 99 to 258 times higher than Benznidazol in the amastigote form and from 333 to 2810 in the trypomastigote form of the parasites. The tested compounds were non-genotoxic in the SOS/umu screening test. According to their preliminary studies, four out of twenty derivatives were selected for an *in vivo* assay in a murine mice model. The *in vivo* acute model showed that the compounds decrease the parasitemia from the beginning of the treatment and parasites were not detected since day 25 post-infection. Additionally, all the compounds showed no reactivation after immunosuppression with a total dose of 100 mg/kg and the lead compounds showed no reactivation also at 50 mg/kg. Also, it seems that these new derivatives could be inhibitors of the Fe-SOD enzyme<sup>3</sup>. Considering the *in vivo* results, two out of four derivatives were selected for their mutagenicity and PK evaluation. It is remarkable to mention that they were non-mutagenic in the Ames test and their bioavailability values are greater than 35% (92.84% and 38.76%). Up to now, these results render these new derivatives as potent oral antichagasic drug candidates and they will be move to an *in vivo* bioluminescence model in collaboration with the LSHTM. The latest results will be presented in this Congress.

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## AS-10: PRE-CLINICAL DATA OF A VERY PROMISING CANCER DRUG CANDIDATE

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**Keywords:** *Apoptosis; Cancer; NF-κB; ROS; Se-Aspirin; Selenium; Synergistic effects.*

Selenium (Se) is a micronutrient for humans with well-proven effects over the redox system. Low serum Se levels are associated with higher risk and poor prognosis of several cancers. For the last few years, mounting evidences have demonstrated that the incorporation of Se atom into organic frameworks is an attractive strategy in Medicinal Chemistry to design anticancer agents.

Continuing with our efforts to develop new Se containing small molecules [1], herein we present the synthesis, structure characterization and pre-clinical evaluation of our newly developed compound **AS-10** [2-((3-(2-acetoxybenzoyl)-1,3-selenazolidin-2-ylidene)carbamoyl)phenyl acetate].

**AS-10** was selectively lethal to a variety of cancer cells as shown by NCI-60 Human Tumor Cell Lines Screen results. **AS-10** presents a mean growth percent value of -37.86% for all sixty cell lines, with melanoma, renal and central nervous system (CNS) cancers being dramatically sensitive. Also, interestingly, **AS-10** inhibited pancreatic cancer (PC) cells growth (IC<sub>50</sub> 2.5-5.0 μM) for which no effective therapy currently exists. **AS-10** induced G1/G2 cell cycle arrest which was associated with increase of cell cycle inhibitory proteins p21 and p27, and induced apoptosis as evidenced by caspase 3/7 activity, PARP cleavage and Annexin V staining. **AS-10** also inhibited NF-κB DNA binding activity as well as NF-κB translocation to the nuclei upon stimulation by TNFα. Notably, **AS-10** potentiated cytotoxic activity of gemcitabine in PC cells. Furthermore, in LNCaP prostate cancer cells, **AS-10** decreased protein level of AR and its best known target PSA, and led to increased caspase-mediated apoptosis and expression of p53-DNA damage response proteins such as p21 and p-H2A.X. **AS-10** induced ROS in cancer cells as likely primary biochemical event. Finally, **AS-10** (47 mg/kg, *i.p*) inhibited subcutaneous colon tumor growth by ~70% without any apparent systemic toxicity.

**Intellectual disclosure.** All the information presented here is under protection: U.S. Utility Patent Application No. 15/457,587. The Penn State Research Foundation.

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## A POSITIVE ALLOSTERIC MODULATOR OF THE SEROTONIN 5-HT<sub>2C</sub> RECEPTOR FOR OBESITY

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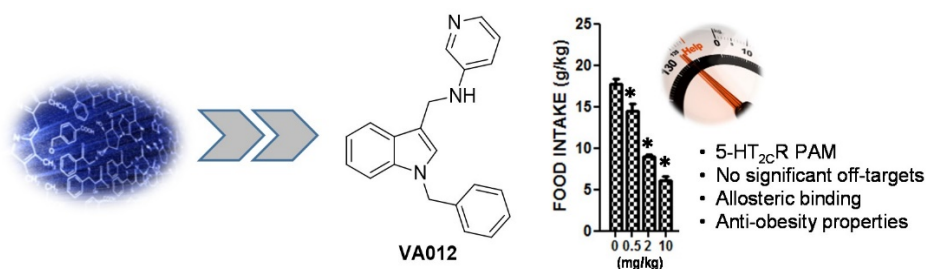
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**Keywords:** 5-HT<sub>2C</sub> receptor, positive allosteric modulator, obesity

Stimulation of serotonin 5-HT<sub>2C</sub> receptor (5-HT<sub>2C</sub>R) is a promising intervention for the treatment of obesity[1]. However, one of the main obstacles of this approach is to obtain truly selective agonists, as related off-target effects on 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> subtypes are associated with unacceptable central nervous system and cardiac risks. The use of allosteric modulators (AMs) is an attractive alternative, since enhanced subtype selectivity profiles may be obtained, potentially leading to improved safety and pharmacology profiles[2][3]. In this context, our research project is focused on the development of 5-HT<sub>2C</sub>R AMs as safer anti-obesity drugs.

In a screening of Vivia's library (ca. 1600 compounds) using the high sensitivity automated flow cytometry platform ExviTech®, hit VA240 was identified as a moderate positive allosteric modulator (PAM) of the 5-HT<sub>2C</sub>R (20% potentiation of 5-HT E<sub>max</sub> at 10 μM). A medicinal chemistry program around this hit led to compound VA012 that exhibits enhanced efficacy (35% potentiation of 5-HT E<sub>max</sub> at 10 μM), no significant off-target activities, and no competition with the endogenous agonist. The compound was found to be very active in feeding models in rodents, reducing both food intake and body weight gain without causing CNS-related malaise when administered subchronically. The effects were not related to 5-HT<sub>2A</sub>R activation and a potentiation of the anorectic action of VA012 was observed when administered in combination with the SSRI sertraline, which suggests an allosteric modulation of serotonin effect in vivo. These results support the interest of a 5-HT<sub>2C</sub>R PAM as a promising therapeutic approach for obesity.



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## DESIGN, SYNTHESIS, AND FUNCTIONAL CHARACTERIZATION OF NEW PHOTOSWITCHABLE NEUROMUSCULAR LIGANDS

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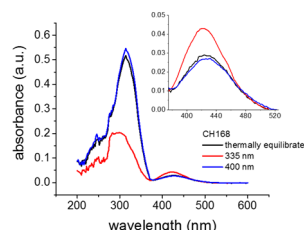
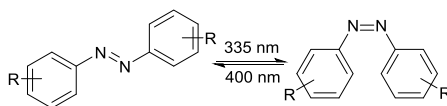
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**Keywords:** *nicotinic receptors, neuromuscular ligands, photopharmacology*

Nicotinic acetylcholine receptors (nAChRs) are widely distributed in both central and peripheral nervous system and are composed by combinations of  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ , and  $\epsilon$  subunits. nAChRs can be classified into neuronal nAChRs (e.i.,  $\alpha 7$  or  $\alpha 4\beta 2$ ) and skeletal muscle nAChRs (mainly composed by  $\alpha \gamma \alpha \delta \beta$  subunits). In the PNS, muscle-type nAChRs mediate synaptic transmission at the neuromuscular junction [1]. The alkaloid pancuronium is commonly used in general anesthesia as muscle relaxant although it causes a number of adverse side effects, mainly due to its interaction with neuronal nAChRs [2].

Recently, we have designed, synthesized, and biologically evaluated new selective photoswitchable muscular nAChR ligands with lower affinity for



neuronal receptors, by combining structural requirements of pancuronium with a photoisomerizable azobenzene scaffold [3]. The objective is to induce light-controlled skeletal muscle paralysis hence reducing CNS-related adverse effects.

These compounds display good water solubility, can be easily isomerized by irradiation (335-400 nm) and are potent nicotinic ligands with a clear selectivity (up to 60-fold) for the muscular nAChRs ( $K_i = 35\text{-}42$  nM), compared to neuronal  $\alpha 7$  and  $\alpha 4\beta 2$  nAChRs. Moreover, all compounds are predicted to be not able to enter in the CNS, thus avoiding potential undesired central side-effects.

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## ANTICANCER ACTIVITY OF NOVEL PHOSPHORATED QUINOLINES

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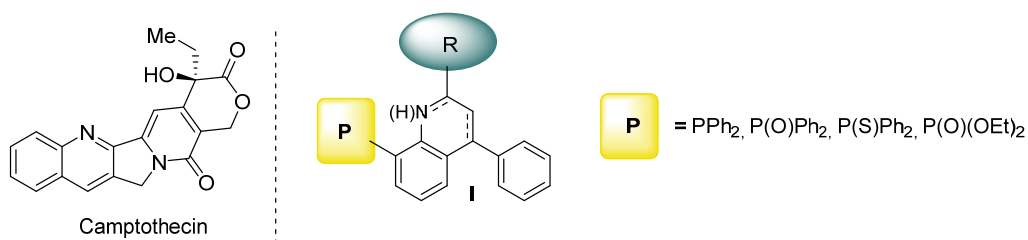
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**Keywords:** *Phosphorated Quinolines, Topoisomerase I, Enzyme inhibition, Antiproliferative effect*

The Povarov reaction [1] is a highly atom-economic tool for the incorporation of nitrogen into chemical compounds, such as quinolines, one of the privileged scaffolds present in drugs and natural products. Moreover, organophosphorus derivatives are interesting compounds from a biological point of view, since it is known that phosphorus substituents may affect the reactivity of heterocycles and regulate important biological functions [2]. In this sense, in an effort of finding new candidates with improved anticancer activity and based on the success of camptothecin (CPT) and its derivatives as inhibitors of Topoisomerase I (TopI) [3], we report here novel phosphorated quinolines as new possible candidates for Top I inhibition.

Povarov reaction led to the formation of *endo* tetrahydroquinoline derivatives with the control of two stereocenters in a regio- and stereoselective manner and in the presence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  as Lewis acid [4].

Some of the prepared products **I** showed excellent activity as TopI inhibitors. The cytotoxic effect on cell lines derived from human lung adenocarcinoma (A549), human ovarian carcinoma (SKOV03) and human embryonic kidney (HEK293) was also screened.



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## NOVEL MULTITARGET NRF2 INDUCERS WITH POTENT ANTIINFLAMMATORY PROPERTIES AND NEUROGENIC EFFECT FOR THE TREATMENT OF ALZHEIMER DISEASE

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**Keywords:** *Neurodegenerative diseases, neuroinflammation, oxidative stress, Nrf2 induction, Innovative drugs.*

Strategies aimed at the development of drugs for Alzheimer's disease based on the classic targets have failed in clinical practice. The number and interrelation of pathological events of Alzheimer's disease have redirected the search for drugs.<sup>1</sup> Thus, strategies based on new therapeutic targets and their combination in a single drug are emerging paradigms on the development of new treatments. Following these premises, we present the design, synthesis and pharmacological evaluation of a new family of multitarget compounds, the 3-alkylamino-1H-indolyl acrylate derivatives. Novel compounds have been designed to act on unconventional targets for the treatment of Alzheimer's disease including the Nrf2 factor. The transcription factor Nrf2 plays an important role in the defense against oxidative stress and neuroinflammation, two of the main pathological pathways connected to the advance of the disease. Besides, the Nrf2 pathway is deregulated in Alzheimer's disease.<sup>2</sup> Novel compounds have been designed to act on unconventional targets for the treatment of Alzheimer's disease.<sup>3</sup> The *in vitro* and *ex vivo* models performed raised compound 1 as lead compound, demonstrating its activity on several nodes of the pathological network of the disease, and its capacity to avoid neuronal death. In addition, it also has neurogenic properties, making it an excellent candidate for the treatment of Alzheimer's disease.

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# UNEXPLORED CHEMISTRY OF ISOCYANIDES: MODULAR ACCESS TO N-HETEROCYCLIC SCAFFOLDS WITH APPLICATIONS IN MEDICINAL CHEMISTRY

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**Keywords:** *Isocyanides, Multicomponent reactions, Heterocycles, Anti-infective agents*

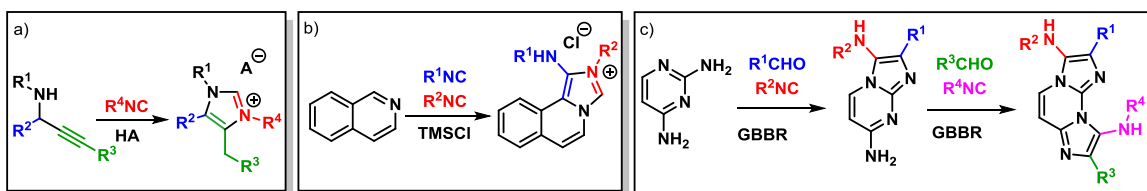
Multicomponent reactions (MCRs) are influential in modern medicinal chemistry in several ways, as the synthetic route to many bioactive compounds and rapid generation of lead libraries for screening purposes [1]. Isocyanides are popular components in MCRs due to their unique reactivity.

This work tackles some unexplored chemistry of isocyanides for the modular synthesis of novel bioactive scaffolds and studies their applications in medicinal chemistry:

- The interaction of isocyanides and propargylamines yielded tetra-substituted imidazolium salts [2] that demonstrate antiparasitical activity against *Trypanosoma cruzi* and *brucei* at nonomolar level. (**Figure a**)

- A TMSCl catalyzed Reissert-type reaction, featuring the novel insertion of isocyanides to N-Si bond as the mechanistical key step, was exploited to yielded a library of aminoimidazo(iso)chinolinium salts. Some of the synthesized compounds displayed potent antiparasitic properties against *T. brucei* and *T. Cruzi* [3]. (**Figure b**)

- The application of multiple Groebcke-Bienaymé-Blackburn reactions on polyaminoazines yielded a variety of new N-fused heterocyclic scaffolds (aminoimidazopyridines) with several diversity points. Some adducts displayed pH and environment sensitive fluorescent properties. A novel BODYPY-type adduct was synthesized and used for staining lysosomes in mammal cells. Moreover, some adducts demonstrated potent antiviral activity against human Adenovirus. Furthermore, selected compounds showed selective affinity to G-quadruplex DNA sequences, suggesting potential applications in medicinal and biological chemistry. (**Figure c**)



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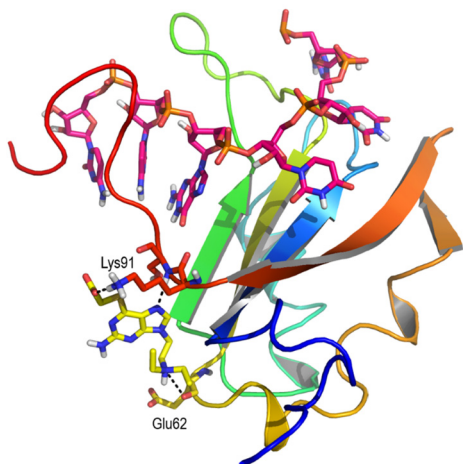
## IN SILICO IDENTIFICATION AND IN VIVO CHARACTERIZATION OF SMALL MOLECULE THERAPEUTIC HYPOTHERMIA MIMETICS

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Hypothermia has been proven to have a beneficial effect on several pathologies.[1-2] CIRBP is one of the so termed cold-shock proteins involved in this process.[3] In this work, we have detected small molecules capable of modulating the activity of CIRBP in the absence of a cold stimulus, by High Throughput Virtual Screening (HTVS) of the Diversity Set IV of the NCI and 30 compounds of our in-house database. A docking based virtual screening of 1626 compounds as potential ligands to the N- and C-terminal ends of CIRBP led to the selection of 26 compounds that followed the criterion “small molecules that interacted with the flexible part of the molecule and the RNA-binding site, so that they could modulate the activity of the protein with a reasonable binding energy”. These 26 compounds were selected from the HTVS to carry out a second screening through a cell-based Western blot assay to test their ability to modulate CIRBP activity. The combination of both methodologies allowed us to select compound **zr17-2** [4] for an in vivo experiment, which showed an interesting increase of CIRBP expression in several organs of experimental animals. Therefore, we have demonstrated that the effect of hypothermia can be mimicked by small molecules, which can be developed as first-in-class new drugs for the treatment of several diseases. (P201730249).



