XV CONGRESO DE LA SOCIEDAD ESPAÑOLA DE QUÍMICA TERAPÉUTICA

Estrategias y retos para el S.XXI en el descubrimiento y desarrollo de fármacos

San Lorenzo de El Escorial

11-14 Sep. 2007

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Programa

Martes, 11 de septiembre de 2007

15:30-17:30 Recogida de documentación en la Secretaría del Congreso, en el vestíbulo del Euroforum

17:30-19:30 Acto de apertura del Congreso

Entrega de premios de la SEQT

Conferencia plenaria inaugural (CP-1)

Dr. Horst Kessler, Technische Universität München

Modified selective integrin ligands for cancer therapy, molecular imaging and for improvement of biomaterials

20:00 Cóctel de bienvenida, en el Euroforum Infantes

Miércoles, 12 de septiembre de 2007

Sesión de mañana Moderadores: Dra. M.T. García López, Dra. M.L. Jimeno
Dr. D. Andreu, Dra. R. Herranz

9:00-9:30 Conferencia invitada (CI-1)

Dr. Manuel Guzmán, Universidad Complutense de Madrid

Cannabinoids as potential anti-tumour agents

9:30-10:00 Conferencia invitada (CI-2)

Dra. Teresa Carlomagno, Max Planck Institute

Structural basis of ligand activity studied by NMR

10:00-10:30 Conferencia invitada (CI-3)

Dr. Federico Gómez de las Heras, GlaxoSmithKline

Nuevos antimaláricos

10:30-11:00 Café

11:00-11:30 Conferencia invitada (CI-4)

Dr. Carlos García-Echeverría, Novartis

Identification and development of PI3K inhibitors for cancer therapy

11:30-12:00 Conferencia invitada (CI-5)

Dr. Javier Botet, Centro de Investigación del Cáncer, Salamanca

The use of genome-wide yeast mutant collections to identify the molecular targets of drugs

12:00-13:00 Comunicaciones orales (O-1, O-2, O-3, O-4)

13:00-15:00 Almuerzo

Sesión de tarde Moderadores: Dr. F. Alcudia, Dra. P. Goya

15:00-16:00 Sesión de pósteres

16:00-16:30 Conferencia invitada (CI-6)

Dr. José López Barneo, Universidad de Sevilla

Terapia celular en enfermedades neurodegenerativas

16:30-17:15 Comunicaciones orales (O-5, O-6, O-7)

17:30 Visita al Monasterio de El Escorial

Jueves, 13 de septiembre de 2007

Sesión de mañana Moderadores: Dr. F. Fernández, Dr. C. Puig
Dr. J. Fdez Gadea, Dr. C. Fdez Masaguer

9:00-9:30 Conferencia invitada (CI-7)

Dra. Ana Martínez, Neuropharma

Del mar al tratamiento de las enfermedades neurodegenerativas

9:30-10:00 Conferencia invitada (CI-8)

Dr. Aurelio Orjales, Faes Farma

Bilastine: a new antihistamine for the XXIst century

10:00-10:30 Conferencia invitada (CI-9)

Dra. Anna Grandas, Universidad de Barcelona

Modification of oligonucleotides for potential therapeutic applications

10:30-11:00 Café

11:00-11:30 Conferencia invitada (CI-10)

Dr. André Luxen, Université de Liège

Positron Emission Tomography (PET) brain imaging

11:30-12:00 Conferencia invitada (CI-11)

Dr. Bernat Vidal, Almirall-Prodesfarma

Discovery of novel potent, selective and orally efficacious A_{2B} adenosine receptor antagonists

12:00-13:00 Comunicaciones orales (O-8, O-9, O-10, O-11)

13:00-15:00 Almuerzo

Sesión de tarde Moderadores: Dra. A. Díez, Dra. A. Marquina

15:00-16:00 Sesión de pósteres

16:00-16:30 Conferencia invitada (CI-12)

Dr. Paolo Mascagni, Italfármaco

Histone deacetylase as a new target in cancer and inflammation

16:30-17:00 Conferencia invitada (CI-13)

Dra. Rosario González, Lilly

From peptides to small molecules: The design and synthesis of efficacious BACE inhibitors

17:00-18:00 Asamblea general de la SEQT

20:30 Cena de clausura en el Club de Golf La Herrería

Viernes, 14 de septiembre de 2007

Sesión de mañana Moderadores: Dr. F. Gago, Dr. J. Quintana
Dra. M.J. Camarasa, Dra. M.L. López Rodríguez

10:00-10:30 Conferencia invitada (CI-14)

Dr. Didier Rognan, CNRS - Université Louis Pasteur Strasbourg

From the compound to the target: development of in silico-guided target fishing strategies

10:30-11:00 Conferencia invitada (CI-15)

Dr. Leonardo Pardo, Universidad Autónoma de Barcelona

Diseño molecular de agonistas y agonistas inversos de receptores acoplados a proteínas G

11:00-11:30 Café

11:30-12:00 Conferencia invitada (CI-16)

Dr. Gregorio Asensio, Universidad de Valencia

Reacciones de acoplamiento cruzado $C(sp^3)$-$C(sp^2)$ catalizadas por paladio

12:00-12:30 Comunicaciones orales (O-12, O-13)

12:30-13:30 Conferencia plenaria de clausura (CP-2)

Dr. Rob Liskamp, Utrecht Institute for Pharmaceutical Sciences

Dendrimers and click chemistry in the design and synthesis of bioactive molecules

13:30-14:00 Acto de clausura del Congreso

14:00-16:00 Almuerzo

Conferencias Plenarias

CP-1

HORST KESSLER

♦

Technische Universität München

Horst Kessler was born in Suhl (Thuringia) Germany in 1940. He studied chemistry in Leipzig and Tübingen, where he received his Ph.D. degree with Eugen Müller in 1966. Shortly after his habilitation in 1969 he was appointed full professor for organic chemistry at the J. W. Goethe University in Frankfurt in 1971. In 1989 he moved to the Technische Universität München. He is also head of the Bavarian NMR Center.

Prof. Kessler is the recipient of the Otto Bayer award (1986), the Max Bergmann medal for peptide chemistry (1988), the Emil Fischer medal (1997), the Max-Planck-Forschungspreis (2001), the Vincent Du Vigneaud Award of the American Peptide Society (2002), the Hans Herloff Inhoffen Medal (2002) and the Burkhart Helferich Award (2005). In 2002 he received the honorary degree of the University of Leipzig. He is a member of the "Bayerische Akademie der Wissenschaft" and the "Deutsche Akademie der Naturforscher Leopoldina", Halle. Guest professorships lead him to Halifax, Tokyo, Madison, Haifa, Austin, and Jerusalem.

His current interests are in the area of bioorganic and medicinal chemistry, with specific focus on the study of biological recognition phenomena and on conformationally oriented design of biologically active molecules, such as peptides, peptidomimetics and carbohydrates. Another field of interest is the development and application of new NMR techniques to peptides, proteins and nucleic acids as well as their complexes.

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MODIFIED SELECTIVE INTEGRIN LIGANDS FOR CANCER THERAPY, MOLECULAR IMAGING AND FOR IMPROVEMENT OF BIOMATERIALS

♦

Horst Kessler

Department Chemie, TU München, Lichtenbergstr. 4, 65824 Garching

Cell adhesion is mediated via the cellular bidirectional receptors integrins. The peptide sequence RGD is recognized by several integrin subtypes (e.g. αvβ3 on osteoblasts and migrating endothelial cells (involved in cancer metastasis and angiogenesis) but also αIIβ3 on platelets (involved in thrombosis). Distinct cyclic RGD peptides (general structure: c(RGDfX)) have been designed to bind specifically to αv integrins with high activity[1]. The cyclic peptide with X = NMeVal is presently in clinical phase III as anti-cancer drug ("Cilengitide" Merck KGaA, Darmstadt)[2] to treat glioblastomas (brain tumors). The structures of these rigidified cyclic peptides were used for the design of non-peptidic mimetics to improve bioavailability[3].

The X group in the cyclic peptide can be used to anchor it to an implant for improving bone formation on biomaterials. Different anchors and spacers have been developed for coating different materials and tested in vitro and in vivo[3]. Recently it could also be demonstrated that non-peptidic integrin ligands can be used for this purpose[4].

X-modified peptides can also be used to SPECT or PET imaging of cancer metastases when labeled with radioisotopes.[5,6] Different modifications improve the contrast and can be applied in animals as well as in man.

[1] M. Aumailley, M. Gurrath, G. Müller, J. Calvete, R. Timpl, H. Kessler; Arg-Gly-Asp constrained within cyclic pentapeptides: strong and selective inhibitors of cell adhesion to vitronectin and laminin fragment P1; *FEBS Lett*. **1991**, *291*, 50-54. [2] M. A. Dechantsreiter, E. Planker, B. Mathä, E. Lohof, G. Hölzemann, A. Jonczyk, S. L. Goodman, H. Kessler; *N*-Methylated Cyclic RGD Peptides as Highly Active and Selective $\alpha_V ß_3$ Integrin Antagonists; *J. Med. Chem*. **1999**, *42*, 3033-3040. [3] A. Meyer, J. Auernheimer, A. Modlinger, H. Kessler; Targeting RGD Recognizing Integrins: Drug Development, Biomaterial Research, Tumor Imaging and Targeting; *Curr. Pharm. Des.* **2006,** 12(22), 2723-2747. [4] C. Dahmen, J. Auernheimer, A. Meyer, A. Enderle, S.L. Goodman, H. Kessler; Improving implant materials by anchoring non-peptidic, highly specific integrin ligands; *Angew. Chem.* **2004**, *43*, 6649-6652. [5] R. Haubner, H.-J. Wester, W. A. Weber, C. Mang, S. I. Ziegler, S. L. Goodman, R. Senekowitsch-Schmidtke, H. Kessler, M. Schwaiger; Noninvasive Imaging of $\alpha_v\beta_3$ Integrin Expression Using ^{18}F-labeled RGD-containing Glycopeptide and Positron Emission Tomography; *Cancer Res*. **2001**, *61*, 1781-1785. [6] R. Haubner, W. A. Weber, A. J. Beer, E. Vabuliene, D. Reim, M. Sarbia, K.-F. Becker, M. Goebel, R. Hein, H.-J. Wester, H. Kessler, M. Schwaiger; Noninvasive Visualization of the Activated αvβ3 Integrin in Cancer Patients by Positron Emission Tomography and [^{18}F]Galacto-RGD; *PLoS Medicine* **2005**, *2*, 244-252.

Rob M. J. Liskamp

♦

Utrecht Institute for Pharmaceutical Sciences

Rob Liskamp studied chemistry and did his Ph.D. Bio-organic Chemistry at the University of Nijmegen, The Netherlands (1982) working with Harry Ottenheijm. Post-doctoral research (1983-1986) was carried out in the group of I. Bernard Weinstein in The Institute of Cancer Research and in the group of W. Clark Still, Department of Chemistry, Columbia University, New York. In 1986 he moved to the University of Leiden. In 1991 he was a visiting professor at the University of California in Los Angeles in the group of François Diederich. In 1994 he became associate professor at Utrecht University and in 1996 professor of molecular medicinal chemistry. He is head of the group medicinal chemistry and chemical biology (www.pharm.uu.nl/medchem). He has a joint appointment at the departments of Pharmaceutical Sciences and Chemistry.

He is a Member of the executive board of the Netherlands Proteomic Centre, member of the international advisory board of the European Journal of Organic Chemistry and the editorial advisory boards of ChemBioChem, a European Journal of Chemical Biology, and QSAR & Combinatorial Science.

His research interests include biologically active modified peptides and peptidomimetics, dendrimers, peptide folding, molecular recognition, synthetic receptors, protein mimics including synthetic antibodies and vaccines.

His scientific contributions so far are among others ca. 200 publications, book chapters and patents.

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Dendrimers and Click Chemistry in the Design and Synthesis of Bioactive Molecules

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Rob M. J. Liskamp

Utrecht Institute for Pharmaceutical Sciences

The powerful spectrum of chemical synthesis ranges from the synthesis of small molecules -especially sought after in drug-related research- to the very large (bio)polymeric molecules. An increasing number of synthetic challenges is found in the design and molecular construction of molecules of "intermediate" size (ca 4000 > mw > ca 500), especially for use and applications in a biological context.

In the area of modulation of interaction and affinity of carbohydrate-protein, peptide-peptide and peptide-protein interactions we use large molecular scaffolds based on dendrimers and small CTV and TAC-based scaffolds. We have developed a versatile synthesis for (non-natural) amino acid based dendrimers. These dendrimers are now widely used in multivalent approaches to increase the (low)affinity of especially carbohydrate ligands as anti-adhesion compounds to prevent bacterial infection and for binding to carbohydrate-binding proteins among others for targeting and imaging applications. For this purpose we have also developed an efficient method for "clicking" carbohydrates and peptides to dendrimers using a microwave-assisted cycloaddition reaction for preparation of multivalent glycodendrimers and dendrimeric peptides. In collaboration with the Radboud University Nijmegen, dendrimeric (cyclic)peptides are applied for tumor and infection imaging and/or treatment.

In addition to using "click" chemistry involving a 1,3-dipolar cycloaddition reaction in chemoselective (bio)conjugation reactions of carbohydrates and peptides for the preparation of multivalent molecular constructs, we have expanded its applications towards the preparation of peptide-based polymers, which may open up possibilities for the synthesis of new biopolymers. Moreover, we are investigating expansion of the arsenal of cycloaddition reactions, which can be performed under mild conditions, and used for a variety of applications. So far examples include new coupling methods to be used in the preparation of peptides and a new sulfonamide linker for solid phase peptide synthesis.

Conferencias Invitadas

MANUEL GUZMÁN

♦

Universidad Complutense de Madrid

Manuel Guzmán was born in Madrid (1963) and took his BSc (1986) and PhD (1990) in Biology from Madrid Complutense University. Subsequently he performed his postdoctoral research at the University of Utrecht (The Nertherlands) and the Hannah Research Institute (Ayr, UK). He is presently Professor of Biochemistry and Molecular Biology at Madrid Complutense University. His PhD and postdoctoral research focused on the regulation of liver fatty acid metabolism. During the last ten years he has been mostly involved in the study of the molecular mechanisms of cannabinoid action, with especial emphasis on how cannabinoids modulate neural cell proliferation, differentiation and survival, and how cannabinoids induce cancer-cell death and exert anti-tumour effects. These studies have allowed the characterization of new processes and signalling pathways coupled to cannabinoid receptors, and overall support the notion that cannabinoids impact very basic events underlying the control of cell fate.

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CANNABINOIDS AS POTENTIAL ANTI-TUMOUR AGENTS

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Manuel Guzmán

Departamento de Bioquímica y Biología Molecular, Facultad de Ciencias Químicas, Universidad Complutense de Madrid

Δ^9-Tetrahydrocannabinol (THC) and other cannabinoids inhibit the growth of glioma cells and other types of cancer cells both in vitro and in animal models of cancer. Cannabinoid anti-tumour activity is dependent on the engagement of cannabinoid CB receptors and the modulation of key cell signalling pathways. This reduces in turn cancer cell survival by at least two mechanisms: induction of apoptosis and inhibition of angiogenesis. Remarkably, this anti-proliferative effect seems to be highly selective for cancer cells, supporting the notion that cannabinoid receptors regulate cell survival/death pathways differently in tumour and non-tumour cells. Recently we have identified a new route that mediates cannabinoid-induced apoptosis of cancer cells via the sphingolipid ceramide and the endoplasmic reticulum stress response, and have conducted a pilot clinical trial in which patients with recurrent glioblastoma multiforme were administered THC intra-tumourally. The fair safety profile of THC found in that study, together with its growth-inhibiting action on cancer cells, may set the basis for future trials aimed at evaluating the potential anti-tumour activity of cannabinoids.

TERESA CARLOMAGNO

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Max Planck Institute

Teresa Carlomagno has obtained her Ph.D. from the University of Naples Federico II in 1997 with a thesis on “NMR Multidimensional Techniques for a Structural Analysis in Solution of Biologically Relevant Molecules”. From 1997 to 1999 she has been a post-doctoral fellow in the group of Prof. C. Griesinger at the University of Frankfurt, while from 2000 to 2001 she has worked as a research assistant at the Scripps Research Institute, California, with Prof. James Williamson. Since 2002 she is the head of the group of “Liquid-state NMR” at the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany. She investigates the structural basis of intermolecular interactions by nuclear magnetic resonance in solution. Her research focuses on the study of complexes between small organic molecules and both proteins and RNAs, on large RNA/protein complexes and on catalytic RNAs. Additionally, her group develops novel NMR techniques for structural investigation of biomolecules. She has about 40 publications in peer reviewed journals and has recently obtained the “Habilitation“ from the University of Hannover, where she holds lectures. At the end of the year she will move to the EMBL in Heidelberg, where she will hold the position of group leader in biological NMR spectroscopy.

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STRUCTURAL BASIS OF LIGAND ACTIVITY STUDIED BY NMR

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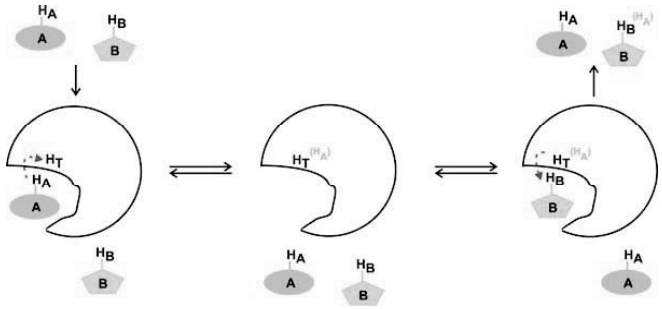
J. Orts, M. Reese, C. Griesinger , T. Carlomagno
Max Planck Institute for Biophysical Chemistry, Göttingen, Germany

In structural based drug design knowledge of the orientation of the ligand in the receptor-binding pocket plays a central role in the elaboration of a high affinity drug. In this case it is desirable to develop a method that allows the determination of the ligand orientation (binding mode). Recently, we have developed a novel approach, called INPHARMA (Interligand Noes for PHARmacophore MApping), which allows the determination of the relative orientation of two competitive ligands in the receptor-binding pocket [1]. The method is based on the observation of interligand, spin diffusion mediated, transferred-NOE data, between two ligands A and B, binding competitively and weakly, to a macromolecular receptor T. During the mixing time of the NOESY experiment, the ligand A binds to the receptor and transfer the magnetization to the receptor proton, from H_A to H_T. Then ligand A dissociates from the protein and ligand B binds during the same mixing time of the NOESY experiment. The magnetization that was transferred from H_A to H_T is now transferred from H_T to H_B and leads to an intermolecular peak between H_A and H_B. Here, we compare the biding mode of two ligands derived from the INPHARMA method to the available crystal structure and demonstrate the solidity of the method. Theoretical investigations of spin diffusion under chemical exchange are also presented. The new method represents a rapid tool for determining the relative binding mode of competitive ligands and is expected to have a considerable impact on structural based drug design.



[1] V.M. Sanchez-Pedregal *et al., Angew. Chemie* **2005**, *44*, 4172.

Federico Gómez de las Heras

♦

GlaxoSmithKline

Federico Gómez de las Heras es Doctor en Ciencias Químicas por la Universidad Complutense de Madrid (1972). Realizó una estancia post-doctoral en el Sloan-Kettering Institute for Cancer Research, New York (1974-1975).

Inició su carrera investigadora en el Consejo Superior de Investigaciones Científicas como Colaborador Científico en 1974, en donde fue nombrado sucesivamente Investigador Científico, Profesor de Investigación y Director del Instituto de Química Médica.

En 1989 entró a formar parte del grupo Glaxo como Director de Investigación Química. En 1993 fue nombrado Director de Investigación de Glaxo Wellcome en España, y desde 2001 hasta la actualidad es el Director de Investigación del Centro de Enfermedades de Países en Desarrollo de GlaxoSmithKline.

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Nuevos Antimaláricos

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Federico Gómez de las Heras
GlaxoSmithKline. Enfermedades de Países en Desarrollo.

Aunque la malaria continua siendo un importante problema de salud en algunas partes de Asia y Sudamérica, su mayor impacto tiene lugar en el Africa Subsahariana donde se producen aproximadamente el 90% de las muertes. Más de un millón de niños mueren en Africa por malaria cada año.

La malaria fue erradicada de Estados Unidos y la mayor parte de Europa en torno a la mitad del siglo XX. La ausencia de malaria en los paises desarrollados y el fracaso del programa global de erradicación de la malaria, que se basaba en el uso de Cloroquina para combatir al parásito Plasmodio, y de DDT para combatir al vector de la enfermedad, el mosquito anofeles, llevó a una pérdida de interés por la investigación y la mejora de la terapia antimalárica por un período de unos 25 años, desde principios de 1970 hasta finales de 1990. Esto condujo a un aumento de la mortalidad en el Africa Subsahariana. Esta tendencia se ha invertido y durante los últimos cinco años ha crecido el interés por la malaria en los países más ricos del mundo.

En la actualidad, hay un número limitado de medicamentos contra la malaria y una falta de nuevos medicamentos accesibles. El progreso en el conocimiento del mecanismo de acción y resistencia a los medicamentos tradicionales, la aparición de artemisininas como una de las clases de antimaláricos más importantes y los recientes proyectos ya completados de secuenciación del genoma han proporcionado a la comunidad científica una gran cantidad de datos, que han permitido aumentar y mejorar los programas de descubrimiento y desarrollo.

Esta presentación revisa el proceso de descubrimiento de medicamentos contra la malaria, con un enfoque especial en los nuevos antimaláricos.

CARLOS GARCÍA-ECHEVERRÍA

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Novartis

Carlos Garcia-Echeverria received his Ph.D. degree in organic chemistry under the supervision of Profs Fernando Albericio and Miquel Pons. After a 3-year post-doctoral stay at the University of Madison-Wisconsin with Prof Daniel Rich, he joined the Exploratory Research Unit of Ciba-Geigy (now Novartis Institutes for Biomedical Research) in 1993, and the Oncology Research Group in 1995. He has been the medicinal chemistry sponsor and team head of different programs involving tumor cell growth control and apoptosis. Recently, he has been appointed Executive Director, Head Oncology Drug Discovery. His research activities have been mainly focused on the identification and development of inhibitors of protein and lipid kinases, proteolytic enzymes and intracellular protein-protein interactions. He is an inventor on 22 patents (issued or pending), and has published 10 book chapters and more than 100 articles and review papers. He has been honored with the Novartis Leading Scientist Award (2002), the Novartis Oncology President's Award (2003) and the European Peptide Society - Leonidas Zervas Award (2006) for his seminal contributions to oncology drug discovery. He is senior editor of “Chemical Biology & Drug Design” and board member of “Drug Design Reviews-Online”, “Expert Opinion on Therapeutic Targets”, “Journal of Peptide Research and Therapeutics”, “Current BioData”, “Recent Patent Reviews on Anti-cancer Drug Discovery” and “The Open Cancer Journal”.

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IDENTIFICATION AND DEVELOPMENT OF PI3K INHIBITORS FOR CANCER THERAPY

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Carlos García-Echeverría

Oncology Drug Discovery, Novartis Institutes for Biomedical Research, Basel, Switzerland

The phosphatidylinositol 3-kinases (PI3Ks) are widely expressed lipid kinases that phosphorylate phosphoinosites at the D-3 position of the inositol ring. These enzymes function as key signal transducers downstream of cell-surface receptor tyrosine kinases. The eight members of the PI3K family are grouped into three classes based on their primary amino acid sequence, *in vitro* substrate specificity, structure and mode of regulation. Class I PI3Ks -PI3Kα, β, γ and δ- catalyzed the formation of phosphatidylinositol-3,4,5-triphosphate, PtdIns(3,4,5)P3 -also referred to as PIP3-, a process that is reverted by the action of a phosphatase, phosphatase and tensin homologue deleted on chromosome 10 (PTEN). Genetic aberrations within class I PI3Ks are common in human cancer due to amplification, overexpression or somatic missense mutations in the PI3KCA gene. Other biological alterations can also affect the correct regulation of PIP3 signal transducers. In this context, loss of the PTEN protein or function has been found in a large fraction of advanced human cancers.

Downstream of PI3K is the 3-phosphoinosite-dependent protein kinase-1 (PDK1). The attractiveness of PDK1 as a potential anticancer target is linked to its ability to control the activity of a diverse set of AGC kinase members, in particular the three PKB isoforms. Full activation of PKB requires phosphorylation at two sites, one within the activation loop (e.g., Thr-308 for PKBα) and one within the C-terminus (e.g., Ser-473 for PKBα). Phosphorylation of the critical and conserved threonine residue in the activation loop of the three PKB isoforms is carried out by PDK1 at the plasma membrane.

Whatever the mechanism, the prevalence of PI3K/PKB signaling abnormalities in human cancers and its potential biological effects (e.g., competitive growth advantage, evasion from apoptosis and therapy resistance) has suggested the potential use of PI3K/PKB pathway modulators as novel targeted therapeutic agents in oncology. Following this strategy, a number of compounds have demonstrated antitumour activity in preclinical and clinical settings by targeting directly or indirectly the different components of this pathway. This oral presentation will detail our structure-based design efforts to identify modulators of PDK1 and PI3K, and will highlight the evolution of our targeted therapeutic strategies for the PI3K/PKB survival pathway. To this end, we have identified a clinical candidate -NVP-BEZ235-, which exhibits potent antiproliferative activity against a broad panel of tumour cell lines by specifically blocking the biological function of PI3K signaling components (e.g., IC_{50} = 10 ± 1 nM, p-PKB inhibition in U87MG cells). The activity of this PI3K inhibitor in cellular settings translates well in *in vivo* models of human cancer. Thus, the compound was well tolerated and displayed disease statis or tumour regression when administered orally -25 to 50 mg/kg/day-, and enhanced the efficacy of other anticancer agents when used in *in vivo* combination studies. Ex-vivo PK/PD analyses of tumour tissues showed a time-dependent correlation between compound concentration and PI3K/PKB pathway inhibition. Contrary to other modulators of PI3K/PKB pathway, and upon comparison with the mean glucose level of the control animals, no elevated blood glucose levels were observed in the treated animals after *in vivo* efficacy experiments. Phase I clinical studies with NVP-BEZ235 in cancer patients started at the end of 2006.

JAVIER BOTET
♦
Centro de Investigación del Cáncer
Salamanca

Licenciado en Biología por la Universidad de Salamanca, realizó su doctorado en el departamento de Microbiología y Genética de dicha universidad, bajo la dirección del Dr. José Luis Revuelta. Durante su tesis doctoral ha empleado la colecciones de mutantes deficientes en cada uno de los genes de la levadura *Saccharomyces cerevisiae* para determinar el mecanismo de acción de fármacos. Su perfil investigador ha estado enfocado en la planificación y desarrollo de escrutinios químico-genómicos a gran escala, empleando las herramientas genómicas disponibles en la levadura, con objeto de profundizar en el mecanismo de acción de compuestos con actividades antitumorales, antifúngicas, oxidantes y genotóxicas. Su especialización se completó durante una estancia en *The Scripps Research Institute* y en el *Genomics Institute of the Novartis Research Foundation* (San Diego, California), concretamente en el laboratorio de la Dra. Elizabeth Winzeler, considerada una de las científicas pioneras en el trabajo con las colecciones de cepas deletantes de la levadura. Desde hace un año, se incorporó al grupo del Dr. Sergio Moreno en el Instituto de Biología Molecular y Celular del Cáncer de Salamanca, donde mediante el mismo tipo de aproximaciones genómicas masivas, trabaja en colaboración con la empresa PharmaMar, en la identificación de las dianas moleculares y en el estudio del mecanismo de acción de varios compuestos antitumorales de nueva generación que se unen al ADN.

♦♦♦♦♦

The Use of Genome-wide Yeast Mutant Collections to Identify the Molecular Targets of Drugs

♦

Javier Botet and Sergio Moreno

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A big challenge in drug discovery is to uncover the cellular targets and the precise mechanism of action of bioactive molecules. The yeast *Saccharomyces cerevisiae* is an excellent eukaryotic model system to study basic cellular processes and human diseases because many genes have been conserved through out evolution from yeast to humans. This easily genetically tractable organism is at the forefront of large-scale functional genomic and proteomic approaches. Many of these new technologies are readily applicable to drug target identification and drug mechanism of action studies.

Chemical genomics cell-based screenings are designed to identify compounds that cause a desired physiological change, without immediate concern about their precise targets. However, it is often difficult to correlate global cellular phenotypes with the underlying molecular mechanisms. In this regard, a major break-through has been the generation of a complete collection of yeast deletion strains. This collection of yeast knock-out mutants, consists in ~6000 strains that each possess a precise deletion in one of ~5000 nonessential and ~1000 essential yeast genes. Growth of this mutant collection in the presence of a chemical compound allows the quantitatively measure of the relative "fitness" of every mutant strain, and has been successfully used to identify drug-susceptible strains and, thus, gene products that play a role in specific drug-inhibitory mechanism.

I will present an overview of the high-throughput experimental approaches to simultaneously screen this collection of "6000 knock-out genomes" towards the understanding of drug action *in vivo*. The deep knowledge of the biochemical mechanisms and the underlying cellular responses that are triggered by bioactive molecules is essential to rationally design new compounds with superior pharmacological profiles, but also may provide new therapeutic strategies and reveal unwanted secondary effects.

José López Barneo

♦

Universidad de Sevilla

José López Barneo (21 de febrero de 1952), doctor en Medicina y Cirugía, es Catedrático de Fisiología de la Facultad de Medicina de Sevilla (1986) y Jefe de Servicio de Investigación del Hospital Universitario Virgen del Rocío (1999). Ha desempeñado numerosos cargos en comisiones técnicas nacionales e internacionales y actualmente es Director del Instituto de Biomedicina de Sevilla y del Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas. Sus líneas de investigación fundamentales se relacionan con las respuestas celulares a la hipoxia, la regulación de la contractilidad del músculo liso arterial y la terapia celular aplicada a la enfermedad de Parkinson. Es autor de más de 100 publicaciones de difusión internacional y miembro de los comités editoriales de las revistas más prestigiosas en su campo (The Journal of Physiology, Pfluegers Archiv-European Journal of Physiology, Physiological Reviews, entre otras). Ha recibido numerosas distinciones por su labor académica, de entre las que destacan: Premio Juan Carlos I de Investigación Científica y Técnica (1993), Premio Jaime I de Investigación (1998), Premio Maimónides de Investigación en Andalucía (2002), Premio Lilly de Investigación Básica (2003) y Premio de Investigación Javier Benjumea de la Fundación Focus-Abengoa (2006). Es Académico Numerario de la Real Academia de Ciencias de Sevilla (2004) y Académico correspondiente de la Real Academia de Ciencias Exactas y Naturales (2005).