PyMOL stick and cartoon representation of the predicted binding mode of compound **zr17-2**(yellow sticks) to RNAbound CIRBP model. RNA (magenta sticks). The rainbow coloring of the protein highlights the N-terminal end in blue and the C-terminal end in red.

*This work was supported by the US Department of Defense, Grant MR130239.*

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## DESIGN, SYNTHESIS AND EVALUATION OF SULFONAMIDE-BASED MICROTUBULE DISRUPTORS CAUSING MITOTIC ARREST

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**Keywords:** cytoskeleton, mitotic arrest, apoptosis, sulfonamide, cell death, colchicine.

Tubulin is a heterodimeric protein formed by  $\alpha$  and  $\beta$  subunits, whose polymerization leads to microtubule constitution. Disrupting microtubule dynamics is a successful therapeutic strategy for cancer treatment because microtubules take part in several functions such as cell division, which is enhanced in tumor cells [1].

Among tubulin binding pockets, we are focused on the design of colchicine binding site analogues with the purpose of increasing cytotoxic activity with attenuated side effects and also improving relevant ADME properties, since one of the main drawbacks of the established compounds so far, is the low-hydrosolubility profile. With this aim, we have designed a new family of derivatives (Fig.1), based on published ligand-protein X-ray structures and preliminary work performed in our lab [2].

The *in silico* docking studies yielded a few compounds that have been synthesised and then, we have performed tubulin polymerization inhibition assay in order to test the target. Most of these new ligands have shown IC<sub>50</sub> below 100 nM when tested against tumor cell lines. We have also checked the cell cycle distribution by flow cytometry as they act through G<sub>2</sub>/M arrest with its resulting apoptosis, and microtubule disruption by confocal microscopy. We have obtained hydrosolubility values by a shaking flask assay and by NMR.

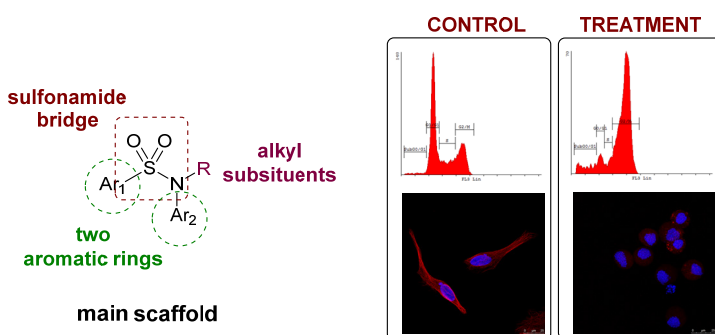


Fig.1. Basic structure of the new family, effect in cell cycle distribution and microtubules captured by confocal microscopy.

### Acknowledgements

This work was funded by Consejería de Educación de la Junta de Castilla y León and FEDER funds (SA030U16) and the Spanish Ministerio de Economía y Competitividad (SAF2014-59716-R).

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## FLASH PRESENTATIONS

# AMIDE-CONTROLLED, ONE-POT SYNTHESIS OF TRI-SUBSTITUTED PURINES GENERATES STRUCTURAL DIVERSITY AND ANALOGUES WITH TRYPANOCIDAL ACTIVITY

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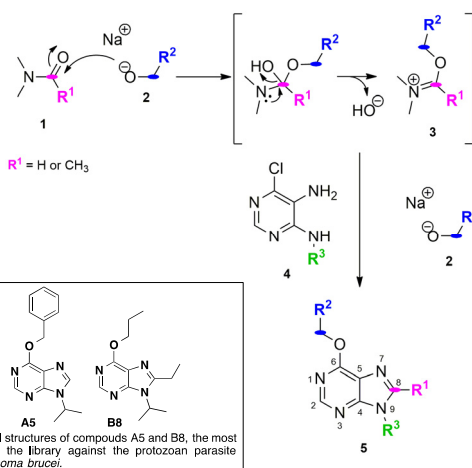
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**Keywords:** *Purine, Medicinal Chemistry, Synthesis*

A one-pot synthetic method to prepare poly-substituted purines from 4-alkylamino-5-amino-6-chloropyrimidines using primary alcohols, sodium hydride and N,N-dimethylamides is reported<sup>1</sup>. Under the same reaction conditions, reactants underwent diverse synthetic routes based on the amide employed, leading to different polysubstituted purines. While one of the processes has been previously described<sup>2</sup>, the second one is a novel tandem reaction initiated by a metal-free conversion of the primary alkoxide into the corresponding aldehyde, followed by base Schiff base formation via condensation with the pyrimidine amino group in C5 and subsequent annulation driven by an oxygen-promoted alkaline oxidation.



Among the variety of structures generated, two purine analogues (A5, B8) displayed trypanocidal activity<sup>3</sup> against the protozoan parasite *Trypanosoma brucei* with IC<sub>50</sub> < 5 μM, being each of those compounds obtained through each of the synthetic pathways.

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## ALKALOID-LIKE, BENZO-FUSED DIAZABICYCLIC COMPOUNDS AS NEUROPROTECTIVE AGENTS

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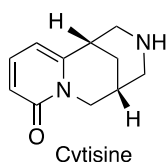
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**Keywords:** *Neurodegenerative diseases, antioxidant compounds, diazabicyclic compounds, neuroprotection.*

Increased oxidative stress is one of the most important events involved in the neuronal damage leading to the development of neurodegenerative diseases.<sup>[1]</sup> Therefore, therapies based on molecules with strong antioxidant properties represent an effective way to prevent or decrease neuronal death.<sup>[2]</sup>

Cytisine, a *Fabaceae* alkaloid, has been identified as an agonist of  $\alpha_7$  nACh receptors, and may therefore be expected to induce the antioxidant transcription factor Nrf2.<sup>[3]</sup> Based on this hypothesis, we have synthesized two series of analogues of this natural product starting from suitably functionalized tetrahydroquinolines obtained by an aza-vinylogous Povarov reaction.<sup>[4]</sup>



The compounds synthesized generally displayed a good direct antioxidant capacity in the ORAC assay, compared to the reference compound (trolox). They also showed the ability to induce Nrf2, as assessed in AREc32 cells, and had neuroprotective effects in two cellular models of oxidative stress: rotenone/oligomycin A and okadaic acid. Further investigations are in progress to elucidate more precisely the role of nAChR modulation in these neuroprotective effects.

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## PROMISING HITS AS SELECTIVE MMP13 INHIBITORS

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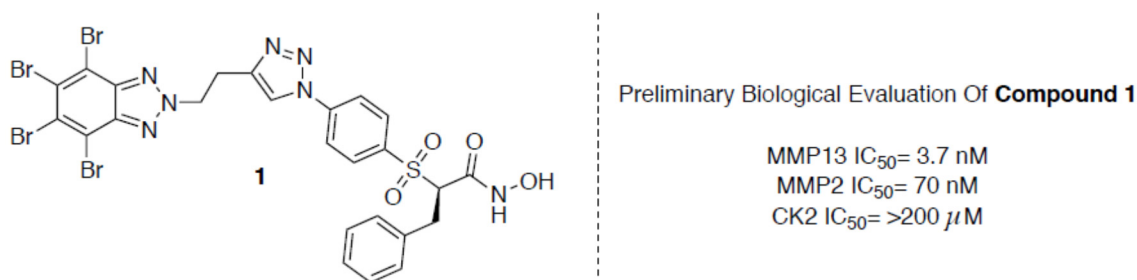
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**Keywords:** *Matrix Metalloproteases, Design and synthesis of MMP inhibitors.*

Matrix metalloproteinase-13 (MMP13) is considered as an important target in diseases in which this enzyme is overexpressed and/or where excessive collagen degradation is involved. Examples of such pathological states are breast cancer, including the process of metastasis, osteoarthritis, and rheumatoid arthritis [1].

A broad-spectrum MMP inhibitors have been developed preclinically and many have continued to clinical trials for various diseases, but no MMP inhibitor has been approved for use in patients [2]. Significant challenges exist for the development of MMP13 inhibitors, and because MMPs play such a significant role in human physiology, non-selective inhibitors within the family often produce a variety of undesired side effects.

In our group, we are currently working on the design of dual CK2/HDAC and CK2/MMP inhibitors [3]. Recently, we have found that **Compound 1**, which was designed to behave as a dual CK2/MMP inhibitor, is completely inactive on CK2, but shows a potent and selective activity towards MMP13. Based on this result we have designed and synthesized a series of compounds with promising activity and selectivity to be developed as new antiinflammatory and anticancer agents.



**Figure 1.** Chemical structure of **Compound 1** and *in vitro* data.

**Acknowledgment.** This work is supported by (CTQ2014-52604-R) and (CEU MPC 15/11)

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## SYNTHESIS OF NEW AMINOGLICEROL DERIVATIVES AS POTENTIAL ANTIBACTERIAL AGENTS

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**Keywords:** *Urea, aminoglycerol, antibacterial agent*

Based on our previous work in the synthesis of new small libraries of compounds with potential antimicrobial activity [1,2] the major aim of this report is to present the design and synthesis of three collections of urea derivatives from aminoglycerols as new potential antibacterial agents.

The prototype was 1-(4-Chlorophenyl)-3-[2,3-bis-(2-methylbenzoyloxy)propyl]urea, that has shown antibacterial activity against colistin-resistant clinical strains of *Acinetobacter baumannii*. A central core was an aminoglycerol, that was functionalized with a urea group on the nitrogen atom, because it could be important for biological activity [1], and alcoholic functions were both functionalized with acyl groups.

According to these result three new collections of prototype analogues were synthesized by a short and high yielded methodology. The 3-amino1,2-propanediol, commercially available, was employed as precursor of new compounds. In the first route, the urea group was introduced through reaction with different substituted phenylisocyanates. In the second route, sulfonic ester group or acyl functions with electron withdrawing or electron donating groups were introduced, to obtain the final molecules.

The antibacterial activity of synthesized compounds was evaluated against seven strains representing different types of gram-positive and gram-negative bacteria: *Bacillus subtilis*, *Staphylococcus aureus*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella enterica*, *Serratia mercenscens*. Antifungal activity is also evaluated against *Candida albicans*.

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## TOWARDS SELECTIVE PHOSPHATASE INHIBITION: A NEW PTPRZ1 BINDING MODE PROPOSAL PROMOTES RATIONAL DESIGN OF COMPOUNDS THAT INCREASE PTPRZ1/PTP1B SELECTIVITY.

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**Keywords:** *PTPRZ1, PTP1B, SBDD, docking, MD, drug discovery.*

Protein tyrosine phosphatases (PTP) have been long studied as novel pharmacological targets implicated in several diseases such as cancer, Parkinson and diabetes. Selective inhibition of phosphatase activity has been challenging to achieve, due to the high structural and sequence homology among PTPs. PTP inhibition has mainly targeted the phosphatase active site, leading to analogues which have shown promiscuous activity. [1] For this reason, allosteric inhibition and cryptic pocket exploration have emerged as a new strategy to modulate PTP activity. Based on this strategy, our goal is to reach selective inhibition of PTPRZ1, due to its interesting pharmacological properties and specially to its implication in alcoholism and degenerative diseases. [2]

A so called “superopen conformation” has been proposed as an alternative binding mode for PTPRZ1 inhibition. [3] This conformation arises from the opening of the WPD-loop (Trp-Pro-Asp) next to the active site and seems to be induced upon binding of halogen-containing derivatives. This ligand-induced cryptic pocket, has been thoroughly studied by computational methodologies, mainly Molecular Dynamics (MD) simulations. Taking into account these molecular modeling studies, we have designed and synthesized new analogs based on the structure of a recently reported 4-trifluoromethylsulphonylbenzyl[4]. The *in vitro* results show high activity towards PTPRZ1 and selectivity against PTP1B which has been used as PTP reference. The proposed bindingmodes and binding affinities were assessed by means of molecular dynamics studies (including MD-ISMSA [5]).

**Acknowledgment:** This work is supported by Ministerio de Sanidad (MSSSI), Plan Nacional Sobre Drogas (PNSD2015I001) and MINECO (CTQ2014-52604-R). BdiG thanks Fundación Universitaria San Pablo CEU and Ministerio de Educación, Ciencia y Desarrollo (MECD) for FPI and FPU15/02857 scholarships, respectively.

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## ANTIMITOTIC AMIDES BASED ON COMBRETASTATIN A-4

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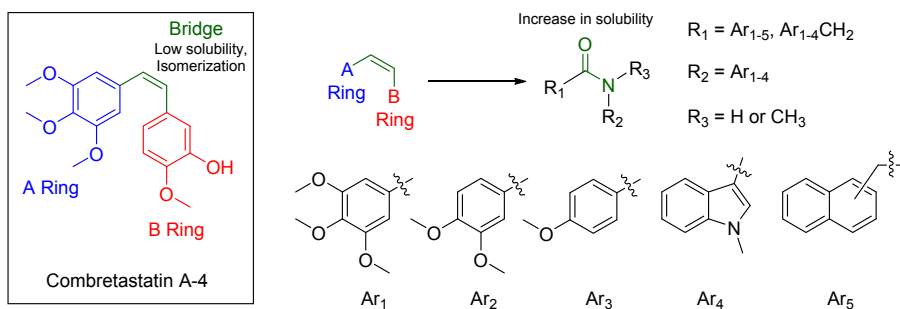
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**Keywords:** *tubulin, colchicine, combretastatin A-4, amides.*

Microtubules are formed by self assembly of  $\alpha$  and  $\beta$  tubulin heterodimers, and their crucial role in mitotic cell division makes them an attractive target for the design and development of natural and synthetic anticancer drugs.

Combretastatin A-4 (CA-4) is a natural product that affects microtubule dynamics by binding to the colchicine site of tubulin and shows potent cytotoxicity. However, its main disadvantages are the low solubility in aqueous media and the isomerization of the cis-configured double bond [1].

On one hand, to address the drawbacks, the olefinic bridge has been changed for an amide moiety in order to improve hydrosolubility. In the synthesized compounds, we explored the importance of the trimethoxyphenyl ring by removing some of the methoxy groups. Meanwhile B ring was substituted by different moieties, like indole, naphthalene, methoxyphenyl and dimethoxyphenyl. On the other hand, the nitrogen of these amide analogues of CA-4 has also been substituted with a methyl group.



The synthesis of compounds, its biological evaluation (including cytotoxicity against cervix cancer cell line HeLa, as well as tubulin polymerization inhibition) and docking studies will be presented in this work.

### Acknowledgments

Financial support came from Consejería de Educación de la Junta de Castilla y León (SA030U16) and FEDER funds.

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## SYNTHESIS OF FALCARINOL-TYPE COMPOUNDS AND *IN VITRO* LEISHMANICIDAL ACTIVITY

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**Keywords:** *Tridax procumbens*, *falcarinol-type*, *synthesis*, *SAR*, *Leishmania*, *in vitro*.