♦♦♦♦♦

Terapia Celular en Enfermedades Neurodegenerativas

♦

José López Barneo

Laboratorio de Investigaciones Biomédicas, Hospital Universitario Virgen del Rocío, Universidad de Sevilla, Sevilla

Las enfermedades neurodegenerativas, como la enfermedad de Parkinson o la de Alzheimer, se producen por mortalidad neuronal progresiva debido a causas desconocidas. El objetivo de la terapia celular aplicada a estas enfermedades es intentar restituir las neuronas que se han destruido por otras células nuevas. El reto metodológico de estas terapias es incorporar células dentro del cerebro de forma segura, que restituyan las funciones de las neuronas destruidas y que se mantengan estables (sin destruirse o proliferar en tumores) una vez trasplantadas. Durante las últimas décadas se han ensayado diferentes tipos celulares con resultados variables. Actualmente se investiga si las células madre adultas o las embrionarias podrían servir de base para estrategias terapéuticas realistas. Las células madre embrionarias han despertado un gran interés social y se han realizado inversiones multimillonarias en compañías privadas de los países punteros, aunque por el momento los resultados obtenidos en modelos animales anuncian limitaciones serias para la transferencia de estas tecnologías al hombre. En principio, la terapia celular, sobre todo la que se basa en células madre embrionarias, sólo será útil en lesiones muy localizadas. Por ejemplo, en la enfermedad de Parkinson, cuyos síntomas se deben a la muerte de neuronas en una zona muy localizada del cerebro y a la falta de una sustancia, la dopamina, que ellas producen. De hecho nuestro grupo ha desarrollado una nueva técnica de trasplante celular, experimentada en modelos animales y en enfermos parkinsonianos, que se basa en el uso de células del cuerpo carotídeo y en progenitores de las mismas descubiertos en este órgano. La aplicación de la terapia celular a enfermedades neurodegenerativas que presentan lesiones muy difusas en todo el cerebro (como la enfermedad de Alzheimer) parece, por el momento, lejana.

Ana Martínez

♦

Neuropharma

La Dra. Ana Martínez obtuvo el título de Doctor en Ciencias Químicas por la Universidad Complutense de Madrid en 1987, ocupando una plaza de científico titular en el Instituto de Química Médica del CSIC desde 1989. Durante estos años ha sido investigador responsable de numerosos proyectos de investigación todos ellos relacionados con la química médica y el diseño racional de fármacos aplicados a áreas terapéuticas diversas como anticancerosos, antivirales, y activadores de canales de potasio. Desde 1995 sus intereses científicos se centraron en la investigación de fármacos eficaces en procesos neurodegenerativos, especialmente para el tratamiento de la enfermedad de Alzheimer y concretamente en la línea de inhibidores de GSK-3 y moduladores de la biopatología del péptido amiloide, donde ha llevado en la actualidad dos fármacos hasta fases de desarrollo clínico. Es autora de libros, más de un centenar de publicaciones científicas y de una veintena de patentes activas. En Enero de 2002, obtuvo una plaza de investigador científico del CSIC, incorporándose en Febrero de 2002 a Neuropharma como director de I+D. Ha implementado desde su inicio la estrategia de I+D de la compañía así como los actuales laboratorios de investigación desde donde coordina las actividades de investigación básica que van desde el cribado biológico de moléculas hasta la prueba de eficacia de los candidatos seleccionados en diferentes modelos animales.

♦♦♦♦♦

DEL MAR AL TRATAMIENTO DE LAS ENFERMEDADES NEURODEGENERATIVAS

♦

Ana Martínez

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Durante los últimos 20 años, más de la mitad de los fármacos introducidos en el mercado han sido derivados directa o indirectamente de pequeñas moléculas de origen natural.[1] Los productos naturales son moléculas orgánicas sintetizadas por macromoléculas pertenecientes a seres vivos y dirigidos a interaccionar específicamente con receptores biológicos para efectuar funciones fisiológicas. Por tanto, ofrecen un gran atractivo desde el punto de vista de la química médica como punto de partida en el desarrollo de un nuevo fármaco. Mientras que la gran mayoría de los productos naturales han sido aislados de organismos terrestres, durante los últimos años el mar se ha convertido en una fuente rica en compuestos con actividades biológicas prometedoras en diversas áreas terapéuticas como la oncología, los procesos inflamatorios, la analgesia, la inmunomodulación, la alergia o las enfermedades virales. Un gran número de compuestos de origen marino han entrado ya en ensayos clínicos aumentando su potencial impacto en la industria biomédica y farmacéutica.[2] Más aún, en los últimos años, fármacos que provienen del mar están empezando a ser desarrollados en áreas terapéuticas nuevas como es el caso de las enfermedades neurológicas.[3] [4]

En este contexto, en NeuroPharma se han establecido varios proyectos de investigación que, utilizando como fuente de biodiversidad los productos naturales marinos, tratan de buscar fármacos eficaces para la enfermedad de Alzheimer y otros procesos neurodegenerativos. La mayoría de estos proyectos se encuentran en fases avanzadas de investigación preclínica, y algunas de las moléculas desarrolladas han empezado a mostrar eficacia en diferentes modelos animales. Las distintas aproximaciones farmacológicas seguidas en el cribado combinatorial de compuestos marinos así como los procesos de optimización de candidatos, que permitan un aumento en la eficacia terapéutica y/o en las propiedades farmacocinéticas, para conseguir nuevos fármacos eficaces con potencial neuroprotector serán descritas en esta comunicación.

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[1] Kingston DG, Newman DJ. Natural products as drug leads: An old process or the new hope for drug discovery?. *Idrugs* 2005, 8:990-992.

[2] Newman DJ, Cragg GM. Marine natural products and related compounds in clinical and advanced preclinical trials. *J. Nat. Prod*. 2004, 67:1216-1238.

[3] Alonso D, Castro A, Martinez A. Marine compounds for the therapeutic treatment of neurological disorders. *Expert Opin. Ther. Patents* 2005, 15:1377-1386.

[4] Martinez A. Marine-derived drugs in neurology. *Current Opin. Investig. Drugs* 2007, 8:525-530.

CI-8

AURELIO ORJALES

♦

Faes Farma

Información personal

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EXPEDIENTE ACADEMICO

Títulos universitarios

1. Licenciado en Ciencias Químicas, Universidad de Santiago de Compostela, en marzo de 1969.
2. Doctor en Ciencias Químicas, Universidad de Santiago de Compostela, en marzo de 1972.

EMPLEOS

1. Técnico de Síntesis Química, Departamento de Investigación de FAES, S.A., desde 1972 hasta 1977.
2. Jefe del Departamento de Investigación de FAES, S.A. desde 1977 hasta 1981.
3. Director de Investigación de FAES FARMA, S.A. (anteriormente FAES, S.A.), desde 1981 hasta la fecha.

PUBLICACIONES

a. **Trabajos científicos.** Un total de 52 trabajos científicos originales han sido publicados en revistas internacionales reconocidas, cubriendo fundamentalmente aspectos de la Química Médica y Orgánica, Farmacología, Farmacocinética y Desarrollo farmacéutico**.**
b. **Comunicaciones a Congresos y Simposia.** Más de 100 comunicaciones a congresos y simposia científicos, cubriendo fundamentalmente aspectos de la Química Médica y Orgánica, Farmacología, Farmacocinética y Desarrollo farmacéutico.
c. **Patentes.** Más de 65 patentes sobre síntesis química y productos farmacéuticos.

OTROS MÉRITOS

Congresos y Simposia: Asistente a numerosos congresos y simposia nacionales e internacionales de Química, Biofarmacia, Farmacología y otros.
Comisiones: Vocal de comisiones gestoras de diversos Planes concertados de investigación. Ponente en la "Revisión del Plan Nacional de I+D". Madrid, 1995.
Tesis doctorales: Miembro de diversos tribunales de tesis doctorales en las Universidades del País Vasco, Santiago de Compostela, Alcalá de Henares, Granada, Madrid y Navarra.

♦♦♦♦♦

BILASTINE: A NEW ANTIHISTAMINE FOR THE XXIST CENTURY

♦

Aurelio Orjales

FAES FARMA, S. A., Máximo Aguirre 14, 48940 Leioa (Vizcaya), España

H_1-antihistamines have been used since 1942 in the treatment of the symptomatology of allergy, in particular seasonal and perennial rhinitis and urticaria. Hydroxycine, diphenhydramine and chlorpheniramine are classical first generation H_1-antihistamines, widely used along many years. However, their side effects, mainly sedation and mouth dryness, had been a common problem to all of them. Attempts to find new compounds devoid of such unwanted side effects led to a new generation of H_1-antihistamines, from which terfenadine and astemizol are outlined because of their worldwide use until recent years. A research programme on selective H_1-antihistamines devoid of the aforementioned side effects was conducted by us a few years ago focused on chemical structures derived from benzimidazole. Alinastine (pINN) was discovered as a potent non-sedating, non-anticholinergic, highly selective H_1-antihistamine. However, at the start of its development a great concern went off on cardiovascular side effects of marketed H_1-antihistamines as it was found that they can cause enlargement of the QT interval with risk of ventricular arrythmia. This led to the withdrawal from the pharmaceutical market of astemizol and terfenadine. A similar effect was detected in alinastine and its development discontinued. A new research project with alinastine as lead compound was initiated with the aim to achieve new molecules devoid of the unwanted side effects while maintaining the main pharmacological activity. Results from this project have already been communicated before.[1,2,3]

Bilastine (pINN) has shown to be the best molecule in this chemical family.[4] Besides its excellent H_1-antihistaminic activity it is devoid of anticholinergic activity both *in vitro* and *in vivo*, and it is not able to cross the blood brain barrier, as demonstrated in functional assays and QWBA studies with [^{14}C]-bilastine. No effect on the cardiovascular system has been detected even at doses 10-fold those for therapeutic use after specific QT clinical trials after single and multiple dose administration. This profile leads to regard bilastine as a new H_1-antihistamine with the ideal characteristics for the treatment of both seasonal as perennial allergic diseases, in particular rhinitis and urticaria.

Acknowledgement: Thanks to Dr. Mara Bordell for her encouragement and support.

[1] Bordell, M.; Mosquera, R.; Orjales, A.; Rubio, V. XII Congreso Nacional de la SEQT, Sevilla, 2001. [2] Orjales, A.; Mosquera, R.; Rubio, V.; Bordell, M.; Labeaga, L.; Innerárity, A.; Berisa, A. XIII Congreso Nacional de la SEQT, Santiago de Compostela, 2003. [3] Bordell, M.; Rubio, V.; Canal, G.; Innerárity, A.; Berisa, A.; Labeaga, L.; Mosquera, R.; Orjales, A. XIX ISMC, Istambul, 2006. [4] Orjales, A.; Rubio, V.; Bordell, M. Patent US 5877187.

ANNA GRANDAS

♦

Universidad de Barcelona

Anna Grandas graduated in Chemistry and got her PhD degree at the University of Barcelona. In 1989 she was appointed Profesora Titular at the Depatment of Organic Chemistry of the University of Barcelona, and has recently attained the full professorship degree. During the PhD thesis and the first postdoctoral period in Barcelona she worked in peptide chemistry. After a postdoctoral stay in Prof. Marvin H. Caruthers' laboratory at the University of Colorado at Boulder (1988), she directed her research interest towards nucleic acids. In the field of nucleic acids chemistry her main contributions have been related to the development of methodology for the preparation of nucleic acids analogs, in particular of different types of peptide-oligonucleotide hybrids.

♦♦♦♦♦

MODIFICATION OF OLIGONUCLEOTIDES FOR POTENTIAL THERAPEUTIC APPLICATIONS

♦

Anna Grandas

Departament de Química Orgànica, Facultat de Química, Universitat de Barcelona, Martí Franquès 1-11, 08028 Barcelona

The potential therapeutic use of synthetic oligonucleotides is mainly based on the exploitation of their capacity for recognizing and interacting with complementary sequences. Over the past thirty years, nucleic acid chemists have introduced all kinds of modifications in oligonucleotide chains to allow their evaluation and possible use either in diagnostics or as drugs. The low stability of oligonucleotides in physiological media and their difficulty to get through cell membranes and reach their target are two of the main problems to be addressed, but the modifications introduced to overcome these problems must not reduce their affinity for the target.

This presentation will cover some of the work carried out in our group to develop methodology for the preparation of oligonucleotide analogs. In particular, the synthesis of peptide-oligonucleotide conjugates using the Diels-Alder cycloaddition in water, and the formation of cross-links between platinated oligonucleotides and complementary chains will be described.

For the synthesis of peptide-oligonucleotide conjugates, the oligonucleotide chain was derivatized with a diene, and a maleimide moiety, which was used as dienophile, was incorporated at the N-terminal of peptides.[1] The preparation of regioselectively platinated oligonucleotides was accomplished by appending imidazole and thioether groups from the nucleobases of residues in neighboring positions.[2]

[1]V. Marchán, S. Ortega, D. Pulido, E. Pedroso, A. Grandas. *Nucleic Acids Res.* **2006**, *34*, e24.
[2]B. Algueró, J. López de la Osa, C. González, E. Pedroso, V. Marchán, A. Grandas. *Angew. Chem. Int. Ed.*, **2006**, *45*, 8194-8197.

CI-10

André Luxen

♦

Université de Liège

Professor André Luxen is the Director of the Cyclotron Research Centre at Liege University.
His research focuses on the study of the biological basis of the cerebral processes in humans using functional neuroimaging techniques such as positron emission tomography, electroencephalography, transcranial magnetic stimulation, and functional magnetic resonance imaging. During the last years, he has leaded the development and production of radiopharmaceuticals labelled with a short-life radioisotope. Radiopharmaceuticals include analogues of sugar and amino acids, specific ligands for enzymes and receptors. These radiolabelled compounds are validated in small animals before they are used on humans. He actively investigates the patterns of regional cerebral blood flow which characterise various levels of consciousness and vigilance (conscious wakefulness, hypnotic state, sleep states, vegetative state, coma) and may be early markers of disabling degenerative disorders (for example, Alzheimer type dementia or corticobasal degenerative disease). He is also interested in the functional neuroanatomy of cognitive and neuropsychological higher functions: implicit and explicit learning (while awake or while asleep), long term memory (procedural, episodic and spatial), executive systems (working memory and supervision systems), and upper limb praxis among other cognitive functions, both in normal and pathological populations. He currently tries to merge the analysis of data obtained by using different techniques in order to improve the spatial and temporal accuracy of our model of cerebral functioning.

♦♦♦♦♦

POSITRON EMISSION TOMOGRAPHY (PET)

BRAIN IMAGING

♦

André Luxen

Centre de Recherches du Cyclotron, Université de Liège

Translational research is a very important area of work within the drug discovery field today, with the aim of ensuring a more reliable and predictive connection between basic research and testing in the clinic. Imaging techniques play a key role in the development of this concept, being positron emission tomography (PET) one of the most informative techniques we have at hand. Radiopharmaceutical chemistry includes the selection, preparation and preclinical evaluation of radio labelled compounds. The lecture will describe the selection criteria for candidates for PET, some methods for their preparation and their use in *in vivo* studies both in animals and humans.