Leishmaniasis is caused by protozoan *Leishmania* parasites and is transmitted to humans by the bite of infected female phlebotomine sandflies [1]. The WHO includes leishmaniasis among the **Neglected Tropical Diseases** (NTDs). The treatment of leishmaniasis depends on several factors including type of disease, concomitant pathologies, parasite species and geographic location. Nowadays, there is no effective vaccine against this disease in humans, and the common therapeutic approach is limited to a reduced number of drugs, including toxic pentavalent antimonials (Sb<sup>V</sup>), miltefosine and amphotericine B (AmB) [2]. Consequently, new drugs against leishmaniasis are urgently demanded.

Biodiversity remains as a largely unexplored and practically unlimited source of medicinal and bioactive substances useful in therapeutics, especially against cancer, virus, or microbial and parasitic infections. Mexico is among the richest countries in biodiversity, and the study and validation of its medicinal natural resources are considered priorities among the objectives of the research aimed at combating the endemic diseases in the country. *Tridax procumbens* is a medicinal plant belonging to the *Asteraceae* family. It is attributed analgesic, antidiabetic, anti-inflammatory and antiparasitic properties among others [3].

Fatty alcohols such as those of falcarinol-type are common components of *T. procumbens*. The synthesis of some falcarinol-type molecules and their leishmanicidal activity will be discussed [4]. The results of the relationship between the structure and the activities (SAR) will be presented.

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## PARKINSON'S DISEASE: POTENTIAL THERAPEUTIC ALTERNATIVES BASED ON THE COUMARIN SCAFFOLD

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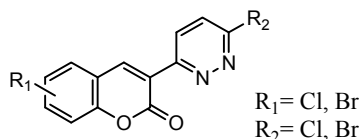
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**Keywords:** *Coumarins, MAO-B inhibition, Parkinson's disease, Reserpine model*

Parkinson's disease (PD) is the second most common neurodegenerative disease. Monoamine oxidase B inhibitors are used in the treatment of this disease concomitantly with levodopa or in monotherapy [1]. Due to the limited number of MAO-B inhibitors (MAOI-B) in the clinic, numerous research efforts continue to address the discovery of new MAOI-B. Most existing MAO inhibitors produce side effects due to lack of affinity and selectivity. Currently, there is an urgent need to develop novel, potent, reversible and selective inhibitors for MAO-B [2].

In recent years our group has demonstrated that the coumarin structure is a scaffold suitable to obtain new potent and selective MAOI-B. In continuation of our research on novel MAOI-B of 3-heteroaryl coumarin structure [3], we describe herein a new series of halogenated coumarins substituted at C3 with a functionalized pyridazine ring.



Most of the 3-heteroaryl coumarins in this series have proved to be potent and selective MAOI-B with activity in the nanomolar range in the *in vitro* studies. Therefore, the most potent derivative of the series, was selected for *in vivo* studies in hypokinetic reserpine-treated mice. In this model of Parkinson's disease it was observed that this derivative (100 mg/kg) caused a significant reversal of the effects of reserpine on motor activity compared to the control. The results obtained demonstrate the potential of this series of compounds as potential drug candidates for the treatment of Parkinson's disease.

### Acknowledgments

Financial support from Universidade de Vigo, Universidade de Santiago de Compostela, the Consellería de Cultura, Educación e Ordenación Universitaria (CN2012/184, 2017-PU027, EM2014/016 and Centro singular de investigación de Galicia acreditación 2016-2019, ED431G/05) and the European Regional Development Fund (ERDF), is gratefully acknowledged.

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## EXPLORATION OF THE $\alpha\beta$ TUBULIN INTERFACE AT THE COLCHICINE-DOMAIN THROUGH CYCLOHEXANEDIONE DERIVATIVES

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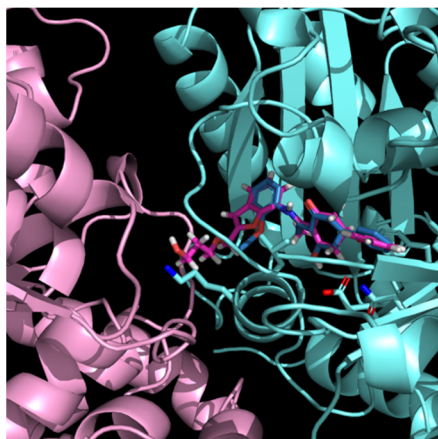
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**Keywords:** *Colchicine, tubulin, dimer interface, structure-based design*

Compounds binding at the colchicine site in tubulin are interesting antitumor agents due to their vascular-disrupting activity, in addition to their antimitotic action [1]. Structural information about the binding of these compounds at the colchicine domain can be extremely useful for the design of new chemical prototypes or the optimization of existing ones.



We have reported that cyclohexanedione derivatives are a new family of colchicine-site binders, the prototype being TUB075. This compound binds tubulin with an affinity constant of  $1.3 \times 10^7 \text{ M}^{-1}$  and has shown antiproliferative activity in the low sub $\mu\text{M}$  range [2]. The structure of its complex with tubulin has recently been solved and new derivatives have been designed based on affinity maps [3]. Interestingly these new compounds present an improved affinity for tubulin. Docking studies, followed by molecular dynamics

simulations with one of these new ligands (TUB125), have shown that the compound occupies a large area at the colchicine domain, from the deeper pocket at the  $\beta$ -subunit towards the  $\alpha\beta$ -interface. Based on this binding mode, new derivatives have been designed locating polar groups at the dimer interface.

**Acknowledgements:** This project has been financed by the Spanish SAF2015-64629-C2-1-R (MINECO-FEDER), BFU2016-75319-R (AEI/FEDER, UE) from MINECO, and the COST action CM1407 (to M-J. P.-P. S.L. and J.-F.D.)

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## TUNABLE HEPARAN SULFATE GLYCOMIMETIS FOR PROMOTE NEURAL DIFFERENTIATION

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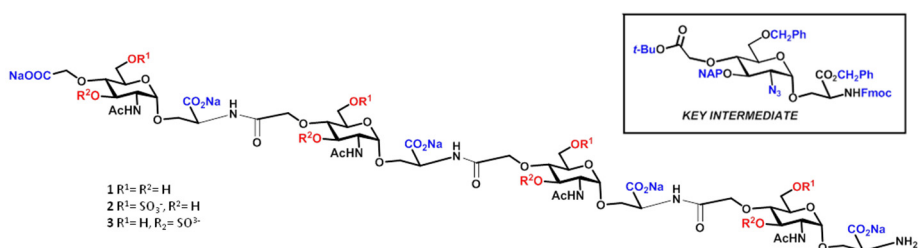
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**Keywords:** *glycosaminoglycans, heparan sulfate glycomimetics, neurotrophic factors*

Heparan sulfate (HS) glycosaminoglycans regulate a variety of cellular processes by binding to a number of growth factors and morphogens. However, a limitation in the study of these processes is the chemical complexity and heterogeneity of HS from biological sources. Moreover, the chemical synthesis of these molecules is difficult due to the multiple steps normally required in carbohydrate synthesis and the control of the stereo selectivity in the glycosidation reactions [1]. Because of this, a detailed understanding of sulfation pattern -activity relationships of HS are lacking. Recently our group has developed a divergent strategy to afford heparan sulfate glycomimetics, in which different combinations and sequence of transformation steps can be applied with only one intermediate leading up to multiple target products with different sulfation profiles (3- or 6-monosulfated, 2-N-monosulfated, 3,6-disulfated, etc., or a combination thereof) in simple and direct synthesis.



Herein we described the synthesis and the interaction of 3- and 6- monosulfated derivatives with fibroblast growth factor-2 (FGF-2). Finally, the capability of comprehensive sugar libraries in providing key insights in glycan–ligand interaction has been studied by molecular docking calculation.

**Acknowledgments:** The authors gratefully acknowledge financial support provided by the Spanish Ministerio de Economía y Competitividad (Grants MAT2015-65184-C2-1-R and MAT2015-65184-C2-2-R).

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## NEW HYBRIDS DERIVED FROM PODOPHYLLIC ALDEHYDE AND DITERPENYLHYDROQUINONES SELECTIVE TO OSTEOSARCOMA CELLS.

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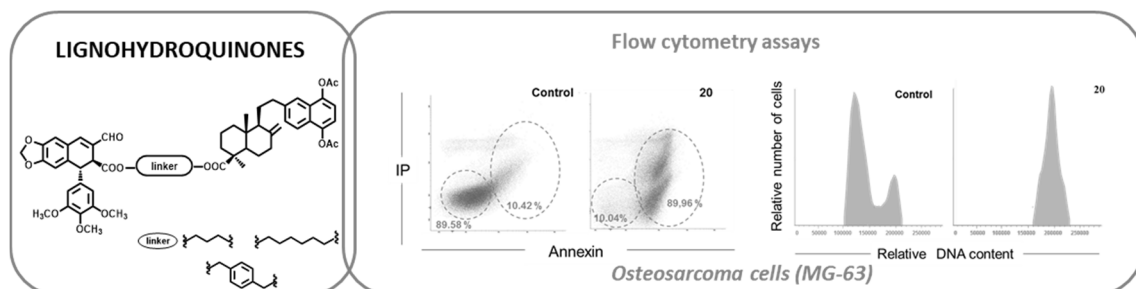
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**Keywords:** *Cyclolignans; natural product hybrids; podophyllic aldehyde; diterpenylanthrohydroquinones; cytotoxicity; flow cytometry.*

A new family of molecular hybrids, between cyclolignans related to podophyllic aldehyde [1] and several diterpenylhydroquinones,[2] was prepared. Both fragments are obtained from the natural products podophyllotoxin and the diterpenoid myrceocommunic acid, isolated from their natural sources.

The precursors of the hybrids, were attached by aliphatic and aromatic linkers through ester bonds. Final compounds and intermediates were evaluated *in vitro* against three solid tumour cell lines (MCF-7, MG-63 and HT-29), presenting an interesting cytotoxicity depending on the linker used for the synthesis.

Flow cytometry assays showed that the new hybrid family was selectively cytotoxic on the osteosarcoma cell line MG-63 and the presence of an aromatic ring as a linker gave the most potent and selective agent, improving the cytotoxicity of the parent compounds. Cell cycle studies [3] demonstrated that this hybrid induces a strong and fast apoptosis effect and arrests cells at the G2/M phase of the cell cycle.



**Acknowledgement:** Financial support from Junta de Castilla y León, co-financed by Fondo Social Europeo (SA221U13, LE182U13 and predoctoral fellowship to A.P.H.G.) and MINECO (CTQ2015-68175-R).

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## DIVERSITY-ORIENTED SYNTHESIS OF PYRROLE-RELATED FRAMEWORKS FOR LEAD DISCOVERY VIA HIGH-THROUGHPUT SCREENING

M. Leonardi<sup>1</sup>, M. Villacampa<sup>1</sup>, J. C. Menéndez<sup>1</sup>

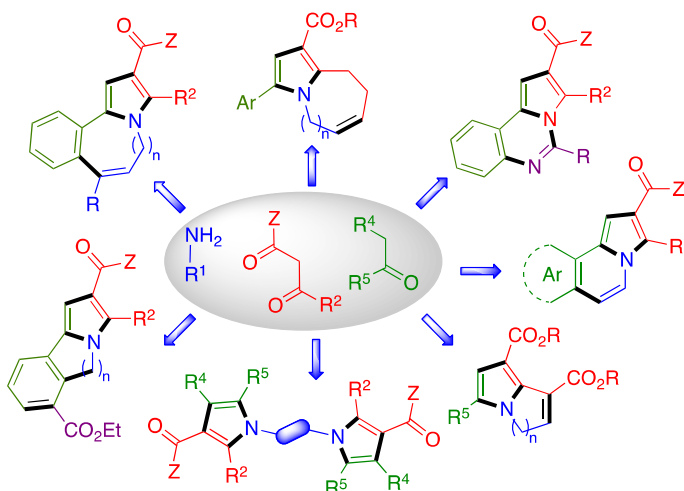
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**Keywords:** *Build/couple/pair strategy, multicomponent reactions, high-speed vibration milling, high-throughput screening.*

Using the *build/couple/pair* strategy[1], we describe the generation of diversity-oriented libraries from pyrrole cores. The starting materials were prepared by a solvent-free mechanochemical methodology developed by our group[2,3], involving a generalization of the traditional Hantzsch pyrrole synthesis under High-Speed-Vibration-Milling (HSVM) conditions from primary amines,  $\beta$ -dicarbonyl compounds and ketones. The target frameworks were constructed in an additional step *via* a variety of complexity-generating reactions such as intramolecular cycloadditions, Heck, metathesis and C-H activation reactions. Exploiting the same mechanochemical methodology, double and triple Hantzsch-like reactions were also possible.

The libraries thus obtained were studied through the Eli Lilly Open Innovation Drug Discovery (OIDD) program and have led to several interesting hits in the areas of inflammation and neurodegenerative diseases.



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## SYNTHESIS AND METAL CHELATING PROPERTIES OF AMINOPHENANTHRIDINONES AS POTENTIAL THERAPEUTIC AGENTS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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**Keywords:** *Alzheimer's disease, metal chelation, aminophenanthridinone.*

Alzheimer's disease (AD) is the most common form of dementia, affecting millions of patients worldwide. AD is characterized by the aggregation and accumulation of two proteins in the brain, beta-amyloid (A $\beta$ ) and tau, which are the pathological hallmark of this disease. On the other hand, a growing body of evidence supports important role of the dyshomeostasis of certain cations, such as copper (Cu), zinc (Zn) and iron (Fe) in AD.<sup>1</sup> Thus, elevated brain iron levels and accumulation of copper and zinc, enhances the formation of cerebral beta-amyloid deposits in AD patients. The development of compounds designed to target the interactions of A $\beta$  and metal ions has been hampered by poor ion specificity and the inability of most chelating agents to cross the blood brain barrier (BBB). Thus, only a few chelators, most notably clioquinol and its derivatives, have been explored as potential therapeutic agents for the treatment of AD.

In this context, our group has reported a new one-pot methodology for the synthesis of m-teraryl compounds.<sup>2</sup> As an extension to this work and due to our interest in the discovery of small molecules for the treatment of neurodegenerative diseases, we describe in this communication the synthesis of phenanthridin-6(5*H*)-ones in one additional step by a microwave-assisted nitro reduction/cyclization/water elimination sequence in the presence of zinc. The ability of the synthesized ligands to bind metals such as Cu(II), Zn(II), Fe(II), Cd(II), Hg(II) and Pb(II) was investigated by UV-vis spectroscopy at physiological pH at 10  $\mu$ M - 200  $\mu$ M concentrations for both ligand and metal. In order to enhance the differences among spectra and to resolve overlapping bands, derivative spectroscopy was applied. The interaction of the phenanthridone derivatives under study with Cu(II), Zn(II) and Cd(II) was confirmed.

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## A ROBUST SENSING SYSTEM FOR ELECTROCHEMICAL DETECTION OF PROTEASES

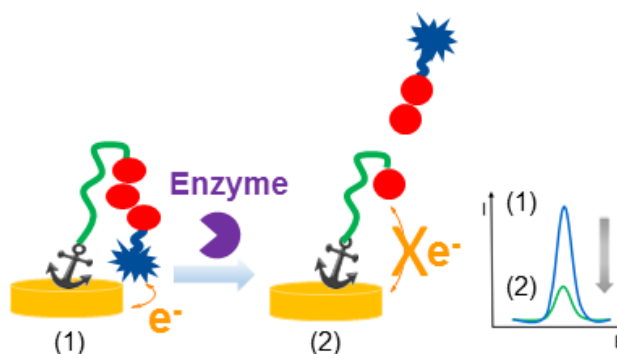
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**Keywords:** *Electrochemical biosensors, peptide chemistry, cancer therapy, protease detection*

Proteases play a pivotal role in many physiological processes and they are associated with a wide range of illnesses. In particular, the proteolytic activity of both intracellular and extracellular proteases, such as matrix metallo-proteinases, contributes to cancer progression in all its stages. In the light of this, many proteases have been identified as potential diagnostic targets increasing the demand for selective and sensitive tools for their *in vivo* detection. Peptide-based electrochemical biosensors are valuable tools for the detection of proteins. These biosensors consist of a peptide labelled with a redox tag and tethered to an electrode surface [1]. When a target enzyme cleaves the peptide, the redox-labelled probe fragment is released, creating a measurable decrease in the electrochemical signal (Fig. 1). A “spacer” is often introduced to make the cleavage location accessible to the enzyme accessibility and to increase the flexibility of the probe. We have reported a systematic study of the effect of polyethylene glycol (PEG)-based spacer length on the performance of such biosensors [2]. We now present a study of different anchoring approaches that improve the stability and robustness of the sensor system.



**Fig. 1.** Principle of detection for the peptide-based electrochemical platform.

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## MULTITARGET DIRECTED LIGANDS FEATURING AN NMDA ANTAGONIST MOIETY: NEW STRATEGIES OF POTENTIAL INTEREST FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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**Keywords:** *Alzheimer's Disease, dual target compounds, neuroinflammation, NMDA, P2X7, MTDL, AChE.*

Multitarget directed ligands [1] are a new hope for the treatment of multifactorial complex diseases as Alzheimer's Disease (AD). Herein, we present compounds aimed to target simultaneously the NMDA receptor and either the AChE or the P2X7 receptors. Our molecules embody a different approach to AD therapy: on the one hand, we seek to delay neurodegeneration by targeting the glutamatergic NMDA receptor and on the other hand, we add on the reduction of neuroinflammation, either by targeting P2X7 receptors or the symptomatic relief by targeting the AChE.

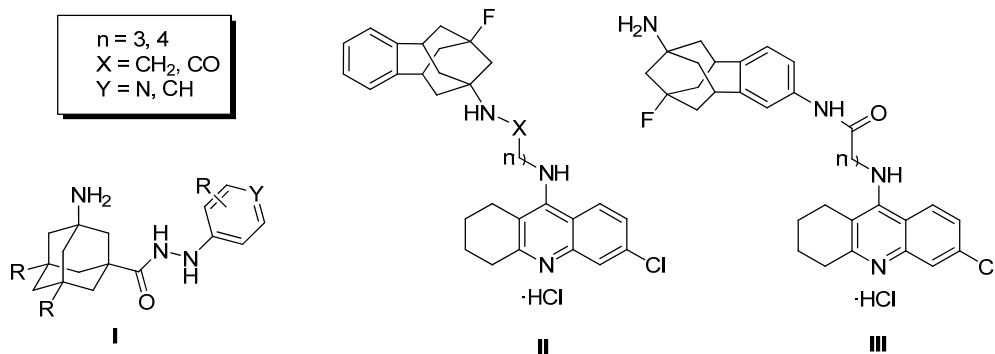


Figure 1. General structures of the two series of benzoadamantane-tacrine hybrids (II-III) and NMDA-P2X7 antagonists (I).

On top of this, meanwhile the NMDA receptor and the AChE are widely recognized as therapeutic targets in AD, the P2X7 receptor is a largely unexplored receptor for this purpose. Therefore, the dual NMDA-P2X7 inhibitors herein presented represent the first members – prone to a severe optimization - of a new class of multitarget-directed ligands.

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## FIRST NON-PEPTIDE DIMERIZATION INHIBITORS OF TRYPANOTHIONE REDUCTASE WITH POTENT *IN VITRO* LEISHMANICIDAL ACTIVITY

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**Keywords:** *Leishmaniasis, Trypanothione Reductase, dimerization, proteomimetic*

Leishmaniasis is a neglected disease caused by *Leishmania* protozoan whose classical treatment requires the administration of toxic and poorly tolerated drugs<sup>1</sup>.

Searching for new alternatives for the treatment of the disease, Trypanothione Reductase (TryR) appears as a selective and validated<sup>2</sup> target because this oxidoreductase enzyme is exclusive and essential for the parasite survival. Since the biologically functional form of the enzyme is a homodimer, our group studies a new inhibition mechanism based on the design of protein-protein interaction (PPI) disruptors. Molecular modeling and site-directed mutagenesis studies identified Glu436 (located in an  $\alpha$ -helix from P435 to M447) as hotspot for catalytic activity and structural integrity of the dimer. Based on these results, a series of peptides and peptidomimetics (derived from the  $\alpha$ -helix containing this hotspot) emerged as potent inhibitors of both the activity and the dimerization of TryR of *L.infantum*<sup>3-5</sup>. However, the use of these compounds as antileishmanials is hampered by their susceptibility to proteolysis and their poor bioavailability. In order to improve the drug-like properties of the previous peptide-based prototypes, we herein report a series of non-peptide *proteomimetics*, based on an imidazole-phenyl-thiazole *scaffold*, that allocate the key residues at the i,

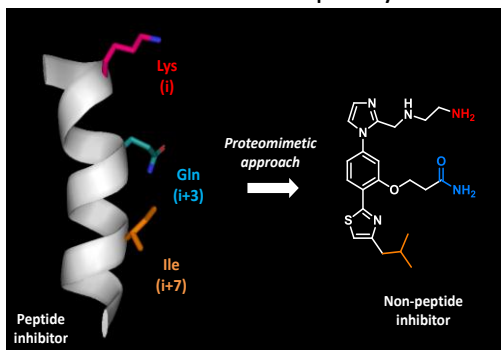


Figure: From peptide inhibitors to non-peptide  $\alpha$ -helix mimetics

i+3 and i+7 positions in a spatial orientation similar to that in the native helix (Figure). Compounds proved to be potent inhibitors of both the activity and dimerization of the enzyme. They also displayed potent *in vitro* leishmanicidal activity against extracellular parasites as well as intracellular amastigotes of *L.infantum* grown in macrophages. The design, synthesis and biological evaluation of these non-peptide  $\alpha$ -helix mimetics will be presented.

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## MODIFIED TRYPTOPHAN DERIVATIVES AS DUAL INHIBITORS AGAINST HIV AND ENTEROVIRUS 71 (EV71) REPLICATION

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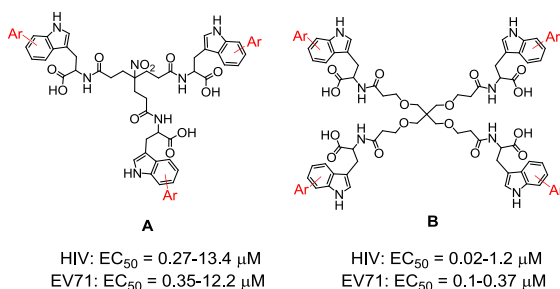
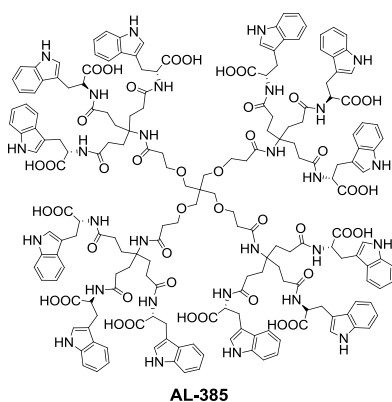
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**Keywords:** *Antiviral agents; AIDS; HFMD; HIV; EV71; Tryptophan; indole; Palladium-catalyzed C-H activation*

We have recently reported a family of Trp dendrimers that are dual inhibitors of HIV and EV71.[1] The prototype compound of this family (**AL-385**) is a pentaerythritol derivative with 12 Trps on the periphery.[2] In the present study, we investigated whether truncation of the prototype could lead to reduced size compounds that retain activity. With this aim, analogues of the prototype with only 3 or 4 Trps have been first prepared. These compounds resulted completely inactive against both viruses. To restore the activity, we decided to introduce aromatic rings functionalized with different groups at the N1, C2[3] and C7[4] positions of the indol moiety.

Biological results showed that only compounds of general formula **A** and **B** bearing phenyl (di)carboxylate groups at the C2 or C7 positions of the indole ring were active against HIV and EV71, while the N1 arylated compounds were inactive against both viruses. The synthesis and antiviral activity against HIV and EV71 of these compounds will be here described.



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## iLAB: DRUG DISCOVERY AND DESIGN RESEARCH IN CO-CREATION

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**Keywords:** *ilab, drug discovery, drug design, co-creation, lab space, expertise, manpower*

Innovation Labs (iLabs)<sup>1</sup> are fully equipped innovation labs that allows the access to companies and academia to research facilities, students and expert scientists in a co-creation setting. The iLab in the HU-University of Applied Sciences Utrecht offers access to over 25 laboratory spaces with up-to-date and specialized equipment to perform life sciences and chemistry experiments in Drug Discovery and Drug design fields. iLab also harbors a chemical engineering hall to explore methods and for pilot testing. Furthermore, iLab offers a team including experienced postdoctoral scientists, technicians and bachelor students for consultancy and manpower to develop your research project. iLab works with three basic models:

1. Our bachelor students perform your research project and our scientists supervise and review the results for you.
2. You come and use our facilities to perform the experiments you desire yourself.
3. A collaboration in which we will work on your project with you hopefully resulting in a long-lasting and sustainable partnership. This is our favorite option.

iLab wants to ensure that practical research projects, in which industry and research institutions work together, contribute to the professional innovation and further professionalization of training. The joint research projects provide industry access to knowledge, skills and costly research facilities. Students will be better prepared for professional work, while scientists can keep their knowledge and skills up to date. Whether you are facing the challenge or seeing opportunities, iLab will explore your specific situation to provide a tailor-made solution to help you to answer your research question.

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[1] [www.ilab-utrecht.nl](http://www.ilab-utrecht.nl)

## SYNTHESIS AND PLATINUM (II) COMPLEXES OF POLYAZACYCLOPHANE RECEPTORS AS POTENTIAL THERAPEUTIC AGENTS

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**Keywords:** *platinum complexes, polyazacyclophanes, coordination chemistry*

During the last years, research on coordination chemistry of platinum has aroused great interest due to their potential biological applications.<sup>1,2</sup> Herein, we report the interaction of  $\text{PtCl}_4^{2-}$  with different polyazacyclophanes containing a pyridine unit as aromatic spacer. Formation of complexes has been studied by  $^1\text{H}$  and  $^{195}\text{Pt}$  NMR spectroscopy. Analysis of the recorded spectra of  $\text{D}_2\text{O}$  solutions containing L and  $\text{PtCl}_4^{2-}$  in a 1:1 molar ratio at acidic pH shows the evolution with time of the  $^1\text{H}$  and  $^{195}\text{Pt}$  signals. Different crystal structures have been solved by X-ray diffraction analysis. At acidic pHs, the metal ion is coordinated by the central amino group of the macrocyclic cavity and three chloride or bromide atoms, in a square planar geometry. Formation of  $[\text{Pt}(\text{H}_2\text{L1})\text{Br}_3]\text{Br}$  (**1**) and  $[\text{Pt}(\text{H}_2\text{L2})\text{Br}_3]\text{Br}$  (**2**) reveals the rapid substitution of chloride ligands in  $\text{PtCl}_4^{2-}$  by bromide ligands. However, as reveals the crystal structure obtained for  $[\text{Pt}^{\text{IV}}\text{L3Br}_2](\text{PtBr}_4)(\text{H}_2\text{O})$  (**4**), at slightly higher pH values, the metal ion is coordinated through all nitrogen atoms of the macrocyclic cavity and an oxidation to Pt(IV) occurs. Four specific oligonucleotides have been selected in order to analyze the interaction of these platinum complexes towards different sequences.

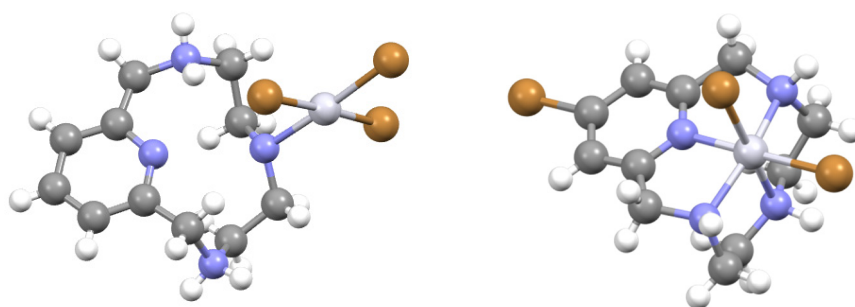


Figure 1. X-Ray crystal structure of the cations  $[\text{Pt}(\text{H}_2\text{L1})\text{Br}_3]^+$  and  $[\text{Pt}^{\text{IV}}\text{L3Br}_2]^{2+}$

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## SYNTHESIS AND STUDY OF NEW CHIRAL MELATONIN – ACETYLCHOLINESTERASE INHIBITOR HYBRIDS TO TREAT NEURODEGENERATIVE DISEASES

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**Keywords:** *Enantioselective organocatalysis, multitarget directed ligands, neurodegenerative diseases*

In the last century, the mean life expectancy has increased around four decades[1]. However, aging has also caused the growth of diseases that a century ago were not frequent such as neurodegenerative diseases (NDDs).

Due to their great complexity, NDDs are considered as multifactorial diseases. This had led to propose and develop the new paradigm of multitarget directed ligands. This strategy emerged on the basis of an assumption that the design of structures able to hit multiple targets could decrease the redundancy effects of the pathological process [2].

In this context, this projects seeks strategies towards the control of neuro-inflammation and oxidative stress, by combining the induction of Nrf2 transcription factor, restoration of cholinergic function and free radical scavenging effect, which would promote the neuroprotection and slow or stop the disease progression.

The synthesis of our target molecules has been designed taking into account the previous premises. After the thorough optimization of the synthetic process, a library of 15 compounds has been obtained with very good yields and enantiomeric excesses.

The new compounds have been evaluated as free radical scavengers, Nrf2 inducers, acetylcholinesterase inhibitors, and neuroprotective agents. Six of them, show all these properties to a promising degree, and therefore we plan to continue their study in more complex models.

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## DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL TOP I INHIBITORS

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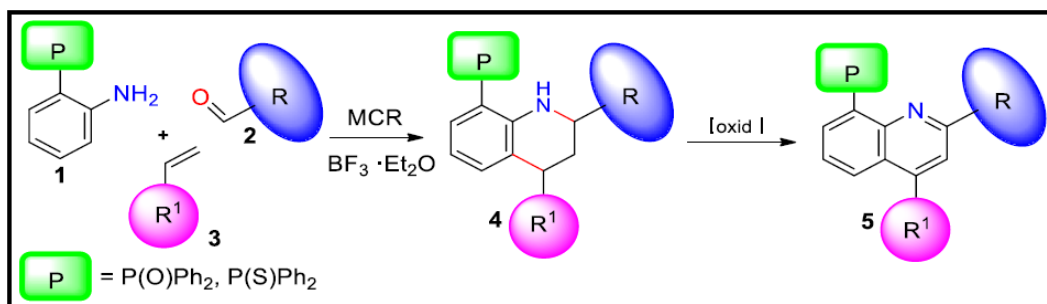
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**Keywords:** *Topoisomerase I, Povarov, MCR*

Among the nitrogen-containing heterocycles, the quinoline is considered a privileged scaffold in the field of Medicinal Chemistry and is found in many bioactive molecules and drugs [1]. Moreover, quinoline structures occupy a prominent position in drug design and development in the area of antitumoral agents and TopI (topoisomerase I) inhibitors [2]. In this context, the Povarov reaction represents a powerful approach to prepare six-membered nitrogen-containing heterocycles [3] and multicomponent reactions (MCR) offer considerable advantages over classic step-by-step strategies [4].