BERNAT VIDAL

♦

Almirall-Prodesfarma

Datos personales:
Nombre y apellidos: Bernat Vidal Juan
Fecha y lugar de nacimiento: 11/08/1968, Porreres (Mallorca)

Licenciado en Farmacia: Facultad de Farmacia, Universidad de Barcelona (1991)

Doctorado en Farmacia: Facultad de Farmacia, Universidad de Barcelona (1991-1996)
Supervisores: Prof. Joan Bosch y Prof. M.L. Bennasar.
Título: "Biomimetic synthesis of indole alkaloids. First total synthesis of alkaloids of the ervitsine-ervatamine group"

Experiencia postdoctoral: Dpt of Chemistry, Stanford University (1997)
Supervisor: Prof. Barry M. Trost.
Título del trabajo: "Novel ruthenium catalyzed reactions and development of new chiral bidentate ligands for the ruthenium atom".

Experiencia profesional: Laboratorios Almirall S.A.
1998-2002: investigador, Departamento de Química Médica.
2002-actualidad: jefe de sección (Dept. de Química Médica)

Artículos y patentes:
Autor en 18 publicaciones científicas en diferentes revistas de química orgánica y de química médica y en más de 9 patentes de invención.

Conferencias impartidas en congresos:
- Conferencia invitada: "New Xanthine-Based PDE5 Inhibitors"; XVIIth International Symposium on Medicinal Chemistry (2002), Barcelona (Spain).
- Conferencia invitada: "Combinatorial Chemistry in Industry"; 6th International Conference on Pharmaceutical Sciences (2001), Barcelona (Spain).

Premios:
• Premio Extraordinario de Doctorado (1997)
• Premio Extraordinario Licenciatura (1993)

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DISCOVERY OF NOVEL POTENT, SELECTIVE AND ORALLY EFFICACIOUS A_{2B} ADENOSINE RECEPTOR ANTAGONISTS

♦

Bernat Vidal

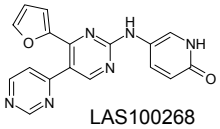
Almirall-Prodesfarma

Substancial experimental evidence highlights the importante of adenosine in the patogenesis of asthma. Inhaled adenosine causes dose-related bronchoconstriction in patients with asthma and COPD but not in healthy volunteers. Adenosine potentiates IgE-dependent degranulation of human mast cells through a mechanism believed to be mediated by the A_{2B} receptor. This argument reinforces a large body of evidences suggesting that blockade of the A_{2B} receptor may provide clinical benefits in the treatment of chronic respiratory diseases.

So far, the identification of potent A_{2B} antagonists, selective versus A_1, A_{2A} and A_3 adenosine receptors and showing good oral bioavailability has been challenging.

Herein we present the discovery and characterization of a novel series of *N*-heteroaryl 4'-furyl-4,5'-bipyrimidin-2'-amines as potent A_{2B} adenosine receptor antagonists and selective versus A_{2A}, A_1 and A_3 receptors.

LAS38096



LAS100268

Compound	hA_{2B}	hA_{2A}	hA_1	hA_3
LAS38096	17 ± 4	>2500 (40% ± 5)	>1000 (14% ± 4)	>1000 (36% ± 4)
LAS100268	16 ± 1	>2500 (25% ± 1)	>10000 (31% ± 5)	>1000 (15% ± 1)

Optimization of the series SAR led to the identification of LAS38096, which displayed a favorable pharmacokinetic profile in preclinical species. Regardless of the species, the compound was absorbed rapidly (t_{max}< 1h) and exhibited good bioavailability (75% and 80% for the rat and dog, respectively).

The encouraging oral bioavailability exhibited by LAS38096 allowed characterization of the efficacy of the compound in a functional in vivo model of allergy and inflammation. Thus, OVA-challenged mice treated orally with LAS38096 (1 and 10 mg/Kg) showed significantly less methacholine-induced bronchial hyperresponsiveness, mucus production and OVA-specific IgE levels.

On the basis of its good in vitro pharmacology, pharmacokinetic, and efficacy profile, LAS38096 was advanced into preclinical in vivo safety and toxicology studies.

CI-12

Paolo Mascagni

♦

Italfármaco

Born in Florence, Dec 3, 1952. In 1978, I graduated in Organic Chemistry from the University of Florence. 1980-1983. Post-doctoral research at the University of Madison-Wisconsin in peptide chemistry and conformational analysis of peptides and natural products by multidimensional NMR and CD spectroscopy. Lecture-Senior Lecturer, School of Pharmacy University of London (1984-1990) and visiting professor at California Institute of Technology (1987). Research activities include chemical synthesis and physico-chemical characterisation of bioactive peptides and proteins (HIV, bacterial heat shock, antigenic peptides etc). In 1991 I joined Italfarmaco, Milan to set-up and run Peptide Chemistry and Computational Modelling facilities and subsequently Medicinal Chemistry. From 1995 Director of Italfarmaco pre-clinical department. Current activities involve the design and development of new drugs (small molecules and peptides) and formulation in CV, infectious and inflammatory diseases and cancer.

♦♦♦♦♦

HISTONE DEACETYLASE AS A NEW TARGET IN CANCER AND INFLAMMATION

♦

Paolo Mascagni

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The epigenetic intervention is emerging as a new and promising therapeutic approach in oncology. In particular, there are a number of different HDAC inhibitors (HDACi), which, either alone or in combination therapies, are currently being evaluated in haemato-oncological indications (e.g. multiple myeloma, leukemias and lymphomas) where they have shown activity. One of these inhibitors, Merck's ZOLINZA™ (Vorinostat, also known as suberoylanilide hydroxamic acid, SAHA) has been recently approved in the US for the treatment of advanced cutaneous T-cell-lymphoma.

Through chromatin modification-dependent mechanisms HDACi's induce apoptosis, cell cycle arrest and differentiation in tumour cells, the latter effect at concentrations generally lower than those necessary for cell death and/or cell cycle arrest.

In addition to developing its own HDAC inhibitor in oncology, Italfarmaco is pioneering pre-clinical and clinical research in auto-immune disorders in general and in pro-inflammatory cytokines dependent diseases in particular. Thus we and others have shown that in human PBMC, concentrations of HDACi's 1-3 logs less than those exerting anti-tumour effect are able to inhibit the synthesis and secretion of a number of pro-inflammatory cytokines, including TNFα, IL1β, IFNγ, IL-12 and IL6. Through acetylation patterns similar to those seen in tumour cells, pro-inflammatory genes are silenced by HDAC inhibition whilst anti-inflammatory ones remain inducible. Antigen-induced tolerance is thus restored in diseased inflammatory cells.

It is believed that different classes of HDAC mediate the different effects of their inhibitors in tumour and non-tumour cells. HDACs are divided in NAD^+ and Zn^{2+}-dependent enzymes. Only inhibitors of the latter have shown anti-tumoral and anti-inflammatory properties. The 11 Zn^{2+}-dependent HDAC isoforms are in turn divided in class I and II sub-families. The structural elements governing subtype recognition are only poorly understood due to difficulties in preparing pure and enzymatically active proteins. However, laboratory experiments have shown that a prevalence of class I activity exists in tumour cells. The specificity for HDAC isoforms not only is important for the development of anti-tumour or anti-inflammatory selective inhibitors but also to reduce the side effects that have been associated with these drugs. Thus thrombocytopenia, leukopenia, diharrea, fatigue are some of the dose limiting toxicities seen in clinical studies.

In conclusion chromatin remodelling through HDAC inhibition is emerging as a novel target for the control of inflammation and cancer. The outcomes of current clinical efforts with pan-inhibitors are encouraging whilst subtype specific molecules are only just leaving the laboratory.

ROSARIO GONZÁLEZ

♦

Lilly

- BSc in Chemistry from the “Universidad de Oviedo” (1989).
- PhD in Chemistry in 1993 from the “Universidad de Oviedo” under the supervision of Prof. J. Barluenga and Prof. F.J. Fañanás. PhD Thesis: Lithiation Reactions of Allylamines and Related Systems. Applications in Organic Synthesis.
- Short stay at the State University of New York at Buffalo in Prof. Turos Research Group (August-October 1993).
- Postdoctoral research at the University of California, Santa Barbara (1994-1996) working in Prof. Wudl group in the functionalization of C60.
- January 1996-June 1998, Research Position at the “Universidad de Oviedo” financed by the Spanish Ministry of Education working in Prof. Barluenga group in the Synthetic Applications of Fischer Carbene Complexes.
- In July 1998, she joined the Lilly Research Center in Spain as a Senior Organic Chemist. She has been working in the Department of Medicinal Chemistry participating in projects in the areas of neuroscience and endocrinology. She has been promoted to Senior Research Scientist in 2004.
- Coauthor of 27 publications and coinventor of 6 patent applications.

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From Peptides to Small Molecules: The Design and Synthesis of Efficacious BACE Inhibitors

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Alzheimer's disease (AD) is a complex neurodegenerative disorder characterized by a progressive loss of cognitive function, which affects almost 10% of the population over age 65, and 40% of the population over 85.[1] In the search for a disease-modifying therapy, much interest has been focused on the amyloid cascade hypothesis. This hypothesis states that Aβ, a proteolytic derivative of the large transmembrane protein, amyloid precursor protein (APP), plays a crucial role in the clinical progression of AD.[2] Since the discovery of BACE in 1999, the aspartic protease that generates the *N*-terminus of Aβ, there has been significant interest in the development of inhibitors of this enzyme.[3] In this lecture, the design and synthesis of efficacious BACE inhibitors will be presented.

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DIDIER ROGNAN

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Didier Rognan heads the "Drug Bioinformatics" Laboratory at the Gilbert Laustriat Institute (CNRS UMR7175-LC1) in Illkirch (France). He studied Pharmacy at the University of Rennes (France) and did a Ph.D. in Medicinal Chemistry in Strasbourg (France) under the supervision of Prof. C.G. Wermuth. After a post-doctoral fellow at the University of Tübingen (Germany), he moved as an Assistant Professor at the Swiss Federal Institute of Technology (ETH) until October 2000. He was then appointed Research Director at the CNRS to build a new group in Illkirch. He is mainly interested in all aspects (method development, applications) of structure-based drug design, notably on G Protein-coupled Receptors. Several of his recent achievements have been currently transferred to a new biopharmaceutical start-up company (IDEALP'Pharma).

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FROM THE COMPOUND TO THE TARGET: DEVELOPMENT OF *IN-SILICO*-GUIDED TARGET FISHING STRATEGIES

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Stimulated by chemogenomic and structural genomic projects, structure-based design of drug candidates has progressively evolved from single target to full protein subfamily-biased approaches. It is therefore of strategic importance to control, as early as possible, the selectivity profile of bioactive compounds towards hundreds of targets. We herewith propose both the development of target libraries and novel *in silico* screening procedures to mine these target libraries. Two main applications will be exemplified: (1) the screening of a collection of druggable active sites to identify the target of a scaffold-focused library (Fig.1); (2) the comparison of active sites to detect local homology in absence of amino acid sequence conservation (Figure 2).

Fig.1: From a focussed library of triazepanedione to their target (phospholipase A2)[1]

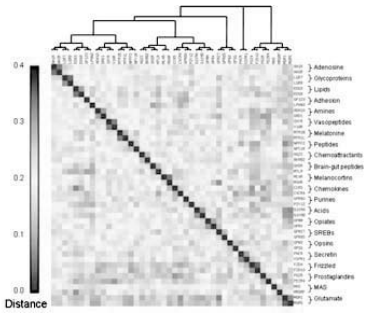

Fig. 2: Distance matrix of 44 human GPCRs from 22 clusters[2]

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LEONARDO PARDO

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Leonardo Pardo obtuvo el título de doctor en Ciencias Químicas por la Universidad Autónoma de Barcelona en el año 1986. Continuó sus estudios en el Department of Physiology and Biophysics del Mount Sinai School of Medicine en Nueva York bajo la dirección del Prof. Harel Weinstein. Se reincorporó a la Facultad de Medicina de la Universidad Autónoma de Barcelona en el año 1990. Su grupo de investigación aplica herramientas bioinformáticas, como alineamiento múltiple de secuencia, métodos estadísticos, búsquedas en bases de datos, gráficos moleculares, 3D-QSAR, y simulaciones de dinámica molecular (*i*) para el diseño molecular de ligandos y (*ii*) para estudiar las relaciones estructura-función de receptores acoplados a proteínas G.

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DISEÑO MOLECULAR DE AGONISTAS Y AGONISTAS INVERSOS DE RECEPTORES ACOPLADOS A PROTEÍNAS G

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Los receptores acoplados a proteínas G (RAPG) constituyen una de las dianas terapéuticas más importantes[1] y están relacionados con diversas enfermedades.[2] El descubrimiento de RAPG capaces de producir la respuesta biológica en ausencia del ligando extracelular (constitutivamente activos), permitió proponer que los RAPG se hallan en equilibrio entre estados inactivo y activo. Un agonista favorece la forma activa, un agonista inverso la inactiva, mientras que un antagonista neutro no modifica este equilibrio. La publicación de la estructura del estado inactivo de rodopsina, unida covalentemente al agonista inverso cis-retinal,[3] ha facilitado el estudio de los mecanismos de unión de este tipo de ligandos al receptor.[4] El estudio de los mecanismos de acción de agonistas, es más complicado porque los agonistas, además de unirse al receptor, promueven o estabilizan un reordenamiento de las hélices transmembránicas induciendo el estado activo, del cual no existe información estructural. La publicación reciente de la estructura intermedia de metarodopsina I[5] ha facilitado el estudio del mecanismo de activación del receptor. En particular, los mapas de densidad electrónica de metarodopsina I han mostrado que en los pasos iniciales del proceso de activación no hay cambios estructurales importantes en las hélices transmembránicas, sino cambios locales de la conformación de las cadenas laterales de algunos amino ácidos. En esta presentación expondré los últimos avances de nuestro grupo de trabajo en el diseño molecular de agonistas y agonistas inversos de receptores de aminas biogénicas, quemoquinas, y prostaglandinas, usando técnicas de modelización molecular, mutagénesis dirigida, y síntesis química.[2,6-10]

Agradecimientos: Este trabajo se ha realizado en colaboración con los grupos de los/as Profesores/as López-Rodríguez (Universidad Complutense de Madrid), Leurs (Vrije Universiteit, Amsterdam), Kostenis (Institute for Pharmaceutical Biology, Bonn), y Dumuis (Institut de Génomique Fonctionnelle, Montpellier). La financiación se ha obtenido del MEC (SAF2006-04966, SAF2007-67008), AGAUR (SGR2005-00390), European Comission (LSHB-CT-2003-503337), y Laboratorios Esteve.