In this work we report the synthesis and the biological evaluation of new candidates for TopI inhibitors with antiproliferative activity. A set of differently functionalized phosphorated quinoline and tetrahydroquinoline derivatives was rationally designed and synthesized by multicomponent reaction (MCR) of anilines **1**, aromatic aldehydes **2** and styrenes **3**, affording tetrahydroquinoline derivatives **4** in a regioselective and diastereoselective way. Afterwards, compounds **4** were dehydrogenated to prepare quinoline derivatives **5**.

Most of the studied compounds have shown a notorious *in vitro* antiproliferative activity against human cancer cell lines SKOV3 and A549, and also presented promising inhibitory effect against TopI mediated DNA relaxation assay.



**Scheme 1.** Synthetic pathway

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# DESIGN AND SYNTHESIS OF NOVEL *m*-TERPHENYLAMINE-TACRINE HYBRIDS COMPOUND AS POTENTIAL MULTITARGET AGENTS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

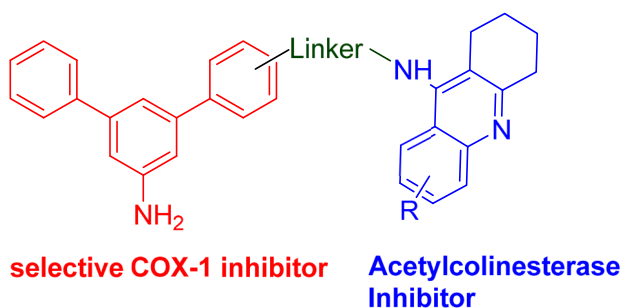
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**Keywords:** *Alzheimer's disease, COX-1, terphenylamines, multitarget drugs.*

Alzheimer's disease (AD) is the most common type of dementia, affecting 1 out of 8 people above the age of 65. It is a complex and multifactorial disease, with several different pharmacological targets that can be tackled, such as: beta amyloid peptides (AB), accumulation of tau protein, decrease in brain acetyl choline (Ach) levels, neuroinflammation, oxidative stress and dyshomeostasis of biometals ( $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Fe}^{2+}$ ). Therefore, it is a suitable disease for the multi-target-directed Ligands (MTDL) approach. Recent studies have shown that COX-1 plays a pivotal role in neuroinflammation and neurodegenerative disease, prompting the current surge in interest in COX-1 selective inhibitors during recent years.<sup>1</sup>

In the context of our interest in the discovery of small molecules for the treatment of neurodegenerative diseases, our group synthesised a family of terarylamine using a route based on a three-component reaction,<sup>2</sup> and as a consequence we discovered a hit compound acting as a selective COX-1 inhibitor. Herein, we present the design and synthesis of first MTDL combining cholinesterase inhibition (tacrine) and selective COX1 inhibitor (terphenylamine).



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## DISCOVERY OF 1,4,4-TRISUBSTITUTED PIPERIDINES AS DUAL INHIBITORS OF INFLUENZA AND HUMAN CORONA VIRUSES

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**Keywords:** *Influenza virus, Coronavirus, piperidine compounds, Ugi four-component reaction*

The recent outbreaks of the highly pathogenic avian A/H5N1 and pandemic A/H1N1/2009 influenza viruses have emphasized the urgent need for the discovery of new anti-influenza compounds. On the other hand, Coronaviruses (CoV) are common etiological agents of acute respiratory tract infections and of potentially pandemic viruses (eg SARS-CoV or MERS-CoV), for which neither a vaccine nor an antiviral therapy is yet available, thus highlighting the need of agents with broad antiviral activity against multiple respiratory viruses.

The piperidine nucleus is an attractive drug template present in agents with applications as anti-histaminic, anti-inflammatory, fungicidal, bactericidal, anticancer, analgesic, CNS stimulant and or anti-depressant activities. In an effort to discover novel broad spectrum antiviral compounds, several molecules of our diverse in-house library were screened against a panel of different influenza virus strains and human 229E coronavirus. Following this approach, we identified 1,4,4-trisubstituted piperidine compounds as interesting *hit* compounds that display antiviral activity against influenza A/PR/8/34 virus (A/H1N1) and coronavirus (229E) in the low micromolar range. To investigate the structure-activity relationships, several analogues were easily synthesized, by a one-step Ugi four-component reaction, from commercially available amines, isocyanides, N-substituted piperidones and a variety of amino acids as carboxylic acid components. Mechanistic influenza experiments consisting of time-of-addition, resistance selection and functional assays for HA-mediated binding or membrane fusion with the most active compound will be reported.

# SYNTHESIS AND STUDY OF NON-HEPATOTOXIC ACETAMINOPHEN ANALOGS

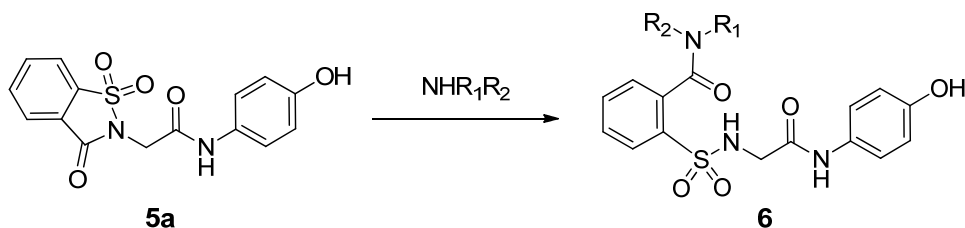
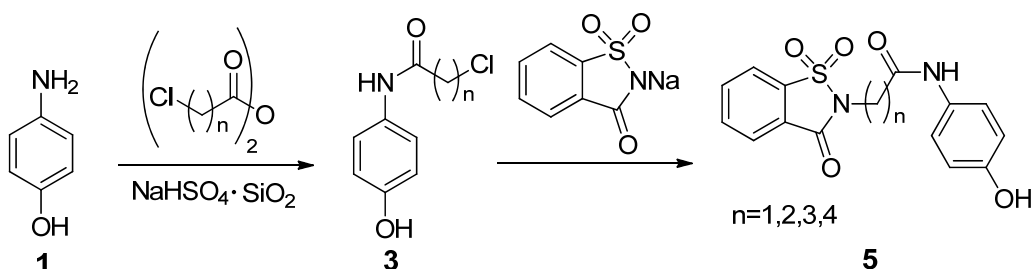
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**Keywords:** *Acetaminophen, Analgesics, Saccharin.*

Acetaminophen (APAP) is typically the analgesic of choice for moderate pain without inflammation. However, it is well established that APAP can cause hepatotoxicity and nephrotoxicity, due the oxidation of APAP to the toxic metabolite, N-acetylbenzoquinoneimine (NAPQI) [1].

A series of compounds bearing the APAP fragment linked to a lipophilic saccharine moiety was synthesized and compounds **5** (Scheme 1) have good analgesic efficacy and devoid hepatotoxicity. In order to modulate the lipophilicity of saccharine derivatives **5**, new series of compounds **6** were synthesized by a ring opening process (Scheme 2) [3][4].



In the present communication, we report the synthesis and the biological results of this novel series of analgesics **6**.

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## NOVEL MITOCHONDRIA-TARGETED, LEISHMANICIDAL DERIVATIVES OF 4-AMINOSTYRYLQUINOLINES

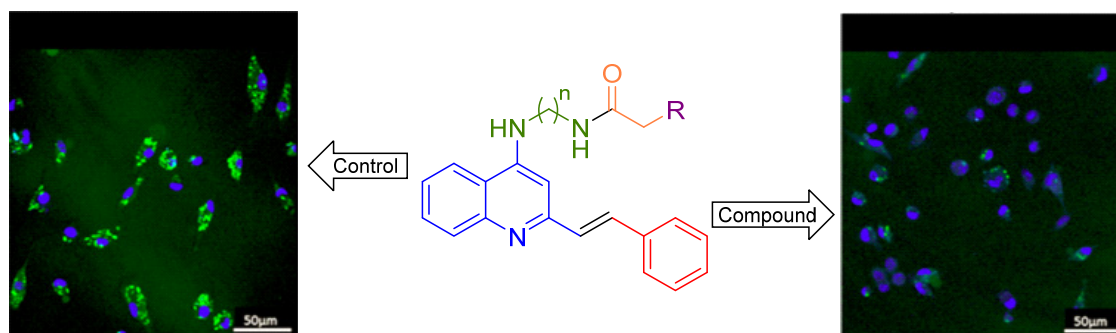
M. Piguero,<sup>1</sup> M. Staderini,<sup>1</sup> M. Nachér-Vázquez,<sup>2</sup> M. A. Abengózar,<sup>2</sup> G. Romanelli,<sup>1</sup> P. López-Alvarado,<sup>1</sup> L. Rivas,<sup>2</sup> M. L. Bolognesi,<sup>3</sup> J.C. Menéndez<sup>1</sup>

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**Keywords:** *Leishmanicidal compounds, neglected tropical diseases, 4-aminostryrylquinoline, mitochondrial-targeted compounds.*

Leishmania is a neglected protozoal tropical disease with a high impact on human health, as it affects more than 2 million patients every year worldwide.[1] Its therapy is currently based on a few drugs with increasing resistance issues,[2] important side effects and relatively high costs and that usually need parenteral administration. Thus, there is an urgent need to develop novel leishmanicidal drugs.[3]

In this context, a new class of quinoline derivatives, bearing amino chains at C<sub>4</sub> and a styryl group at C<sub>2</sub>, were tested on *Leishmania donovani* promastigotes and axenic and intracellular *Leishmania pifanoi* amastigotes. The C<sub>4</sub> substituent improves the activity, due to the interference with the mitochondrial activity of the parasite and its concomitant bioenergetic collapse by ATP exhaustion. Some of these compounds show promising antileishmanial profiles, presenting low micromolar or submicromolar activities on promastigote and amastigote forms.



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## AOX PROPERTIES AND CYTOTOXICITY OF 1,5-BENZODIAZEPIN-2-ONES

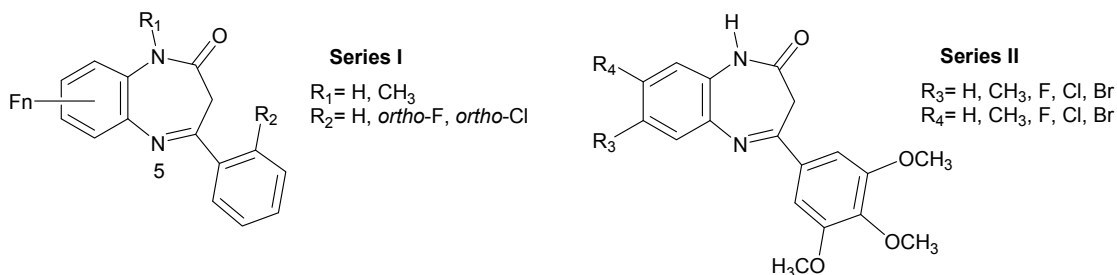
M. Pérez-Torralba<sup>1</sup>, C. López<sup>1</sup>, R. M. Claramunt<sup>1</sup>, A. Ortiz de Zárate<sup>2</sup>, I. Sánchez-Trelles<sup>2</sup>, J. L. Lavandera<sup>2</sup>

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**Keywords:** *benzodiazepinones, solution and solid state NMR, oxidative stress, cytotoxicity*

Two series of benzodiazepinones I and II [1], have been explored for their antioxidant capacity (AOX) and cytotoxicity assays. The *NH* compounds have been prepared by reaction of the appropriate 1,2-benzenediamine with substituted benzoylacetates [2]. Iodomethane/ $K_2CO_3$ /KI in *N,N*-dimethylformamide was used to obtain the *N*-methyl compounds [3].



The antioxidant capacity of these compounds has been determined in the ABTS, DPPH and FRAP radical scavenging assays [4-6], in comparison to Curcumin and Trolox. Also their cytotoxicity in the neuronal cell line SH-SY5Y [7] was better than that found for Curcumin. These activity features make this chemical class an interesting chemotype, worthy to be explored for their potential as neuroprotectant.

**Acknowledgements:** This research has been financed by the Ministerio de Economía y Competitividad of Spain CTQ2014-56833R.

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## MODIFYING THE METHOXY GROUPS OF NEW TUBULIN INHIBITING SULFONAMIDES

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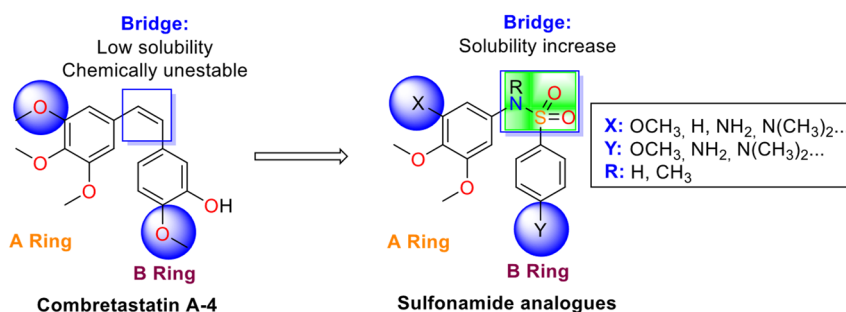
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**Keywords:** *Tubulin, colchicine, sulfonamide, methoxy group.*

Tubulin is a well established anticancer target. Compounds binding at the colchicine site of tubulin are being actively explored as cytotoxic and vascular disrupting agents.

With the aim of obtaining new improved analogues of combretastatin A4 (a potent natural cytotoxic agent which strongly inhibits the polymerization of tubulin, binding at the colchicine site) with better pharmacokinetic profiles and better antimitotic properties, we have explored the colchicine binding site to tubulin by modifying the methoxy groups of the new analogues. The modifications have been carried out by changing the site of the methoxy groups, removing them or replacing them with other groups, like amines. (Fig.1).



**Fig. 1.** Skeleton of the new synthesized sulfonamides.

The results of the tubulin polymerization inhibition (TPI) with *Bos taurus* isolated protein; the cytotoxicity against HeLa and HT-29 cancer cell lines; the water solubility and the results of molecular docking experiments will be presented.

### Acknowledgments

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## DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW MULTITARGET COMPOUNDS FOR THE TREATMENT OF PARKINSON'S DISEASE

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**Keywords:** *Parkinson's disease, dopamine, oxidative stress, Nrf2 factor, MAO-B*

Finding an effective treatment for Parkinson's disease (PD) is one of the major challenges of this century. Currently, there is no curative therapy for PD; there are only symptomatic treatments for this highly complex disease. Depletion of dopamine and selective destruction of dopaminergic neurons, along with the presence of  $\alpha$ -synuclein deposits are typical pathological hallmarks of the disease [1, 2]. In addition, oxidative stress has become as an important target at physiopathological level and it has been currently related with the onset of the disease [3]. It causes deregulation of protein processing, mitochondrial damage and neuroinflammation and these factors, in turn, lead to the increase of oxidative stress, generating a pathological loop that accelerates the progression of PD.

Regarding the complexity of the disease and bearing in mind that it is considered multifactorial, we have designed and synthesized a small chemical library of new multitarget drugs. This design has the objective to combine several activities in one single molecule: (i) NF-E2-related factor 2 (Nrf2) inducing capacity, as Nrf2 factor activates phase II antioxidant response, the principal antioxidant defence of cells; (ii) Monoamine oxidase B (MAO-B) enzyme inhibitory capacity and selectivity, given the importance of dopamine metabolism in the progression of the disease; (iii) Neuroprotective ability. The pharmacological evaluation of the newly synthesized molecules showed a good profile in terms of the desired activities. This allows us to choose a hit compound for perform further structural modifications aiming to develop new effective treatments for PD.

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## CK2/HDAC1 DUAL INHIBITORS: NEW STRATEGY FOR THE DESIGN OF ANTITUMORAL AGENTS

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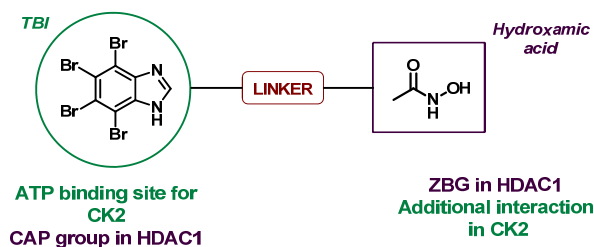
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**Keywords:** HDAC1, CK2, cancer, drug discovery.

The design of multi-target therapeutics has emerged as a novel strategy to treat multigenic diseases such as cancer. This approach has demonstrated a better control of complex diseases than the traditional drug design based on “one-compound to one-target” [1].

The microenvironment of the tumour is known to be a key factor in its progression. Specific changes in histone-modifying enzymes caused by hypoxia, oxidative stress and inflammatory conditions can lead to cell proliferation, invasion and metastasis. Under hypoxic conditions the phosphorylation of HDAC1 (histone deacetylase 1: an enzyme that removes acetyl groups from N-terminal tails of histone and non-histone proteins) is activated by CK2 (protein kinase 2: an eukaryotic serine/threonine protein kinase with multiple substrates and roles in diverse cellular processes) [2]. Therefore, the simultaneous inhibition of both enzymes constitutes a novel epigenetic approach of therapy for cancer.

The current work is aimed at the design, synthesis and biological evaluation of dual inhibitors of these enzymes, based on our previous work [3]. The approach consists on connecting the 4,5,6,7-tetrabromobenzoimidazole ring (TBI), which is a selective CK2 inhibitor [4], to an hydroxamate group (Zinc Binding Group) capable of coordinating the  $Zn^{2+}$  ion present in the catalytic site of HDAC1 [5].



Design of HDAC/CK2 inhibitor

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## MOLECULAR DYNAMICS SIMULATIONS OF AMPK: MECHANISM OF ALLOSTERIC REGULATION BY DIRECT ACTIVATORS

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**Keywords:** *AMPK, molecular dynamics, allosteric mechanism, conformational behavior*

Mammalian AMP-activated protein kinase (AMPK) is a Ser108/Thr132 protein kinase with a key role as sensor in the cellular energy homeostasis (1). This function confers AMPK a major role in numerous metabolic disorders, such as type 2 diabetes, obesity and cancer, and explains the progressive interest as a therapeutic target. AMPK is a heterotrimeric enzyme complex composed by a catalytic  $\alpha$ -subunit and two regulatory subunits,  $\beta$  and  $\gamma$ . It is regulated by several mechanisms, including indirect activators such as metformin, rosiglitazone and resveratrol, and direct activators, such as compound A-769662 (2). The X-ray structure of AMPK bound to the direct activator A769662 has been recently reported (PDB entry: 4CFF), providing a structural basis for the regulation of AMPK activation thanks to the phosphorylated Ser108 (pSer108) located at the CBM of the  $\beta$  subunit (2).

We have carried out a series of molecular dynamic simulations of AMPK in apo and holo states, as well as the holo in presence of ATP to gain insight into the mechanism of AMPK activation. The results point out an overall reduction in the conformational flexibility of holo systems compared to apo, especially significant in the N-lobe region. This fact is most likely due to the strong interactions formed between pSer108 and Lys29/Lys31 upon binding of the activator. Furthermore, the presence of the activator leads to a significant alteration in the protein flexibility, particularly regarding the motion of the N-terminus of the catalytic  $\alpha$ -subunit and the regulatory domain of the  $\beta$ -subunit, as deduced from analysis of the essential motions. The net effect is that the shape and size of the ATP-binding pocket is altered and tends to pre-organize the ATP binding site. Thus, we hypothesize that the activator would act like a glue, filling the space between the N-terminal domain of the  $\alpha$  subunit and transferring the movement of these regions to the ATP-binding site. This effect would rearrange the ATP-binding site, specifically leading to a conformational change in the mouth of the binding pocket, favouring the binding of ATP. Current efforts address the design of novel compounds that may act as activators of the enzyme.

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## NEW SYNTHETIC APPROACH TO QUINOXALINE DI-*N*-OXIDE CONTAINING A PEPTIDE SIDE CHAIN WITH *IN VITRO* ANTI-LEISHMANIAL ACTIVITY

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**Keywords:** *Quinoxaline di-N-oxide, Anti-Leishmanial.*

Leishmaniasis is a group of diseases caused by different species of protozoan parasites of the genus *Leishmania*. Nowadays, leishmaniasis principally affects poor people in under-developed countries in Africa, Asia and Latin America and is endemic in 98 countries worldwide.<sup>1</sup> The drugs currently used for its treatment show its toxicity and side effects that limit their application. Thus, the development of effective, safe and economical new anti-leishmanial drugs is an attractive goal for medicinal chemistry research.

2,5-Diketopiperazine (DKP) is a privileged scaffold for the synthesis of heterocyclic systems.<sup>2</sup> In the context of our work in the development of synthetic methodology based on use of DKPs derivatives as versatile building blocks, we describe in this communication an efficient two-step route to obtain highly functionalized quinoxaline di-*N*-oxides containing a peptide side chain starting from arylmethylene-2,5piperazinediones. A library of 19 such compounds was prepared by this method and their *in vitro* activity against *L. amazonensis* and *L. donovani* promastigotes and amastigotes was determined. Interestingly, nine compounds were more active than the reference drug miltefosine in *L. amazonensis* amastigotes, showing IC<sub>50</sub> values between 6.0 and 31.9 μM. Furthermore, some of these compounds displayed low toxicities in a mouse macrophage cell line (J774) and high IS values; being therefore attractive starting points for future optimization efforts.

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## DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF BIOISOSTERIC INHIBITORS OF CHOLINE KINASE

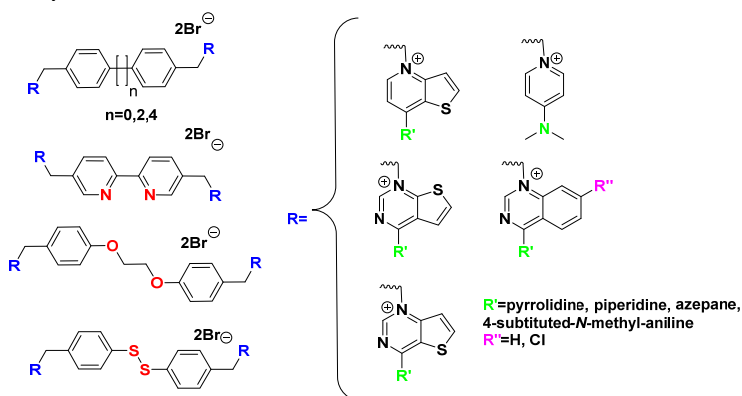
P. M. Luque Navarro<sup>1</sup>, F. Aguilar Troyano<sup>1</sup>, G. Rubbini<sup>1</sup>, A. Fasiolo<sup>1</sup>, M. Á. Gallo-Mezo<sup>1</sup>, C. Marco<sup>2</sup>, M. P. Carrasco-Jimenez<sup>2</sup> L. C. López-Cara<sup>\*1</sup>

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**Keywords:** *Cancer, choline kinase Inhibition*

The alterations of the lipids metabolism could be an interesting method to design board spectrum strategies against cancer<sup>1</sup>. Phosphatidylcholines (PC) is the most abundant phospholipids of the cell eukaryote membrane and it is a fundamental part of the lipoproteins. The PC is synthesized in the Kennedy's route or via CDP-choline, with choline like precursor. The first step of this route is controlled by Choline-Kinase enzyme (ChoK) which is a cytosolic enzyme that catalyze the ATP dependent phosphorylation of the choline with the presence of magnesium<sup>2</sup>. The alteration of metabolism produced in cancer cells generates high phospholipids levels, most especially an increase of PC and all metabolites containing Choline<sup>3</sup>. The overexpression of phosphocholine (PCho) and PC is associated with the higher activation of ChoK. In view of the foregoing, ChoK is considered like a potential therapeutic target, whose inhibition promotes a decrease in PC's biosynthesis and celular proliferation. Herein we report a novel family of Choline Kinasa biscationic inhibitors in which we are currently performing more assays with the object of confirming its antitumoral activity. All this compounds suffered bioisosteric exchanges<sup>2,4</sup> to improve affinity for the binding site and, thereby, increase the antitumoral activity.



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# NATURAL (POLY)PHENOLS AND ALZHEIMER'S DISEASE: THEORETICAL ELUCIDATION OF THE STRUCTURAL DETERMINANTS FOR COVALENT AMYLOID BETA (A $\beta$ ) INHIBITION

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**Keywords:** *QM/MM calculations, Alzheimer's disease, covalent A $\beta$ 42 inhibition, (poly)phenols.*

Alzheimer's disease (AD) is a neurodegenerative pathology which accounts for 60 to 80 % of all the dementia cases. Brain damages related to AD are caused by the deposition of senile A $\beta$ (42) plaques as a consequence of a two-step proteolytic cleavage of the amyloid precursor protein (APP) by  $\alpha$ - and  $\beta$ -secretases.<sup>1</sup> Several epidemiological studies have demonstrated that dietary intake of natural phenolic compounds could attenuate the progression of the disease by reducing or, even in some cases, reversing the cognitive deficits. In this regard, the anti-amyloidogenic activity has been discussed in terms of a structure-dependent categorization that would lead to both covalent and non-covalent inhibition mechanisms.<sup>2</sup>

A protocol consisting on molecular docking, molecular dynamics (MD), QM calculations on reduced models and hybrid Quantum Mechanics/Molecular Mechanics (QM/MM) was applied to elucidate the structural requirements as well as the level of chemical specificity necessary to carry out the covalent inhibition of A $\beta$ 42 aggregation by (+)-taxifolin. The results allowed us to propose a suitable structural model to explain the binding to a model of the A $\beta$ 42 fibril, and the pivotal role exerted by the catechol moiety for A $\beta$ 42 inhibition. These findings may be valuable to ameliorate the pharmacological scenario of AD, paving the way to the generation of a new class of more effective A $\beta$ 42 covalent inhibitors.

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## TRIAZOLOPYRIMIDINE DERIVATIVES AND COMPLEXES: SYNERGIC EFFECT OF METAL IONS AGAINST PARASITIC NEGLECTED DISEASES

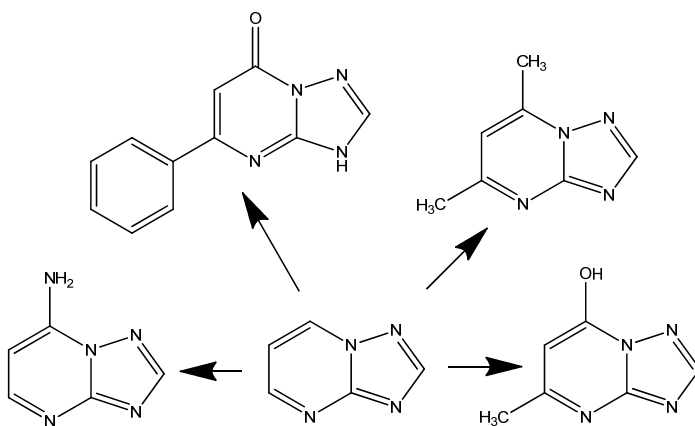
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**Keywords:** *triazolopyrimidine, coordination chemistry, parasitology*

Triazolopyrimidine derivatives constitute biomimetic ligands to purines family that have demonstrated great capacity to form metal complexes with ions of the first transition row, as well as lanthanide trivalent ions. 1,2,4-triazolo[1,5-*a*]pyrimidines are the most used in complex synthesis [1,2].



Triazolopyrimidine complexes have been used as building blocks for MOFs, their luminescent and magnetic properties have been studied and their effectiveness as an anticancer agent has been evaluated, as well as their antiparasitic activity against some of the so-called neglected tropical diseases (*leishmaniasis* and Chagas).

In this communication the excellent antiparasitic properties that they have against different strains of *leishmania* spp and *Trypanosoma cruzi*, showing the last results obtained by our research group.

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## CURCUMIN-COUMARIN ANALOGUES: NEW MAO-B INHIBITORS WITH NEUROPROTECTIVE ACTIVITY

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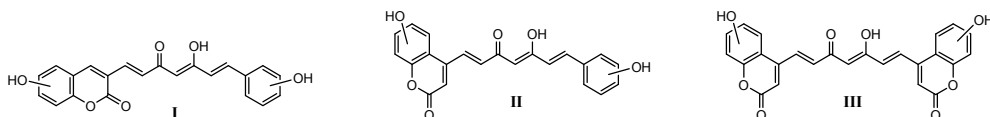
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**Keywords:** *Curcumin-coumarin analogues, MAO-B inhibition, Neuroprotection, Neurodegenerative diseases*

Oxidative stress induced by reactive oxygen species (ROS) plays a pivotal role in neurodegeneration. The high rate production of ROS in addition to a down regulation of antioxidant mechanisms result in the neural death occurred in neurodegenerative disorders [1]. Curcumin, a natural polyphenol extracted from *Curcuma longa* L., neutralizes free radicals and stimulates the antioxidant enzymes in human body. However, one of the major problems with curcumin is perceived to be the bioavailability [2]. Searching for new derivatives with improved pharmacokinetic properties, we have combined curcumin and coumarin structures in order to obtain new curcumin-coumarin analogues (Figure 1). Coumarin structure was selected because of the interesting monoamineoxidase-B (MAO-B) inhibitory properties found in some coumarin derivatives [3]. MAO-B results an important source of ROS whose activity increases with age.



**Figure 1.-** Structure of curcumin-coumarin analogues

As result, most of the curcumin-coumarin analogues synthesized inhibited MAO-B in the micromolar range (5-50  $\mu$ M) and some of them showed neuroprotective properties against damage caused by hydrogen peroxide in motor cortex neuron cultures. In addition, formulation of these compounds in biodegradable nanoparticles of Resomer<sup>®</sup> RG503H (Evonic), a 50:50 copolymer of polylactic acid and polyglycol improved their neuroprotective activity.

### Acknowledgments

Financial support from Universidade de Santiago de Compostela, the Consellería de Cultura, Educación e Ordenación Universitaria (2017-PU027, EM2014/016 and Centro singular de investigación de Galicia acreditación 2016-2019, ED431G/05) and the European Regional Development Fund (ERDF), is gratefully acknowledged.

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## REPLACEMENT OF TRIMETHOXYPHENYL RING OF COMBRETASTATIN ANALOGUES BY PYRIDINE MOITIES. STUDY OF THE BIOLOGICAL EFFECT

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**Keywords:** *tubulin, colchicine, combretastatin, antimitotics, cytotoxicity, pyridine derivatives.*

Antimitotic agents interfere right mitotic spindle formation, which leads to cell cycle arrest and, subsequently, to apoptosis. [1] While Combretastatin A-4 [2] is the reference ligand of tubulin inhibitors that bind to colchicine site, phenstatins and isocombretastatins are related families that have shown promising activity profiles and avoid Z/E isomerization, one of the main drawbacks showed by these potential drugs. [3] Those keeping a trimethoxyphenyl ring combined with either a guaiacol or an indol moiety have shown to be amongst the more potent analogues as shown in Figure 1.