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GREGORIO ASENSIO

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Nacido en Zaragoza en 1948 estudió Ciencias Químicas en la Universidad de Zaragoza doctorándose en esta misma Universidad en 1973 dirigido por los Profesores Gomez-Aranda y Barluenga. Después de una estancia post-doctoral en el grupo del Prof. Geroge A. Olah en la Case Western Reserve University, Cleveland (USA) se reincorporó al grupo del Prof. Barluenga en 1977 siendo ese mismo año Prof. Adjunto de Química Orgánica en la Universidad de Oviedo. Después de siete años de actividad en esa Universidad obtuvo la plaza de Prof. Agregado y seguidamente Catedrático de Química Orgánica de la Universidad de Valencia en 1984 donde continúa.

En su carrera como investigador se ha interesado por diversos temas contemplados siempre más desde el punto de vista mecanístico que sintético. De entre los temas abordados pueden citarse como más significativos el estudio de las reacciones electrofílicas y de los intermedios catiónicos, las oxidaciones particularmente con dioxiranos y, más recientemente, las reacciones en CO_2 supercrítico y la química organometálica con la que cierra por el momento el círculo puesto que en este tema realizó su Tesis Doctoral. Ha simultaneado su trabajo como investigador con diversas tareas de gestión Universitaria, y coordina actualmente el Programa de Doctorado Interuniversitario *Química Orgánica en la Industria Químico-Farmacéutica* y el área de Química de la Anep. Como profesor, disfruta dando clase a buenos estudiantes y en su tiempo libre le gusta viajar y la música clásica.

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Reacciones de Acoplamiento Cruzado C(sp^3)-C(sp^2) Catalizadas por Paladio

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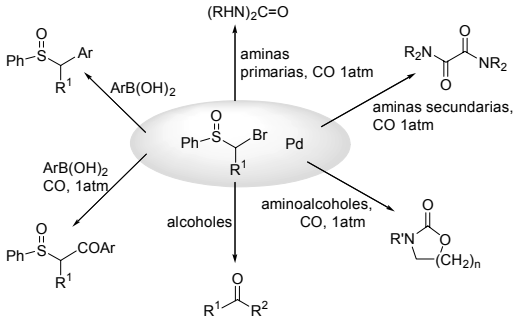
Las reacciones de acoplamiento cruzado catalizadas por paladio se usan como método práctico y general para la formación de enlaces C-C entre dos centros C(sp^2). Por el contrario la formación de enlaces C-C sp^2-sp^3 es mucho menos común y en general esta limitada a la reacción de halogenuros de arilo con enolatos. Debido al uso extendido de los sulfóxidos en síntesis orgánica decidimos explorar la participación de sulfóxidos o sus derivados en procesos de acoplamiento cruzado. En el esquema siguiente se muestra como los sulfóxidos bromados en posición α participan tanto en procesos de acoplamiento cruzado con formación de enlaces C-C sp^2-sp^3 como en los análogos de tres componentes con carbonilación.



Las reacciones tipo Suzuki-Miyaura tienen asimismo lugar cuando el halogenuro de alquilo es secundario en el bromosulfóxido. En este caso se ha demostrado que las reacciones ocurren con total estereoespecificidad e inversión de la configuración. Se han encontrado a su vez grandes diferencias en la reactividad de distintos diastereoisómeros. El complejo intermedio de adición oxidante es estable por lo que ha sido aislando y caracterizado encontrando que tiene algunas propiedades químicas únicas si se le compara con otros complejos de Pd(II) lo que permite utilizarlo como catalizador en otros tipos de reacciones como algunas de las que se recogen en el esquema permitiendo realizar muy fácilmente procesos de carbonilación a presión atmosférica y de oxidación.

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Comunicaciones Orales

IDENTIFICATION OF A NOVEL 2-ARACHIDONOYLGLYCEROL-HYDROLYZING ENZYME BY DEVELOPMENT OF INHIBITORS

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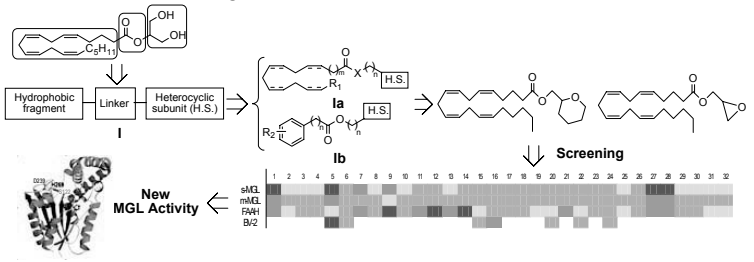
Recently, the enzyme monoacylglycerol lipase (MGL) has been proposed to be the responsible of degradation in brain of 2- arachidonoylglycerol (2-AG),[1] one of the main endocannabinoids and involved in a broad number of physiopathological processes.[2]

The development of potent and selective MGL inhibitors will allow to study the roles played by 2-AG. However, data available regarding the structural features involved in the recognition of substrates by the enzyme are very scarce, and potent and selective inhibitors have not been described.[3]

Considering the lack of the 3D structure and lead compounds for MGL, we have designed and synthesized a series of compounds **I** based on the structure of 2-AG that will enable us to study the structural requirements involved in the recognition of substrates.The most promising compounds emanating from this study were oxiran-2-ylmethyl (5*Z*,8*Z*,11*Z*,14*Z*)-icosa-5,8,11,14-tetraenoate and tetrahydro-2*H*-pyran-2-ylmethyl (5*Z*,8*Z*,11*Z*,14*Z*)-icosa-5,8,11,14-tetraenoate. These compounds constitute the most potent and selective inhibitors reported to date and inhibit cytosolic MGL completely with IC_{50} values of 4.5 and 5.6 μM, respectively. They are less potent inhibitors of membrane-bound MGL (IC_{50}=19 and 26 μM, respectively), and of fatty acid amide hydrolase (FAAH) (IC_{50}=12 and 51 μM, respectively). Moreover, the pyrane derivative has allowed the identification of a novel MGL enzymatic activity in microglial cells. The neuroprotective role of 2-AG and the involvement of this cell type in pathologies such as multiple sclerosis and Alzheimer's disease point out that this novel enzyme can be a key drug target for the treatment of neurodegenerative disorders.



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SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF (*RS*)-6-SUBSTITUDED-7 OR 9-(2,3-DIHYDRO-5*H*-1,4-BENZODIOXEPIN-3-YL)-7*H* OR 9*H*-PURINES WITH ANTI-BREAST CANCER ACTIVITY

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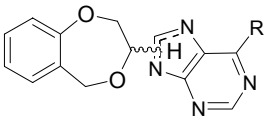
The development of new drugs against cancer belongs among the priorities of the development of science and fundamental research. Because it is difficult to discover novel agents that selectively kill tumour cells or inhibit their proliferation without general toxicity, the use of traditional cancer chemotherapy is still very limited. A series of pyrimidine benzo-fused seven-membered *O*,*N*-acetals were designed and synthesized.[1,2] Later on, the pyrimidine base was substituted for the purine moiety with the objective of increasing both the lipophilicity and the structural diversity of the target molecules.[3] Here we report the design, synthesis and biological evaluation of a series of (6'-substituted)-7 or 9-(2,3-dihydro-5H-1,4-benzodioxepin-3-yl)-7*H*-or 9*H*-purines.



R = cyclohexylmethyloxy, benzyloxy, phenyloxy, allyloxy, phenylthio, benzylthio, 4-phenylthio, 2,4-dichlorobenzylthio, anilino groups

The compounds have been obtained *via* condensation reaction between the seven-membered acetal and the corresponding purine derivative using tin(IV) chloride, TCS and HMDS in dry acetonitrile at 45 ºC for 72 h. It produced the *N*-9' and the *N*-7' cyclic alkylated purine regioisomers, which were separated by flash chromatography. When the reaction was carried out within 5 min by microwave irradiation at 130 ºC only the formation of the *N*-9' isomer was observed. The anticarcinogenic potential of the target molecules is reported against the MCF-7 cancer cell line. The most active compound presents an IC_{50} = 5,04 ± 1,68 μM against the MCF-7 human breast cancer cell line. These results provide promising information for further development of potent antiproliferative agents. At present, studies are being carried out to determine the mechanism of action at the molecular level of the most active compounds.

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TRIAZOLOCARBANUCLEÓSIDOS. PARTE 1: SÍNTESIS Y EVALUACIÓN BIOLÓGICA DE 4-ARIL-[1,2,3]-TRIAZOLO-3'-DESOXI-2'-IODOCARBANUCLEÓSIDOS

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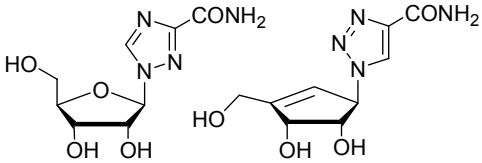
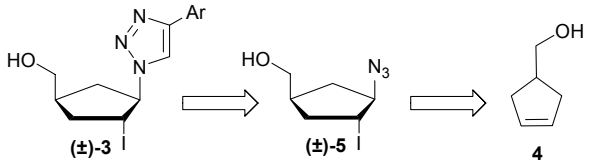
En el contexto general dirigido a la búsqueda de nuevos análogos de nucleósidos dotados de actividad antiviral y/o anticancerígena, una de las posibles variaciones a realizar sobre la estructura de los nucleósidos naturales radica en modificar la base púrica o pirimidínica.[1] Como resultado de ello han surgido algunos análogos de nucleósidos portadores de anillos heterocíclicos de 5 miembros, tales como imidazoles o triazoles. De entre ellos, puede destacarse la Ribavirina[2] (Virazole®, **1**), agente antiviral de amplio espectro usado en el tratamiento de sarampión, paperas, hepatitis etc. En el campo de los carbanucleósidos, ha sido comunicada recientemente la síntesis y evaluación de la actividad biológica de una serie de 1,2,3-triazoloderivados;[3,4] así por ejemplo **2**,[4] que presenta una potente actividad antiviral frente a virus vaccinia (EC_{50} 0.4 μM).



1 **2**

Como parte de nuestro programa de investigación centrado en la búsqueda de nuevos carbanucleósidos con actividad biológica, se presenta aquí la síntesis y evaluación biológica de una serie de 4-aril-[1,2,3]-triazolo-3'-desoxi-2'-iodocarbanucleosidos tipo (±)-**3**, estructuralmente relacionados con la Ribavirina (**1**). La síntesis de éstos fue diseñada siguiendo una estrategia de tipo divergente, utilizando como material de partida el alcohol **4**, que fue convenientemente funcionalizado de forma estereoselectíva empleando una reacción de iodoazidación del doble enlace, para a continuación construir sobre el grupo azida de (±)-**5** el sistema triazólico mediante una cicloadición 1,3-dipolar de Huisgen catalizada por Cu (I), en la que la variabilidad estructural se introduce empleando diversos derivados arilacetilénicos



Los derivados tipo (±)-**3** han sido sometidos a ensayos *in vitro* de actividad antiviral frente a diversos virus de ADN y ARN.

MITOCHONDRIAL THYMIDINE KINASE (TK-2) INHIBITORS: AN OVERVIEW OF THEIR CHEMISTRY, ENZYME KINETICS, AND A PROPOSED MODEL OF INTERACTION WITH TK-2

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Human mitochondrial thymidine kinase, also named thymidine kinase 2 (TK-2), catalyzes the phosphorylation of pyrimidine deoxynucleosides to their corresponding deoxynucleoside monophosphates by γ-phosphoryl transfer from ATP. There is increasing evidence that TK-2 plays a pivotal role in mitochondrial DNA (mtDNA) metabolism. Critical point mutations in the gene encoding TK-2 have been described and correlated to severe mtDNA disorders that can even compromise the individual's survival. TK-2 has also been involved in the mitochondrial toxicity associated to prolonged treatment with antiviral nucleoside analogues, like AZT, which are TK-2 substrates. In this scenario, TK-2 inhibitors could become valuable tools to unravel the role of TK-2 in the maintenance and homeostasis of mitochondrial deoxynucleoside triphosphate pools required for mtDNA synthesis, and to clarify the contribution of TK-2-catalyzed phosphorylation of certain antiviral drugs to their mitochondrial toxicity.

Our research groups have been deeply involved in the identification of TK-2 inhibitors.[1] We have described that acyclic nucleoside analogues, mostly thymine derivatives, can effectively inhibit TK-2 catalyzed thymidine phosphorylation in the submicromolar range. As a general rule, the spacer connecting the thymine base and the distal substituent has a major impact on the potency and selectivity of the inhibitors against TK-2 and related enzymes. On the other hand, substituents attached at the distal site should be aromatic groups such as diphenylmethyl, biphenyl and dibenzyl, and, preferentially, triphenylmethyl (trityl). Enzyme kinetics with some representative examples of our acyclic nucleoside analogues has shown a competitive inhibition against thymidine and uncompetitive inhibition against ATP. With these premises, we have constructed and proposed a model of interaction of our acyclic nucleosides with TK-2 based on a homology model of the latter.[2]

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O-5

CYCLIC PEPTIDES COMPRISING CONSTRAINED AMINO ACIDS AS INHIBITORS OF INTEGRIN-LIGAND INTERACTION

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Integrins are heterodimeric glycoprotein receptors located on the cell surface, which are involved in many biological processes. They mediate cell–cell and cell–matrix adhesion. The interactions of integrins with their natural ligands are the molecular basis of physiological or patho-physiological processes. Thus, small molecules that are able to interfere with this integrin–natural ligand binding process possess pharmacological potential in the therapy of cancer and inflammatory diseases. The amino acid sequence RGD (Arg-Gly-Asp), present on many of the natural ligands, is a prominent recognition motif of integrin ligands. Synthetic peptides containing the RGD sequence have emerged as an excellent starting point for the identification, synthesis and development of selective integrin ligands.[1]

The affinity and selectivity of the peptide ligands towards different integrins depend strongly on the secondary structure of the sequence and the overall three-dimensional shape. Since the three-dimensional structure of most integrins is not yet available, the introduction of local or global conformational constraints on a rational basis can provide information on the structural requirements for the pharmacophoric groups, following a *spatial screening* approach.[2] Cyclization is frequently used as a method to reduce the accessible conformational space. Additionally, the incorporation of non-natural conformationally constrained amino acids, e.g. β-amino acids,[3] can greatly affect the secondary structure of the peptide, in such a way that the synthetic ligands prefer to adopt a particular conformation.

The aim of this investigation are small cyclic peptides containing the RGD motif and constrained aromatic amino acids that exhibit well-defined conformational properties. The present communication describes the synthesis of different RGD peptides and the evaluation of their activity as ligands for the $\alpha_V\beta_3$ integrin, carried out on human cells.

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Desarrollo de nuevos inhibidores del dominio PDZ de la nNOS

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El óxido nítrico (NO) está involucrado como mediador en los mecanismos de transmisión de señales a nivel del sistema nervioso central y periférico. Sus niveles están regulados fundamentalmente por la isoenzima nNOS[1]. Esta isoenzima posee un dominio PDZ que media la interacción con diversas proteínas a través del reconocimiento, entre otras, de secuencias de aminoácidos situados en el extremo carboxilo terminal.

Basándose en este hecho se han desarrollado péptidos inhibidores de las interacciones proteína-proteína mediadas por el dominio PDZ de la nNOS, que pudieran ser de utilidad para bloquear la neurodegeneración mediada por el óxido nítrico[2].

Se ha optimizado la síntesis en fase sólida del nonapéptido VSPDFGDAV, marcado con un resto de dansilo como fluoróforo. Esto ha permitido determinar su afinidad hacia el dominio PDZ de la nNOS, utilizando una proteína recombinante que incluye dicho dominio. Además, se ha procedido a sintetizar en paralelo péptidos, en los que se ha sustituido el resto de Phe por diferentes derivados (Figura 1), al objeto de obtener derivados con una mayor afinidad y establecer relaciones estructura-actividad.

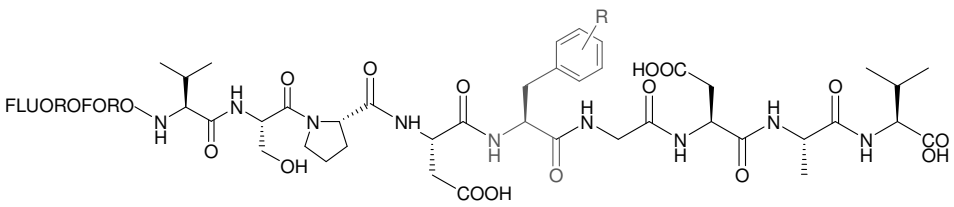

Figura 1

O-7

DISEÑO, SÍNTESIS Y MEDIDA DE PROPIEDADES FÍSICAS DE MOLÉCULAS FLUORESCENTES PENSADAS PARA INHIBIR LA INTERACCIÓN ENTRE LA INTEGRINA VLA-4 Y SU LIGANDO NATURAL VCAM-

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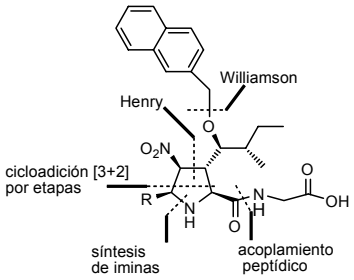
En el presente trabajo de investigación se muestra el diseño, la síntesis y la medida de propiedades físicas de moléculas sintéticas fluorescentes pensadas para inhibir la interacción entre la integrina VLA-4 y su ligando natural VCAM-1.

El interés biológico de estos inhibidores reside tanto en su capacidad de bloquear la interacción entre las proteínas VCAM-1 y VLA-4, cuya vinculación en la metástasis de diversos tipos de cáncer (melanoma, cáncer renal, de estómago, linfomas, etc)[1] está ampliamente recogido en la literatura científica, como en el hecho de que su posible propiedad de emisión de fluorescencia los hace especialmente valiosos en el campo del diagnóstico clínico y de la investigación básica relacionada con la biología molecular.

Los inhibidores poseen un anillo de pirrolidina altamente sustituida que les confiere rigidez conformacional, así como un sustituyente carboximetilamido capaz de coordinarse a la integrina natural para bloquear la adhesión, y además un grupo naftilo que presenta fluorescencia. La ruta sintética está basada en una síntesis convergente cuya etapa clave es una cicloadición [3+2] entre un nitroalqueno homoquiral y un iluro de azometino metalado.



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A SEQUENTIAL MODEL OF LIGAND BINDING AND ACTIVATION FOR CLASS A GPCRS

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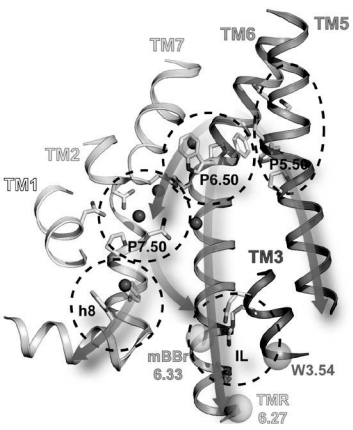
The ß$_2$ adrenergic receptor (ß$_2$AR) is an excellent model system for studying the mechanism of Class A GPCRs activation, as it possesses a wealth of structurally related ligands with functionally diverse properties and a well characterized agonist binding site. Using an array of biophysical and pharmacologic approaches, we have shown that agonist binding is translated into a series of specific conformational changes, related to the stabilization of different active states of the receptor, through a multistep sequential process that can be dissected into its component parts[1,2].

By putting together these results with sequence analyses and mechanistic hypothesis derived for other GPCRs, and using 3D models of the receptor as structural templates, we aim to propose a specific signal transduction pathway for the ß$_2$AR. This pathway is formed by a network of interactions (arrows in the accompanying figure) extending from the ligand-binding pocket to the cytoplasmic region of the receptor, related to G protein binding and activation. *The mechanism of activation progresses through a linking core of residues highly conserved in Class A GPCRs*, which includes residues of the rotamer toggle switch in TM6, the (S/N)xxxNPxxY motif in TM7 and the DRY motif in TM3. This pathway attempts to describe an early stage in the activation process, when side chain relocations have not yet been translated into major structural changes. As this mechanism involves residues highly conserved within Class A GPCRs, it is expected to be shared by other members of this family.



So far, we have been able to directly detect conformational changes in the ß$_2$AR related to the triggering of three of the switches forming part of this proposed activation pathway. Specifically, we have detected a change in the cytoplasmic side of TM6 related with the trigger of the rotamer toggle switch in the same helix, the breaking of an ionic interaction between TM3 and TM6, and a structural rearrangement of the cytoplasmic side of TM5 relative to TM6.

We are starting to put together some of the pieces of the puzzle in the mechanism of activation of Class A GPCRs. Although some of the pieces are still missing, we are starting to see an emerging picture. A better understanding of the complex process of agonist binding and activation may prove valuable for structure-based drug discovery efforts and facilitate the design of more effective and selective pharmaceuticals.

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O-9

DEVELOPMENT OF A PLATFORM FOR THE THROUGHPUT STUDY/IDENTIFICATION OF CARBOXYMETHYLATED PROTEINS

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Reversible carboxymethylation of proteins has been suggested to be a key posttranslational modification for the regulation of protein activity.[1] However, little is known about the biological significance of this modification. This is due to the fact that there is no currently available technique to systematically study carboxymethylated proteins. One approach that has proven successful for identification of low abundance enzymes in whole complex proteomes is the so-called activity based protein profiling coupled to the mass spectrometry technique multidimensional identification technology (ABPP-MudPIT).[2,3] Therefore, we sought to develop a similar strategy that enables the selective capture of the carboxymethylated fraction of the proteome and its subsequent identification by mass spectrometry.

Based on the increased reactivity of methylesters compared to free carboxylic acids, we hypothesized that nucleophiles such as an *O*-alkylhydroxylamine or a primary amine would react selectively with carboxymethyl groups. To this reactive group we appended an alkyne moiety, suitable for latter introduction of a biotin moiety using click chemistry. Both fragments were joined by a linear spacer. Ideally, these probes (**1** and **2**) would enable to target the desired fraction of the proteome and the subsequent enrichment over avidin beads followed by MudPIT (Figure 1).

Since **2** yielded the best results in the preliminary experiments, we used this probe to characterize the carboxymethylated proteome from mouse brain. Among the hits obtained, we succeeded in the identification of several known carboxymethylated proteins such as the catalytic subunit of PP2A or several members of ras family. Although one of the current shortcomings of the method is its low yield in terms of spectral counts, these results suggest that the development of such a platform should be feasible and will facilitate the de novo discovery of methylated proteins.

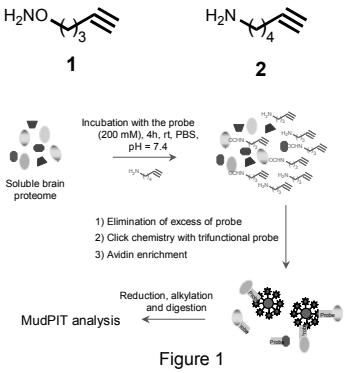

Figure 1

Acknowledgments: This work has been supported by NIH (grant DA015197) and by a postdoctoral fellowship from MEC and the Fulbright Scholar Program (S.O.G.).

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THE CHEMBIOBANK PROJECT: BUILDING AN ANNOTATED MOLECULAR LIBRARY.

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The generation of public databases with chemical and biological information is basic for the advancement of science, since there is a lack of public annotated chemical compounds, which may be critical for the characterization of biological routes (the *chemical map of the cell*)

The goal of the Chembiobank project (CBB) is to build a chemico-biological database, annotated with both biological and bioinformatic data, addressed to the scientific community and to the pharmaceutical and biotech industries. Chemical compounds (natural and synthetic), from academic groups, will be properly characterized using analytical methods (LC/MS) with standards set by CBB. Compound traceability of any compound deposited in the CBB library will be assured, through a logistic procedure that will cover the handling and storage of compounds in conditions that allow their pharmacological characterization in HTS screens, as well as the generation of a database that contains the chemical structures of these compounds. This database will also include the experimental results from pharmacological screening, and the virtual screening results of such compounds on a large variety of biological targets. Currently, the CBB library contains a core of 1000 molecules, which include commercial standards, which should be growing with additional compounds from academic groups.

The Chembiobank project is a joint initiative between the Parc Científic Barcelona (PCB) which, in addition to the chemical and logistics aspects of the project, will also handle its coordination; the Universidad de Santiago de Compostela (USC) which will develop the screening assays for the library compounds; and GRIB (IMIM-UPF), located at the Parc de Recerca Biomédica de Barcelona, which will carry out the virtual screening for these compounds. The implementation of the project will require collaboration agreements with interested academic institutions.

This project is parallel and will be coordinated with initiatives with similar objectives being developed in several European countries, in order to build eventually a European annotated academic molecular library.

O-11

IDENTIFICATION OF NEUROPEPTIDE-PROCESSING PROTEASES BY ACTIVITY-BASED PROTEOMICS

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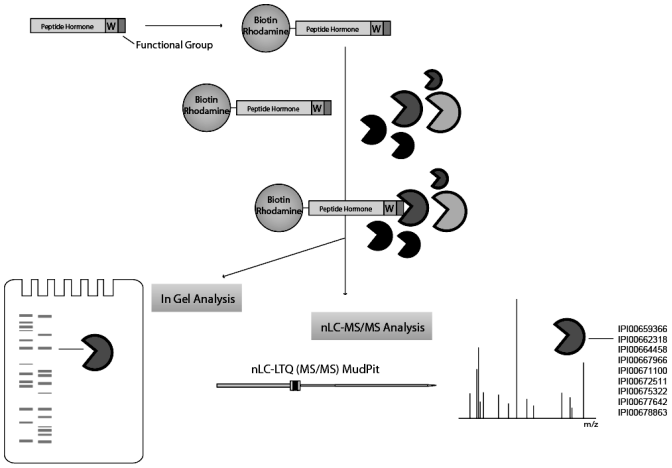
Neuropeptides are produced from precursor proteins by selective cleavage at specific sites. Classical biosynthetic cleavage occurs at basic residues and a relatively small number of peptidases are responsible for processing the majority of neuropeptides[1,2]. However, with the discovery and characterization of new neuropeptides, a new non-classical pathway has been described with cleavage occurring at Tryptophane, Leucine and other amino acids. Neuropeptide-processing peptidases involved in this new non-classical pathway are completely unknown but essential for correct processing of certain neuropeptides. Therefore, our aim is to identify proteases involved in the non-classical neuropeptide processing pathway using activity based proteomics. Some substrate-inspired peptides with a phosphonate functional group were designed and synthesized to identify serine proteases that may be involved in the non-classical neuropeptide-processing pathway. The analyisis of the proteome was done by in-gel analysis and MudPIT nLC-MS/MS analysis. The synthesised peptides were labeled either with a rhodamine or a biotin tag by click chemistry. To validate the methodology some phosphonate inhibitors for the well-known Prolyl oligopeptidase were synthesized to identify this protein among a complex mixture of proteins (mouse brain homogenate). Finally, two mature neuropeptide-based molecules containing Tryptophane and Leucine in their C-terminus were synthesized to identify unknown proteases from mouse pituitary.



Acknowledgements: We acknowledge Prof. Benjamin Cravatt for his advice and support.

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THE CONFORMATIONAL BEHAVIOR AND P-SELECTIN INHIBITION OF A NEW GENERATION OF SIALYL LEX GLYCOMIMETICS

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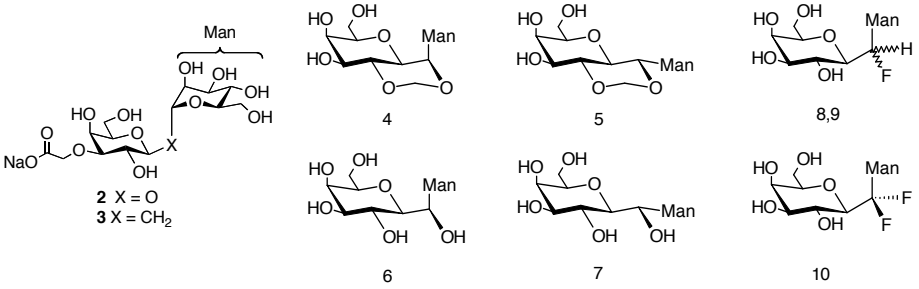
The conformation behaviour of different C-glycosides, synthesized as analogs of a glycomimetic (**2**) of sialyl LeX (**1**), has been studied. Indeed, **1** is a strong antiinflammatory, but it presents lack of stability for glycosidase attack. The first generation of analogs (**3**)[1] showed a moderate biological activity, and thus compounds **4** to **10** were designed to restrict their conformational properties and to obtain increased biological activity.[4]

On this basis, the conformation of **4** and **5,** their analogues **6** and **7**, without the cyclic acetal moiety, and the fluorinated compounds **8-10** has been studied. The conformation has been derived by using an approximation which combines molecular mechanics and dynamics methods with NMR experimental data.[2,3]

It is demonstrated that the conformation of the compounds depends on the nature of the glycosidic linkages and on the presence or absence of the acetalic bridge.

Finally, the inhibition activity of compounds **4**, **5**, **8** and **9** has been determined, and this activity has been related with the observed conformation.



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SYNTHESIS, BIOLOGICAL ACTIVITY AND *DOCKING* STUDIES OF NOVEL ESTROGEN RECEPTOR LIGAND TEMPLATES.

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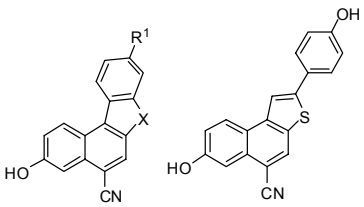


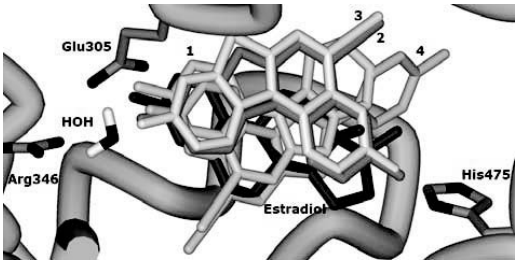
1: X = O, R^1 = H
2: X =O, R^1 = OH
3: X = S, R^1 = OH
4

Selective Estrogen Receptor Modulators (SERMs) have shown interesting applications in the treatment and prevention of breast cancer.[1] The estrogen receptor ER is comprised of two subtypes, ERα and ERβ, which bind 17β-estradiol with similar affinity.[2] The search of ERα and ERβ-selective agents is intensive, as subtype-selective compounds might lead to new therapies, and may contribute to increase the understanding of estrogen biology.

We are currently working on the design and synthesis of new series of non steroidal compounds as potential SERMs, following a synthetic strategy based on a photochemical electrocyclic reaction. Thus, compounds **1-4** have been synthesized as promising scaffolds for the future development of new SERMs.