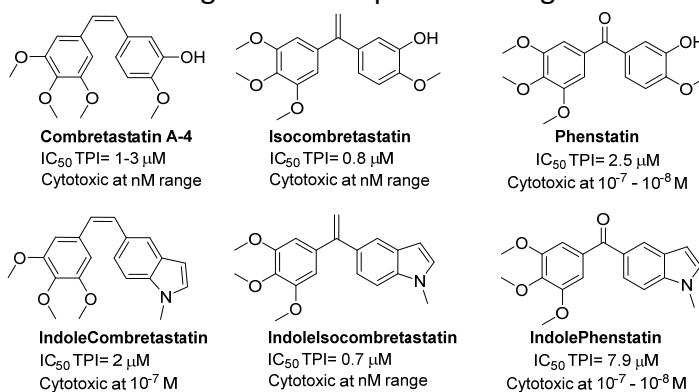


Figure. 1 Tubulin polymerization inhibition (TPI) and cytotoxicity of combretastatins, isocombretastatins and phenstatins carrying a guaiacol or an indole ring.

Now we have explored the effect on the activity when the trimethoxyphenyl ring is replaced by differently substituted pyridine moieties. This approach aim to improve the low aqueous solubility of combretastatin analogues, which is the other main drawback of these drugs, without losing cytotoxic potency. Comparison of inhibition of tubulin polymerization, cytotoxicity and aqueous solubility among both families (trimethoxyphenyl ring / pyridine ring) will be presented.

### Acknowledgements

Financial support came from Consejería de Educación de la Junta de Castilla y León and FEDER funds (SA030U16) and University of Salamanca (Plan Propio de Apoyo a la Investigación).

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## AMINOPHENOL DERIVATIVES AS ANTIBIOTIC ALTERNATIVES

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**Keywords:** *Antibiotic resistance; antimicrobial peptides; phenolic derivatives*

Antibiotic resistance has become a major global public health problem that affects in particular to hospitals and other health care centers. According to a recent report of the World Health Organization, if no initiatives are taken the cost of resistance to antibiotics could exceed \$ 100 billion and lead to the premature death of 300 million people in 2050. Therefore, it is of critical importance to develop new antimicrobial agents in order to substitute or complement currently available antibiotics [1].

Many multicellular organisms produce a variety of peptides, namely antimicrobial peptides (AMPs), which are used as a first line of defense against invading pathogens including bacteria, fungi, viruses and protozoa [2]. AMPs are amphipathic molecules having both hydrophobic residues and hydrophilic positive charges which allow them to bind simultaneously at several sites on the surface of pathogen membranes [3]. AMPs have a direct antimicrobial action affecting integrity of the bacterial membrane, which leads to the leak out of cellular contents. Because of that, the resistance to AMPs is reported to be much lower than in the case of conventional antibiotics [4]. Despite all of these advantages, peptide antibiotics have also several disadvantages that limits their clinical use. Among them, *in vivo* toxicity, limited bioavailability and large production costs. These limitations highlighted the need to obtain more manageable downsized compounds that mimics the properties of the natural AMPs.

Having all of this in mind, we decided to synthesize small amphipathic molecules bearing lipophilic “tails” of different length attached to a cationic component “head”. Both entities were linked through amide bonds that might allow extra hydrogen bonding interactions with the microbial membranes. Here, we describe the synthesis of these compounds and their activity against Gram positive bacteria, including drug-resistant isolates.

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## DESIGN, SYNTHESIS AND ANTIPARASITIC ACTIVITY OF PHTHALAZINONES

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**Keywords:** *drug design, synthesis, in vitro, antihelminthic molecules*

Infections in sheep by trichostrongylid nematodes cause direct and indirect losses with important economic impact, by decreasing production yields and increasing healthcare costs. Current therapeutic treatments are leading to the development of anthelmintic resistance, which becomes a serious problem for the control of gastrointestinal parasitic infections, principally in small ruminants.

Based on the initial screening of several natural and semi-synthetic compounds with good antihelminthic activity, new molecules were synthesised and tested *in vitro* on egg hatch assay (EHA) and larval feeding inhibition assay (LFIA). The effect of compounds on the polymerization of the recombinant tubulin of the nematode *Teladorsagia circumcincta*, isolated from either sensitive or resistant strains has been established.

The EHA was designed basing on the ovicidal property of certain antihelmintics ovicidal, and on the ability of the resistant eggs for embryonating and hatching at higher concentrations than eggs from susceptible strains. Activity of compounds against *T. circumcincta* ovicidal action was tested. The mechanism of action of most potent molecules is been established, either by inhibiting egg embryonated or by preventing its hatching after the embryonated.

In previous studies, forty compounds with structures of dihydrostilbenes, benzalpthalides, phthalazinones and amino alcohols were tested at a single dose of 10 mg/ml. Seven of those showed mild or moderate ovicidal activity, inhibiting egg hatching in a range between 14 and 40%. Two of them showed high activity inhibiting egg hatching In 80 and 93%. New derivatives related to the most potent compounds have been obtained and tested, Structure activity relationship will be discussed. Furthermore, the larvicidal activity of most active compounds will be determined by using the larval feeding inhibition assay (LFIA).

We have found new molecules with excellent ovicidal activity against *T. circumcincta*. Some of them showed also active against resistant strains.

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## NEW NEUROGENIC AND NEUROPROTECTIVE DONEPEZIL - FLAVONOID HYBRIDS AS MULTITARGET DRUGS FOR ALZHEIMER'S DISEASE

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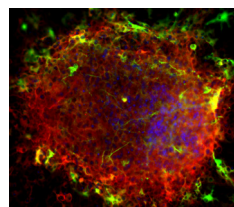
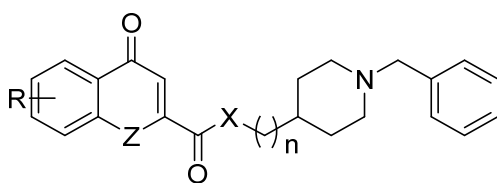
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**Keywords:** *sigma receptors, 5-lipoxygenase, acetylcholinesterase, monoaminoxidases*

The highly complex pathophysiology of Alzheimer's disease (AD) and other neurodegenerative illnesses have led to replace the traditional one-drug – one-target by the multi-target-directed ligands (MTDLs) paradigm, in which a single molecule is designed to be active against several pharmacological targets [1]. Continuing with our interest in neuroprotective and neurogenic compounds [2,3], in this work we describe a new family of donepezil – flavonoid hybrids exhibiting nanomolar affinities for the sigma-1 receptor and a combined inhibition of key enzymes in AD, such as 5-lipoxygenase, acetylcholinesterase, and monoaminoxidases. In general, they scavenge free radical species and are predicted to be brain-permeable. In phenotypic assays, new hybrids protect neuronal cells against mitochondrial oxidative stress and promote maturation of neural stem cells into a neuronal phenotype. Therefore, new donepezil - flavonoid hybrids could contribute to the protection and even, the reparation of neuronal tissues, of great therapeutic interest in AD and neurodegenerative diseases.



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## SYNTHESIS AND BIOLOGICAL EVALUATION OF SELENOCOMPOUNDS AS ANTIOXIDANT AND ANTIPROLIFERATIVE AGENTS

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**Keywords:** *Antioxidants; Cancer, Ebselen-related heterocycles; Selenium; Selenoureas.*

Oxidative stress is a common pathogenic factor associated with aging processes and involves in various diseases, including cancer. Some antioxidant and detoxification enzymes contain selenium (Se) in their catalytic sites, *i.e.* glutathione peroxidases and thioredoxin reductases. Furthermore, several selenocompounds, such as ebselen and PIBSe, have demonstrated to regulate the cell redox status and they are promising compounds for therapy and prevention of diseases directly related with ROS (reactive oxygen species) generation [1, 2]. For these reasons, we consider that Se might be an important tool for the development of new drugs.

In the present work, we have designed and synthesized 37 novel selenocompounds grouped in two series. The first one is ebselen-related heterocycles, the position 5 being modulated with different amides. The second one is selenoureas with several substituents in *N* and *N'*. The cytotoxicity and antioxidant activities for both series were determined by the MTT assay in breast and prostate cancer cell lines and by the DPPH radical scavenging assay, respectively.

The ebselen-related compounds show moderate cell growth inhibition in both cell lines accompanied by a modest antioxidant effect. Nevertheless, several compounds improve the activities showed by ebselen. Additionally, this cytotoxic effect was independent of the apoptosis induction or the cell cycle modulation. On the contrary, selenourea derivatives possess potent cytotoxic activities along with outstanding antioxidant effects. These derivatives present similar antioxidant capacity than ascorbic acid at high doses, some of them being more antioxidant at low doses. Currently, the mechanisms implicated in both effects showed by these selenoureas are being characterized.

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## DESIGN AND SYNTHESIS OF HA-CD44 INTERACTION INHIBITORS AS ANTIPROLIFERATIVE COMPOUNDS

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**Keywords:** *Cancer, cluster of differentiation 44, hyaluronan, heterocycles.*

Hyaluronic acid (HA) is synthesized by the action of hyaluronan synthase (HAS) and fragmented by hyaluronidase (HYAL). High HA levels in tumorous tissues are correlated with the malignancies of tumours. HA functions are mediated by molecular interactions with the cluster of differentiation 44 (CD44) and other hyaladherins. A HA-CD44 interaction initiates signal transduction pathways leading to cancer cell growth, adhesion, migration, invasion and metastasis. Therefore, targeting hyaladherins presents a very promising approach against HA-induced tumourigenesis. Small HA oligosaccharides (HAos) have shown to interrupt HA-CD44 interaction. [1] Anti-CD44 antibodies reduce HA induced vascular smooth muscle cell migration and promote the production of inflammatory cytokines and reactive oxygen species in vascular injured mice. However, a clinical trial initiated to study the utility of CD44 antibodies in cancer chemotherapy was halted due to toxicity. [2]

In 2014 the first nonglycosidic small molecule inhibitors of HA binding were reported. Using biophysical binding assays, fragment screening, and crystallographic characterization of complexes with the HA-CD44 binding domain, an inducible pocket adjacent to the HA binding groove were discovered. [3] Iterations of fragment combination and structure-driven design have established the tetrahydroisoquinoline (THIQ) pharmacophore as an attractive starting point for lead optimization.

Thus, we have designed, synthesized and biologically evaluated a series of THIQ derivatives as antiproliferative compounds.

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## CITOTOXICITY AND NEUROPROTECTIVE EFFECTS OF *N*,*C*-DIARYL-1,2,3-TRIAZOLES

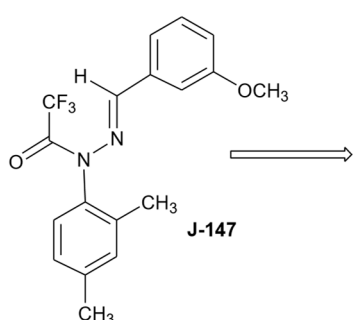
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**Keywords:** 1,2,3-triazoles, J-147, click chemistry, cytotoxicity, neuroprotection

The structural derivative of curcumin, J-147 or (*E*)-*N'*-(3-methoxybenzylidene)-*N*-(2,4-dimethylphenyl)-2,2,2-trifluoroacetohydrazide, has proved to be effective in assays of oxidative stress biomarkers, as well as in inflammation and nerve growth in different nerve cells models of Alzheimer's disease [1]. Structural modifications of the core of the J-147 have led us to the preparation of 1,4-diaryl-1,2,3-triazoles [2] to be tested as new chemotypes in the treatment of neurodegenerative diseases. The synthesis has been performed by click chemistry from conveniently substituted azides and benzyltrifluoromethyl ketones [3].



Comp.	Ar <sub>1</sub>	Ar <sub>2</sub>
AF1	3,4-dimethylphenyl	phenyl
AF2	3,4-dimethylphenyl	3-methoxyphenyl
AF3	2,4-dimethylphenyl	3-methoxyphenyl
AF4	2,4-bis(trifluoromethyl)phenyl	3-methoxyphenyl
AF5	3,4-dimethylphenyl	4-methoxyphenyl
AF6	2,4-dimethylphenyl	4-methoxyphenyl
AF7	3,4-dimethoxyphenyl	3-methoxyphenyl

The cytotoxicity of all of the compounds assayed in the neuronal cell line SH-SY5Y [4] was lower than that found for Curcumin. Some derivatives have also shown neuroprotective effects under oxidative stress conditions. Both, the cytotoxicity and the neuroprotective features of this chemotype, make it attractive for further exploration as new agents for neuroprotection.

**Acknowledgements:** This research has been financed by the Ministerio de Economía y Competitividad of Spain CTQ2014-56833R.

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## ANION RECEPTORS BASED ON PIRAZOLONES

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**Keywords:** *anion receptor, polar solvents*

The halides, as fluoride or iodide, are involved in different medical and metabolic processes. The selective recognition of these anions is a challenge of great interest if it is carried out in polar media, as water or DMSO. Anion recognition needs a major degree of design and complementarity, in order that the non-covalent interactions encapsulate the anion considering the inequitable distribution of the electronic density [1].

Pirazolone skeleton is a suitable candidate for the anionic association due to, in his structure, there exist N–H and O–H bonds that allow the formation of hydrogen bonding. In this work there was synthesized a receptor derived from pirazolone (Figure 1) and studied its halide recognition by RMN–<sup>1</sup>H in DMSO-d<sub>6</sub> as solvent.

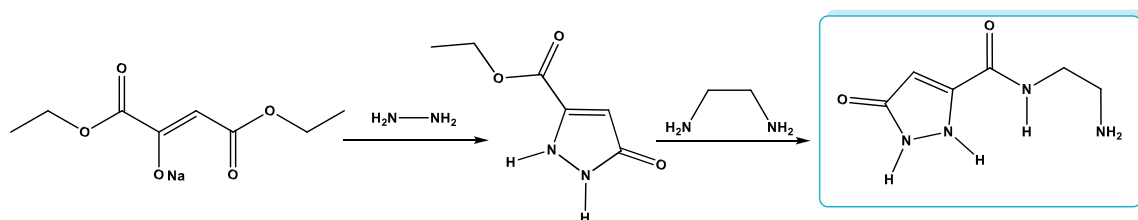


Figure 1. Synthesis and structure of receptor based on pirazolone.

Different behaviour were observed. Fluoride studies revealed that there was an acidbase process instead of the association process. Association studies with chloride showed an association constant of 25 [L mol<sup>-1</sup>]. Finally, the studies with bromide and iodide showed that the association constant, in case they formed a complex with the receptor is below the detection limit of the RMN–<sup>1</sup>H technique.

The difference of the behaviour between chloride, bromide and iodide can be owing to that the hydrogen bond formed between the N–H of the amide group with the chloride is most stable than that the established with major-size halides.

### Acknowledgments

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## NEW POLYAMINE DERIVATIVES AS ANTIPROLIFERATIVE COMPOUNDS

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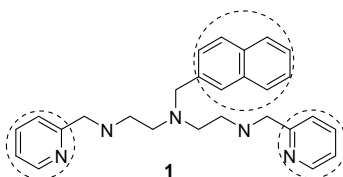
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**Keywords:** Polyamines, cancer, apoptosis

Cancer is the leading cause of death in economically developed countries as well as in developing countries.[1] The use of available chemotherapeutics is often limited, mainly due to undesirable side effects caused by the lack of selectivity as well as the emergence of drug-resistant and multidrug resistant tumors. Research efforts directed at the development of new anti-proliferative agents is clearly a priority.

Polyamines are essential compounds participating in a variety of important functions such as cell growth, survival and proliferation. Based on these observations the polyamine template has become a rational target for chemoprevention and chemotherapeutics.[2] In this context, we have previously shown the *in vitro* antiproliferative activity of polyamine **1**. [3]



In continuation with our studies of compounds with antitumoral activity, we describe the synthesis and antiproliferative activity of novel polyamine analogues based on our lead compound **1**. The compounds were evaluated for their *in vitro* cytotoxic activities against a panel of eight human cancer cell lines including Glioblastoma, Colorectal Cancer, non-Hodgkin Lymphoma and Acute T-cell Leukemia cells. We also present their cellular effects and potential mechanism of action.

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## HIT SELECTION FROM THE GSK TRES-CANTOS ANTI-KINETOPLASTID SET (TCAKS) USING A RAPID *IN VIVO* ASSAY

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**Keywords:** *Chagas disease, Trypanosoma cruzi, in vivo screening, Hit optimization*

Chagas disease, a major cause of cardiac disease in many countries of Latin America, is caused by *Trypanosoma cruzi*, a kinetoplastid protozoan parasite.<sup>[1]</sup> At present there is no vaccine against this illness and the current available drugs (benznidazole and nifurtimox) present severe side effects and show variable efficacy.<sup>[2]</sup> Therefore, new drugs to prevent this disease are needed.

In 2015, GSK Tres Cantos identified and published the TCAKS, which contains 222 compounds as potential hits against *T. cruzi*.<sup>[4]</sup> These compounds shown high potencies, low host cell cytotoxicities and good physico-chemical properties *in vitro*. In this project TCAKS is being evaluated in a rapid and efficient *in vivo* assay developed by Tarleton *et al.* This assay is a moderate screening, as it can evaluate up to 30 compounds in less than 1 week.<sup>[3]</sup> This protocol uses a single oral dose administration using a small quantity of compound (approx. 10 mg) and whole animal imaging pre-and post-treatment to determine *in vivo* efficacy in mice.

In this communication we present the first hits that have been selected from the TCAKS, which have shown similar *in vivo* efficiency indexes as the current chemotherapies. These recent results allow us to start a SAR of these promising families for further lead identification.

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# CONTROLLED RELEASE OF MOLECULES USING MACROSCOPIC IRMOF-10 CRYSTALS

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**Keywords:** IRMOF-10, IRMOF-9, dye

Encapsulation of drugs and their controlled and selective release inside the organism, and the design of suitable structures for this purpose remain a challenge in science nowadays. Metal-Organic Frameworks (MOFs) have been studied as appropriate structures for encapsulation and release of different known drugs.<sup>1,2</sup> However, there is no references regarding the obtention of macroscopic size MOFs, as they used to be obtained as powder. Obtention of single crystals of MOFs would facilitate the handling of the device when it need to be deliver to a patient.

In our group, we have synthesized the well-known IRMOF-10 in macroscopic scale, obtaining big and manageable single crystals. Release of molecules contained into the crystals have been studied in different conditions. As a proof of concept, dye acridine orange has been used to evaluate the release kinetics, as it has a characteristic UV-Vis emission, even at low concentrations. To evaluate the influence in the delivery kinetics of the interpenetration grade in IRMOF-10, it had been synthesized in presence of different modulators to obtain its interpenetrated form, IRMOF-9.

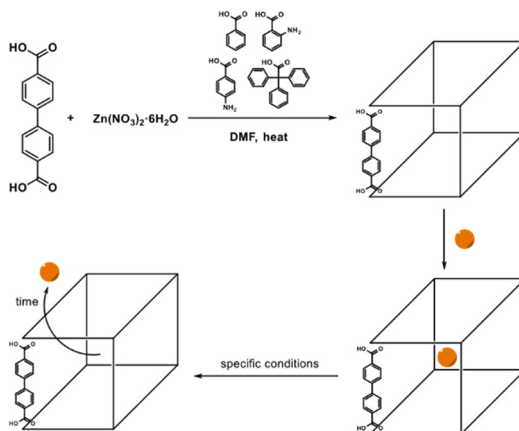


Figure 1. Synthesis of different modulated IRMOF-10 structures and encapsulation and release of a molecule.

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## STRUCTURAL MODULATION OF SALICYLATES REDUCING OXALATE PRODUCTION IN HYPEROXALURIC MOUSE HEPATOCYTES

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**Keywords:** *Primary Hyperoxaluria, alanine-glyoxylate aminotransferase, glycolate oxidase, substrate reduction therapy, salicylates.*

Primary hyperoxaluria type 1 (PH1) is a rare genetic disease due to oxalate accumulation that appears from the early stages of life and supposes a life threatening process. It is caused by the decreased activity of the enzyme alanine-glyoxylate aminotransferase (AGT). The accumulation of its substrate, glyoxylate, leads to its oxidation to oxalate by enzymes such as glycolate oxidase (GO). Oxalate crystals provoke generalized tissue damages and, as a consequence, kidney and liver transplantations become necessary.

Several efforts are underway to find a non-surgical treatment. One of the current approaches is the substrate reduction therapy, targeted to the enzyme GO. Effectiveness of the inhibitor CCPST in reducing oxalate production has been recently proved both in cell culture and *in vivo* experiments [1]. However, this treatment needs a high dose of the drug and therefore the discovery of more potent GO inhibitors is required.

In this sense, and without bibliographical precedents, we have found salicylate derivatives to be active as GO inhibitors [2]. For the first time, salicylic core has been related to GO inhibition and oxalate diminution and two salicylate leads have been found to efficiently reduce oxalate production at low doses. Structural analogues containing a two-atom nitrogen linker have been synthesized and biologically tested.

In addition, docking studies have been carried out in order to identify relevant interactions between these compounds and the enzyme GO.

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## NOVEL DDR1/2 INHIBITORS: FROM HIT IDENTIFICATION (HTS) TO HIT GENERATION BY DRUG DESIGN

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**Keywords:** *DDRs Inhibitors, Hit Identification, Hit Generation, High Throughput Screening, Cancer.*

Discoidin domain receptors (DDR) are transmembrane receptors that belong to the family of receptor tyrosine kinases (RTK) and are involved in several oncogenic malignancies and therefore are considered as potential therapeutic targets against cancer. Concretely, it has been reported they are involved in oncogenic transformation, epithelial-mesenchymal transition (EMT), extracellular matrix remodelling, migration, invasion, tumor growth and metastasis [1,2].

A preliminary screening with 640 compounds was done in order to find the first molecules with inhibitory activity using a DDR1 and DDR2 biochemical assay.

The results obtained from a HTS campaign and analogue testing was used to make some conclusions upon modulation of the activity depending on the substitution patterns. Several compounds have been identified as potent inhibitors at the biochemical and cellular level and the selectivity of the compounds is being assessed. These promising results lead us to continue exploring the chemical series to identify advanced compounds.

Taking into account the structural information of the different DDRs ligands, the Hit Generation phase was started focused on generating novel hit inhibitors, in a free chemical space, susceptible to be included in patent applications. A Type I binding mode was proposed for the chemical series identified in the screening, similar to the reported binding mode of dasatinib compound (multi-kinase type I inhibitor approved for clinical use) in DDR1.

The most promising compounds of the new series were tested in a small panel of 24 kinases. The panel was chosen taking into account the most important off-targets of dasatinib (most of them tyrosine kinases). Tested compounds in the panel showed a different selectivity profile than dasatinib. The results encourage us to increase the chemical exploration including the best substitutions to keep the inhibitory activity and to improve the selectivity and drug likeness properties of the molecules.

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## LEISHMANICIDAL ACTIVITY OF 2-ACYLQUINOLINES AND THEIR HYDRAZONES

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**Keywords:** *Leishmanicidal compounds, 2-acylquinolines.*

Leishmaniasis is classified as a neglected tropical disease and affects several million patients worldwide, being the cause of 20 to 50 thousand deaths per year. Known antileishmanial drugs normally require parenteral administration and show serious toxicity and resistance issues. For these reasons, the development of effective, safe and inexpensive drugs against this disease that are amenable to oral administration is an important goal for medicinal chemistry.

Quinoline is regarded as a privileged scaffold in drug discovery, and is the core of many compounds with anti-leishmanial activity including sitamaquine, a drug in clinical use.<sup>1</sup> Nevertheless, some types of quinoline derivatives have been neglected in these studies because of the lack of suitable synthetic methods. Following our discovery of a general route to 2-acylquinolines based on the aza-vinylogous Povarov reaction,<sup>2</sup> we now describe the leishmanicidal activity of a library of representatives of this structural class, together with some of their hydrazones, totaling 22 compounds. The initial screening was carried out on *Leishmania amazonensis* and *L. donovani* promastigotes. The most promising compounds were then assayed in *L. amazonensis* amastigotes, and their cytotoxicities in a mouse macrophage cell line (J774) were also examined. Some compounds showed activities and selectivity indexes comparable to those of the established drug miltefosine and thus can be considered as interesting leads for further optimization.

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## MULTIPLE TARGET DIRECTED LIGANDS DERIVED FROM A RHO-ASSOCIATED KINASE (ROCK) INHIBITOR FOR THE POTENTIAL TREATMENT OF NEURODEGENERATIVE DISORDERS

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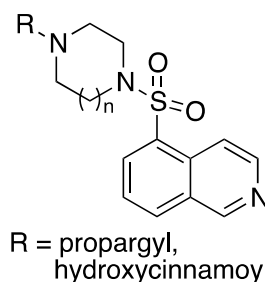
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**Keywords:** *Neurodegeneration, multiple target directed ligands (MTDL), Rho kinase (ROCK), ROCK inhibitors.*

Neurodegenerative diseases are one of the main health-related challenges. Several factors that include the multifactorial character of these diseases render the discovery of new drugs in this area particularly challenging. One strategy that looks promising in drug discovery in this area is the search for multiple target-directed ligand (MTDL) ligands, *i.e.* the design of compounds able to target several of the general pathogenic-related targets including microglial activation, ROS generation, inflammatory response, apoptotic-cascade activation or axon degeneration.<sup>[1]</sup>

Rho proteins are involved in the migration of inflammatory cells, activation of NADPH-dependent enzymes and direct activation of pro-apoptotic factors like glycogen synthase kinase 3 beta (GSK-3 $\beta$ ). Inhibition of Rho-kinase can activate some survival-signaling cascades in neuronal cells that are affected in Parkinson's disease (PD), Alzheimer's disease (AD), ALS (amyotrophic lateral sclerosis) and other neurodegenerative disorders.<sup>[3]</sup> However, fasudil, the only commercially available ROCK inhibitor, is used only against vascular pathologies in clinical practice although several studies of these compounds have been developed to treat CNS (Central Nervous System) disorders. We have developed some fasudil analogs that can enhance its efficacy by resorting to the MTDL strategy. To this end, and taking advantage of the free secondary amine present on fasudil, we have introduced several structural fragments with antioxidant or free-radical scavenging activities.



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## TRYPTOPHAN DENDRONS AS POTENT HIV AND ENTEROVIRUS A71 ENTRY INHIBITORS. SAR IN THE FOCAL POINT

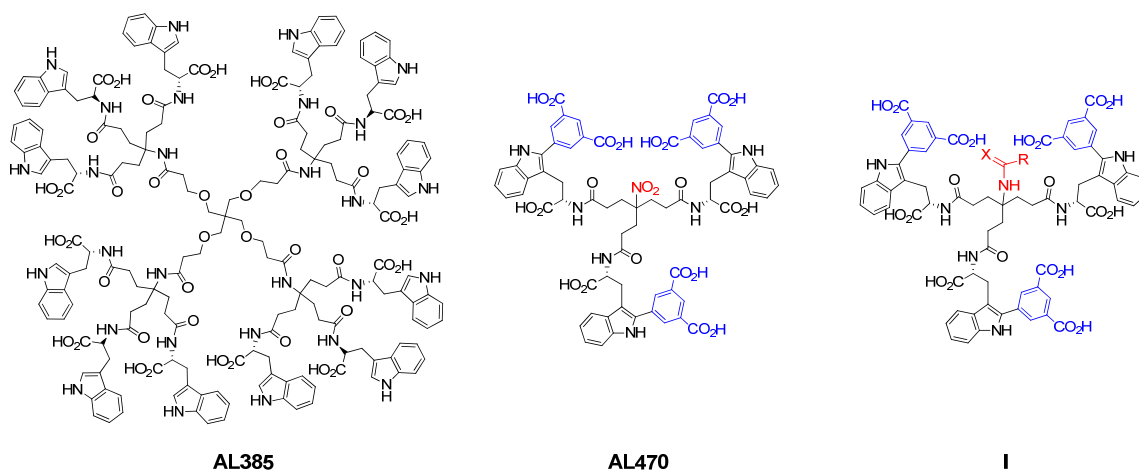
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**Keywords:** dendrimers, tryptophan, SAR, antiviral agents, HIV, EV71

We have recently reported a family of Trp derivatives that are dual inhibitors of the replication of Human Immunodeficiency Virus (HIV) and enterovirus 71 (EV71) [1]. The earlier compounds, whose prototype is **AL385**, were negatively charged dendrimers with 9-12 tryptophan on the periphery. In an attempt to obtain more manageable downsized compounds, trimers and tetramers, with only 3 or 4 Trps have been synthesized. The prototype of this second family is dendron **AL470**, with only 3 tryptophan residues substituted at the C2 position of the indol side-chain with isophthalic acid units and a nitro group at the focal point. Both prototypes inhibit early steps of the replicative cycle of HIV and EV71, probably by interacting with their respective viral surfaces [2,3].



The aim of the current work is the synthesis of molecules of general formula **I** in which the NO<sub>2</sub> group present at the focal point of **AL470** have been replaced by an amino group linked through urea or thiourea moieties to aromatic rings substituted with 1 or 2 COOHs. It was expected that these functional groups can participate in extra interactions with the viral surfaces leading to additional stabilization and increase of activity. The synthesis and antiviral activity against HIV and EV71 of these compounds will be here presented.

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## GOLD-TRIGGERED RELEASE OF HISTONE DEACETYLASE INHIBITOR PANOBINOSTAT FROM A BIOORTHOGONAL PRECURSOR

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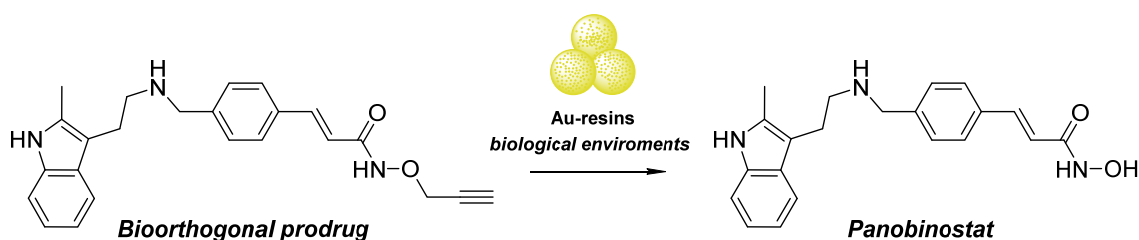
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During the last decade, taking the opposite direction from the now well-established bioorthogonal 'ligation' chemistry,[1] bioorthogonally-triggered bond cleavage reactions have been exploited for a variety of applications including engineering intact cells, protein or *in situ* prodrug activation. In this last respect, palladium or ruthenium catalysts have been widely investigated as bioorthogonal tools to active caged chemotherapeutic agents in order to minimize adverse effects associated to chemotherapy. [2,3]

Although metallic gold is regarded as the most biocompatible metal, its attractive alkynophile properties have been neglected to date in biological environs due to the high affinity of thiols for gold and their ubiquitous presence in peptides and proteins. In this communication, we report the development of a biocompatible heterogeneous gold catalyst able to mediate the specific activation of a novel anticancer prodrug of the histone deacetylase inhibitor Panobinostat in a biological setting.



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Young-Chul, Kim	FL16
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