The affinity of these ligands for ERα and ERβ has been measured in an in vitro coactivator recruitment functional assay.[3]

A computational study of the mode of binding of **1-4** with both estrogen receptors has been carried out in order to understand the activity and receptor selectivity found for these compounds.



Acknowledgements*:* Spanish Ministry of Science and Education (SAF2005-02608 and AGL2006-05453) for financial support. J.J.R. thanks USP-CEU for a predoctoral fellowship and S.M.S. thanks Spanish Ministry of Science and Education for a Ramón y Cajal contract.

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Pósteres

P-1

SÍNTESIS DE AMINOÁCIDOS NO NATURALES PARA LA INHIBICIÓN DE LA INTERACCIÓN LFA-1/ICAM-1

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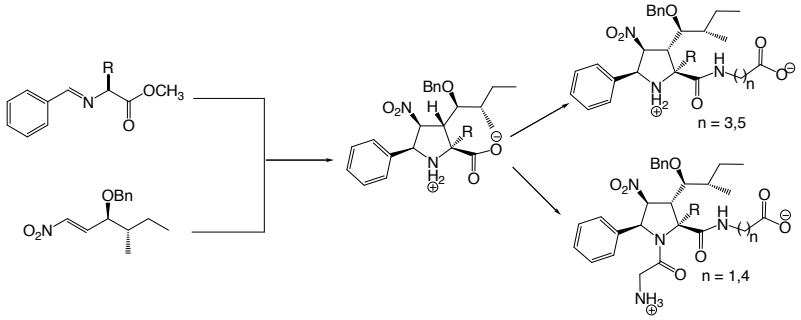
La unión de la integrina LFA-1 con el ligando ICAM-1 está involucrada en patologías como la metástasis de carcinoma gastrointestinal, melanoma[1], linfoma[2], cáncer de colon, así como en enfermedades inflamatorias y autoinmunes. En esta comunicación se describe el diseño y la sintesis de una familia de pirrolidinas candidata a inhibir la interaccion LFA-1/ICAM-1 que se obtienen mediante la cicloadición [3+2] entre nitroalquenos homoquirales derivados de la L-isoleucina, e iminas con sustituyentes aromáticos, mediante una ruta convergente, completamente regioselectiva y estereoselectiva,y versátil .

Alguna de estas moléculas pueden inhibir eficazmente la metástasis de células de carcinoma de colón CT26 en el endotelio sinusoidal hepático, así como la adhesión de células PBLs a ICAM-1 inmovilizada mostrando actividad antiadhesiva[3] *in vivo* reduciendo el volumen de metástasis hepáticas en un 85% y la expresión de Ki67 en un 40%.



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PRODRUGS OF HYDROXY-CONTAINING COMPOUNDS BASED ON THE DPP-IV/CD26

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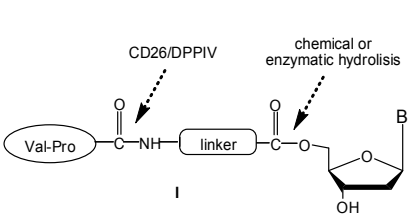
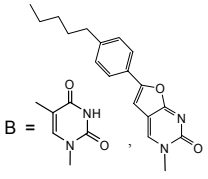
The lymphocyte surface glycoprotein dipeptidyl-peptidase IV enzyme (DPP-IV), also known as CD26, belongs to a group of atypical serine proteases that preferentially cleave X-Pro (or X-Ala) dipeptides from the *N*-terminus of a variety of natural peptides. We have recently described an entirely novel enzyme-based prodrug approach based on conjugates of therapeutic agents with a peptidic moiety as a carrier wherein the conjugate [peptide]-[drug] is specifically cleavable by the endogenous DPP-IV. [1]

This approach was used on drugs containing a free amino group that was directly coupled with the carboxyl group of amino acids *via* an amide bond (bipartate prodrug). [(Xaa-Pro)$_n$]-[drug] conjugates bearing di- and tetrapeptide sequences of different nature were prepared and studied. It was possible to modify the hydrolisis rate (half-life) and the physicochemical properties of the compounds modifying the nature and length of the peptide (di- or tetrapeptides).

We now explore the viability of the DPP-IV/CD26 prodrug approach in hydroxy-containing drugs. Here, we propose conjugates of general formula **I** bearing an heterobifunctional linker able to covalently link both the peptidic sequence (Val-Pro), easily recognized by CD26 in previous studies, and the OH group of a nucleoside (tripartate prodrug). As heterobifunctional linkers, amino acids (i.e. Val, Leu, Phe, Ala) susceptible to be hydrolyzed by esterases are used. Thus, we prepared conjugates of commercially available nucleoside thymidine **Ia** and of a potent and selective inhibitor of Varicella Zoster Virus (VZV) named CF1743 **Ib**. The synthesis of the proposed conjugates and their ability to act as efficient substrates of DPPIV/CD26 enzyme will be described. Oral bioavailability and aqueous solubility studies of conjugate **Ib** will also be reported.



I



Ia **Ib**

linker = Val, Ala, Leu, Phe

Acknowledgements: CSIC is acknowledged for a predoctoral fellowship to A.D.T. (programa I3P predoctorales).

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P-3

DESIGN AND SYNTHESIS OF CONFORMATIONALLY CONSTRAINED PEPTIDOMIMETICS ACTING IN CELLULAR SIGNALING ROUTES: IDENTIFICATION OF MODULATORS OF THE UBC13-UEV1 INTERACTION.

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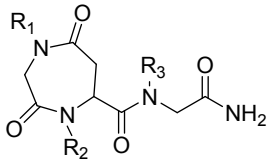
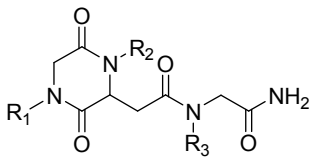
The heterodimeric ubiquitin conjugase UBC13-UEV1 catalyzes non-canonical polyubiquitylation that uses Lys63 of the ubiquitin protein to form isopeptide bonds between ubiquitin moieties.[1] Modification by Lys63-based polyubiquitylation modulates the activities of proteins that exert key functions in DNA repair, signaling, endocytosis and cell motility. We have used the strategy of chemical modulation for optimizing *N*-alkylglycine trimers (peptoids) *hits* implicated in cellular signaling routes such as that involving the UBC13-UEV interaction. The high conformational flexibility of peptoids can generate selectivity problems because of unwanted off-target interactions. Fortunately, their simplicity makes them amenable to structural manipulation, thus facilitating the optimization of hit molecules for drug-like properties. We report here the design and synthesis of conformationally constrained compounds **I** and **II**, derived from the above hit peptoids. For the synthesis of these analogues, an approach combining solid phase synthesis with microwave activation was developed.



I



II

Results on the potent biological activity elicited by representative molecules from these families as potent inhibitors of the UBC13-UEV interaction will be presented. The active analogues discovered constitute the first examples of small molecules eliciting a potent inhibition of the UBC13-UEV interaction.

Acknowledgements: This work was supported by grants from the Spanish Ministry of Science and Education (MEC) (2005-00995/BQU) and CSIC grant (PIF 200580F0202). A predoctoral fellowship from CSIC (I3P program) is also acknowledged.

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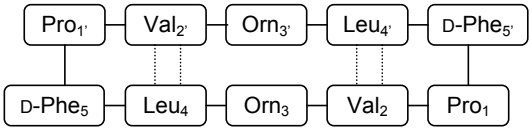
MODIFICATION OF GRAMICIDIN S BY INCORPORATION OF PHENYLALANINE ANALOGUES

Concepción Solanas[a], Beatriz G. De la Torre[b], María Fernández-Reyes[c], Clara M. Santiveri[d], M. Ángeles Jiménez[d], Luis Rivas[c], Ana I. Jiménez[a], David Andreu[b], Carlos Cativiela[a]

[a]Departamento de Química Orgánica, ICMA, Universidad de Zaragoza-CSIC, Zaragoza. [b]Departamento de Ciencias Experimentales y de la Salud, Universidad Pompeu Fabra, Barcelona. [c]Centro de Investigaciones Biológicas, CSIC, Madrid. [d]Instituto de Química Física Rocasolano, CSIC, Madrid.

In recent years, new arising resistant bacterial strains have prompted researchers to the development of new classes of antibiotics. The search for new molecules has led to the study of naturally occurring antimicrobial peptides, and those cationic in nature are the most abundant. Since these molecules target the cell membrane as a whole and not specific receptors, development of resistance is unlikely.

The cationic antimicrobial peptide gramicidin S (GS), isolated from *Bacillus brevis*, is active against a wide range of bacteria and fungi. Unfortunately, GS exhibits a high haemolytic activity, limiting its use as an antibiotic for topical applications. This peptide is a C2-symmetric cyclic decamer that adopts a rigid β-structure, in which the Val, Orn and Leu residues align to form the antiparallel β-strands and D-Phe and Pro induce type II' β-turns.



Structure of gramicidin S (hydrogen bonds are indicated with dotted lines)

There is a wide interest in the generation of new GS analogues in order to dissociate the antimicrobial and haemolytic activities and different sequence modifications have been proposed in the last decades. In addition, gramicidin S provides a suitable model to study the structural preferences of non-natural motifs. The current study deals with the modification of the β-turn region of GS by incorporating non-proteinogenic amino acids in place of both D-Phe residues. All linear peptides were prepared by SPPS using *Boc*-chemistry, cyclized in solution, purified by HPLC and characterized by mass spectrometry. The biological activity of the GS analogues has been evaluated and their different structural properties analysed by NMR.

β-AMINO-γ-SULTONES AS POTENTIAL DIMERIZATION INHIBITORS OF HIV-1 REVERSE TRANSCRIPTASE

Sonsoles Velázquez,[a] M. Teresa Peromingo,[a] Sonia de Castro,[a] Leire Aguado, [a]Jan Balzarini[b] and María-José Camarasa[a]

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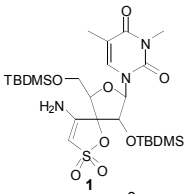
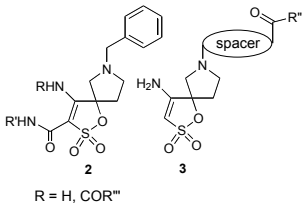


1

Viral Reverse Transcriptase (RT) is a key target in the search for anti-HIV drugs. The biologically active form of the enzyme is an asymmetric heterodimer composed of two subunits p66 and p51. Dimerization is essential for a fully functional RT, therefore, interference with this process constitutes an alternative target to inhibit the enzyme by a different mechanism to those described so far.

TSAO-m^{3}T (**1**), the first example of a small non-peptidic molecule that interferes with the dimerization of the enzyme,[1] destabilizes the p66-p51 heterodimer by its interaction between the palm subdomain of the p66 subunit and the β7-β8 loop region of the p51 subunit.[2] This previously unexplored interface region of the enzyme is a key structural element for RT dimerization and can be considered as a "hot spot" for drug design. The sequence in the loop at positions 134-141 is unique among HIV-1 RTs. Two residues are particularly important for the enzyme stability (and thereby enzyme activity), the highly conserved Asn-B136 and the Glu-B138 (key residue for the interaction of TSAO derivatives, through their 4''-amino group, that have a second polar interaction with Thr-B139).



2 **3**

R = H, COR'''

In order to find novel small molecules based on the β-amino-γ-sultone scaffold (the pharmacophore of TSAOs) that may bind at the β7-β8 loop and interfere with the dimerization of RT, we focused on spiro sultone derivatives (**2**) in which the 4-amino group of the spiro-sultone moiety was maintained (to allow the crucial interaction with Glu-B138) and at the 3- and/or 4- positions were substituted with amide or urea groups (to allow interaction with Asn-B136). Moreover, carbonyl groups linked to the pyrrolidine moiety through spacers of different nature (**3**) to interact with Thr-B139 were introduced. The synthesis and biological evaluation of these compounds will be reported.

Acknowledgements: MEC and the European Commission are acknowledged for financial support

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SYNTHESIS OF ψ-MIRAZIRIDINES AS POTENTIAL ANTICANCER AGENTS

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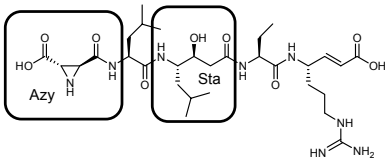
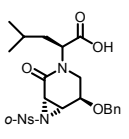
Biosyner, IRB-Parc Científic de Barcelona. 08028-Barcelona, Spain
Laboratori de Química Orgànica. Facultat de Farmàcia. Universitat de Barcelona. 08028-Barcelona, Spain

The pentapeptide miraziridine A (HO-(2*R*,3*R*)-Azy-Leu-(3*S*,4*S*)-Sta-Abu-vArg-OH, Figure 1), isolated from the marine sponge *Theonella aff. Mirabilis*,[1] shows potent and irreversible inhibition of cystein-proteases, mainly cathepsines B and L.[2] The peculiar structure of miraziridine A suggests that the azyridine moiety is responsible for the actual blocking of the thiol group of the cystein-proteases, and that the rest of the molecule may modulate its specificity towards a particular protease. Since statine (4-amino-3-hydroxy-6-methylheptanoic acid) occupies the central position and displays both a hydrophobic part (^{i}Bu) and a hydrophilic function (OH), we have synthesized some conformationally restricted pseudo-statines that contain our typical 3-aminopiperidone backbone,[3] and have used them in the preparation of several constrained pseudo-miraziridines.
Molecular modeling calculations showed that the native miraziridine A has one family of conformations that bends around Sta, and replacement of Sta for its lactam surrogates effectively bends the structure at this site.
We will present the synthesis of the diversely functionalised lactams (pseudo-Sta and pseudo-Azy) (Figure 2), the synthesis of the pseudo-miraziridines, and the structural studies. The anticancer activity evaluation of pseudo-miraziridines is in progress.

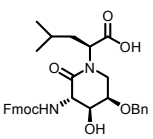


HO-(2*R*-3*R*)-Azy-Leu-(3*S*,4*S*)-Sta-Abu-vArg-OH
miraziridine A (1)

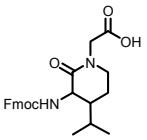
1



ψ-aziridine (2)



ψ-statine (3)



ψ-statine (4)

2

[1] Nakao, Y.; Fujita, M.; Warabi, K.; Matsunaga, S.; Fusetani, N., *J. Am. Chem. Soc.*, **2000**, *122*, 10462-10463
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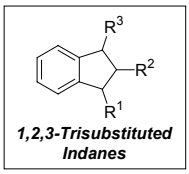
Stereoselective synthesis of indanes

Cristina Navarro, Aurelio G. Csákÿ*

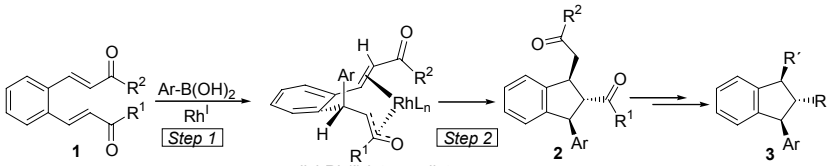
Departamento de Química Orgánica, Facultad de Química, Universidad Complutense. 28040 Madrid. Spain.



1,2,3-Trisubstituted Indanes

The indane skeleton is found in a variety of pharmaceutically active compounds. Recent applications include the development of new sedative agents,[1] inhibitors of P-glycoprotein-mediated transport for the enhancement of the bioavailability and modulation of multi-drug resistance to chemotherapeutic agents,[2] antispermatogenic agents for male contraception,[3] and selective antagonists of endothelin receptors[4] for the treatment of hypertension, congestive heart failure, renal failure, cerebral vasospasm, atherosclerosis, restenosis, myocardial infarction, subarachnoid haemorrhage, and pulmonary disorders such as pulmonary primary hypertension (PPA), which is catalogued as an orphan disease.

We have developed a stereoselective synthesis of trisubstituted indanes based on a novel Rh(I)-catalyzed tandem conjugate addition[5] - Michael cyclization:



Conjugate addition of the Ar-Rh(I) species, generated by transmetalation of the arylboronic acid with the Rh(I)-catalyst, to the CH=CH-COR[1] linkage of compounds **1** (Step 1) affords an oxa-π-allyl-Rh(I) intermediate. This undergoes an intramolecular Michael reaction with the CH=CH-COR[2] moiety to give indanes **2** (Step 2) in a highly diastereoselective fashion. The reactions are carried out in water-containing organic solvents. Post-synthetic elaboration of **2** affords the trisubstituted indanes **3**.

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RIBONUCLEOSIDE ANALOGUES AS POTENTIAL INDUCERS OF LETHAL MUTAGENESIS OF RIBOVIRUSES

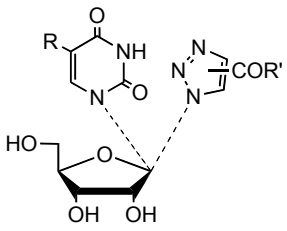
M. Teresa Peromingo,[a] Ana San-Félix,[a] Mercedes Dávila,[b] Ana I. de Avila,[b] Esteban Domingo,[b] and María-José Camarasa[a]

[a]Instituto de Química Médica (CSIC), Juan de la Cierva 3, 28006 Madrid. [b]Centro de Biología Molecular "Severo Ochoa" (CSIC), Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid

Riboviruses are pathogens causing human diseases, ranging from the common cold to exotic illnesses i.e. haemorrhagic fever, and epidemic diseases i.e. AIDS, Hepatitis C, SARS, etc. The development of broadly effective therapeutics has been hampered by the tremendous diversity of riboviruses, as well as by their ability to rapidly adapt and acquire resistance to treatments. Riboviruses exhibited an extremely high mutation frequency. Maintaining such a high mutation frequency, however, is dangerous for the virus. [1]

A recently reported new antiviral strategy called "lethal mutagenesis" attemps to exploit the high mutation frequency of riboviruses by increasing the mutation rate even further and driving the virus population into "error catastrophe" (lethal accumulation of errors). This new strategy was validated with ribavirin (a mutagen).[2] This suggests that RNA virus mutagens may represent a promising new class of antiviral drugs.

We describe here the synthesis and biological studies of potential mutagenic ribonucleosides that may be incorporated into the viral genome during replication and, by mispairing, induce lethal mutagenesis. These ribonucleosides bear universal bases with ambiguous hydrogen bonding properties (hydrogen bonding interactions occur but with different patterns depending on the configuration of the molecule). We have documented various degrees of inhibition of the replication of foot-and-mouth disease virus, encephalomyocarditis virus and lymphocytic choriomeningitis virus in BHK-21 cells by several base and ribonucleoside analogues. The inhibitory activities cannot be accounted for by the toxicity of the drugs on BHK-21 cells. We are currently carrying out experiments to identify the steps in the life cycle of these viruses that may be affected by the drugs.



R = H, CH_3, F, Cl, Br, I; R' = OCH_3, NH_2

Acknowledgements: CSIC is acknowledged for financial support (Proyecto Intramural de Frontera, ref. 2005-20F-0221)

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P-9

DEVELOPING DUAL LIGANDS AS NOVEL THERAPEUTIC AGENTS FOR THE TREATMENT OF CNS DISORDERS

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[b] *Department of Biochemistry and Molecular Biology, Molecular Neurobiology Unit, University of Barcelona, 08028 Barcelona, Spain*
[c] *IRB Barcelona, Barcelona Science Park, University of Barcelona, 08028 Barcelona, Spain*

The increasing number of publications that describe multiple ligands may suggest an on-going re-evaluation of the 'one-disease-one-drug' paradigm that has dominated the pharmaceutical industry for the past few decades. For some CNS disorders, it has been recognised that a balanced modulation of several targets can provide a superior therapeutic effect and a better side effect profile compared to the action of a selective ligand in a single receptor.[1] A relevant example is Parkinson's disease (PD), where patients receiving traditional treatment based on single dopamine interactions, obtain only partial or transient benefits at best.[2] However, balanced modulation of dopamine and adenosine receptors showed promising efficacy and fewer side effects than single-target treatments.[3] Our group has recently reported peptide-heterocycle hybrids as a good starting point for the development of dual ligands at adenosine and dopamine receptors.[4] In the present work, we report the synthesis and biological evaluation of novel compounds with the capacity to interact with both adenosine and dopamine receptors. The combination of the heterocycle indolo[2,3-*a*]quinolizidine with several tripeptide libraries (**1** and **2**) has resulted in heterocycle-peptide hybrids (Figure 1) with dual activity at both receptors. Binding studies, pharmacology and structure-activity relationships of these new molecules will be discussed.

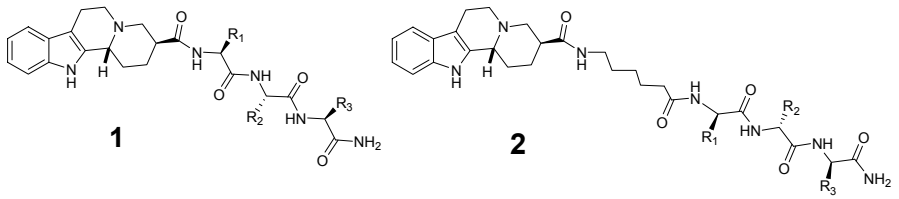

Figure1. General structure of indolo[2,3-*a*]quinolizidine-tripeptide (**1**) and indolo[2,3-*a*]quinolizidine-spacer-tripeptide (**2**).

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EFFICIENT SYNTHESIS OF CONFORMATIONALLY CONSTRAINED CARBOHYDRATE DERIVATIVES FROM A COMMON PRECURSOR

Ernesto Quesada,[a] Alessandra Cordeiro,[a] María-José Camarasa,[a] Miguel Angel Maestro,[b] and Ana San-Félix[a]

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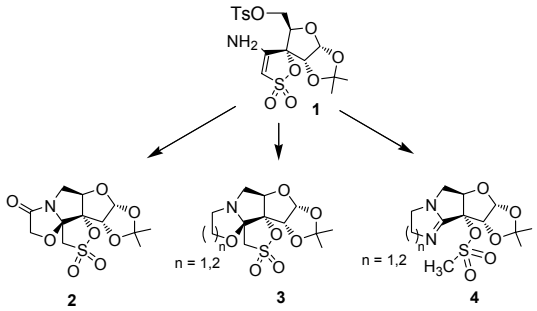
Carbohydrates are natural products of great interest, due to their widespread occurrence, structural diversity, well-defined stereochemistry and high functional group density. These properties make this class of compounds particularly attractive as chiral scaffolds with application in the areas of pharmaceutical and medicinal chemistry.

A potential disadvantage in the application of monosaccharide scaffolds may be their propensity, depending on the nature and spatial orientation of the substituents, to adopt more than one conformation. One possible method for the reduction of molecular flexibility is the introduction of a second, and possibly a third ring onto the sugar backbone.[1]

The synthesis of polycyclic sugar derivatives **2-4** will be presented. These compounds were prepared in very good yields and high degree of chemo-, regio-, and stereoselectivity from the common synthetic precursor **1**, recently developed in our group.[2] The structures of the novel polycyclic sugar derivatives were assigned by NMR spectroscopy. Polycyclic sugar **2** was chosen as a representative compound and unequivocal confirmation of its structure was obtained from X-ray crystal structure analysis.



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P-11

DISEÑO, SÍNTESIS QUÍMICA Y ACTIVIDAD ANTIMETASTÁTICA DE NUEVOS ANÁLOGOS HETEROCÍCLICOS DEL *TRANS*-RESVERATROL

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Los *trans*-estilbenos y, en particular, el trans-resveratrol, son objeto de interés creciente debido a sus amplias propiedades biológicas y terapéuticas[1]. Así, se ha demostrado que el resveratrol previene las enfermedades cardiovasculares y tiene actividad antiinflamatoria, antiviral y neuroprotectora. Asimismo, está bien documentado su papel como agente quimiopreventivo y quimioterápico en el ámbito del cáncer[2]. Sin embargo, los *trans*-estilbenos poseen una inestabilidad química y configuracional que dificulta su síntesis y uso terapéutico.

Con el fin de solucionar este problema, en nuestro laboratorio hemos diseñado y sintetizado una serie de arilpirroles y arilindoles, configuracionalmente estables, que evitan la posibilidad de isomerización cis-trans presente en los estilbenos naturales. La estructura general de dichos compuestos se muestra en la Figura 1.

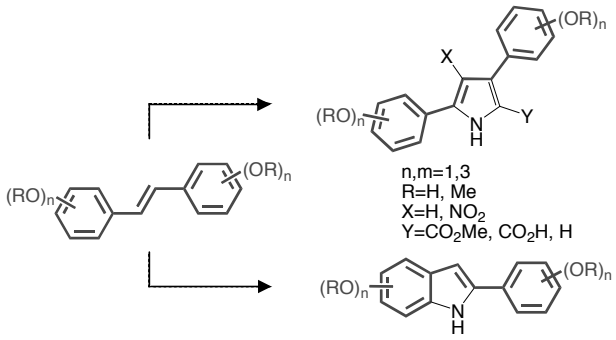

Figura 1.

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DESIGN AND SYNTHESIS OF BINDING SITE-DIRECTED CANDIDATE PROBES FOR THE STUDY OF THE CB_1 CANNABINOID RECEPTOR

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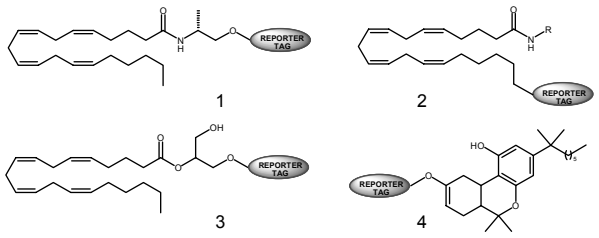
There is increasing evidence that the endocannabinoid system (ECS) is involved in a large variety of physiological processes that include motor activity, analgesia and regulation of neurotransmission.[1] Cannabinoid receptors CB_1 and CB_2 are therefore regarded as targets of paramount interest within the pharmaceutical research field. In spite of all the significant progress made towards the gathering of information regarding molecular recognition of cannabinoid ligands, ligand-receptor binding motives remain generally elusive. Their elucidation is a major challenge in chemical biology.

In this respect, the use of novel complementary techniques, such as bioconjugation and fluorescence labeling, is regarded as a promising means of providing a valuable source of information of the protein target binding domain.[2] This information should give an additional boost to the rational design and identification of new hits, with the subsequent generation of leads in drug discovery programs that target the ECS.

Following this rationale, we have initiated a project aimed at developing probes for the study of CB_1 receptor. These probes (**1**-**4**), inspired in different structural cores endowed with CB_1 agonism, possess two components: i) a bioactive moiety, responsible for the interactions with the binding site and ii) a benzophenone, alkyne, biotin or fluorescent moiety for covalent modification, enrichment or fluorescence labeling of the target protein. These derivatives will allow for the eventual identification of the proper moieties and their optimal position to convert these compounds into probes of high affinity and selectivity towards CB_1.



Acknowledgements: This work has been supported by a MEC predoctoral fellowship (LMC) and grants from the Ministerio de Ciencia y Tecnología (SAF-2004/07103-C02-01) and Comunidad Autónoma de Madrid (S-SAL-249-2006).

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P-13

BENZIMIDAZOLE DERIVATIVES AS NOVEL SEROTONIN 5-HT$_6$ RECEPTOR LIGANDS

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Adenylate cyclase linked G-protein-coupled 5-HT$_6$ serotonin receptor (5-HT$_6$R) is one of the most recently identified subtypes. This receptor has generated considerable interest due to its possible involvement in obesity, certain neuropsychiatric disorders, and cognition[1].

In our research group[2], we have independently developed a pharmacophore model as well as a 3-D computational model for ligand-receptor interaction, which have provided the structural requirements for 5-HT$_6$R antagonists and the molecular details of their recognition.

Using these models, in this work we have designed a series of new benzimidazole derivatives, which have been synthesized and evaluated for binding affinity at the human 5-HT$_6$R. Some of the synthesized compounds show 5-HT$_6$R affinity having K_i values ranging from 8 to 60 nM. The new ligands have also allowed the validation of our proposed pharmacophore and ligand-receptor interaction models.

The benzimidazole derivatives reported herein represent a novel structural class of 5-HT$_6$R ligands, in which compound UCM-236 (K_i = 8 nM)[3] exhibits the highest affinity. The ligands are being characterized for selectivity and functional behavior. In addition, structural changes are in course to obtain new benzimidazole derivatives with higher affinity and selectivity for the 5-HT$_6$R.

The approach presented herein represents the first contribution to the rational design of agents acting at the recently identified 5-HT$_6$ serotonin receptor.

This work was supported by Ministerio de Ciencia y Tecnología (SAF2004-07103-C02-01) and Comunidad Autónoma de Madrid (SAL-0249/2006). T. de la Fuente is also grateful to Fundación Ramón Areces for a predoctoral grant.

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SYNTHESIS OF NEW 5-HT$_7$ SEROTONIN RECEPTOR AGENTS

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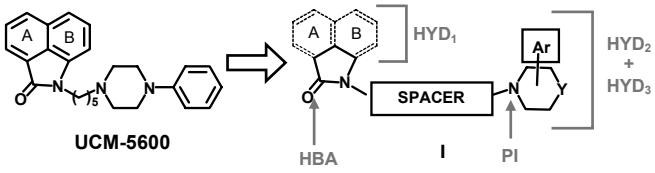
Serotonin 5-HT$_7$ receptor (5-HT$_7$R)[1] represents a promising therapeutic target for certain CNS disorders related to circadian rythms, as well as for migraine in the periphery. In our research group, we are involved in a project aimed at the development of new specific 5-HT$_7$R agents. As a starting point, we postulated a pharmacophore hypothesis for 5-HT$_7$R antagonism, validated through the design and synthesis of a series of naphtholactams and naphthosultams[2]. Analogue UCM-5600 (pK_i = 7,1) was identified as a new lead compound for the search for potent and selective 5-HT$_7$R antagonists.

In this work we have synthesized new compounds of general structure **I** considering structural modifications in the different pharmacophoric elements present in UCM-5600. The new derivatives have been evaluated for affinity at the 5-HT$_7$R and selectivity over the 5-HT$_{1A}$R, both GPCRs with a high homology in their active sites.



The influence of the different pharmacophoric elements has been analyzed using computational simulation studies that have determined the molecular details of ligand-receptor interaction. The models are consistent with the binding data and have revealed that a hydrogen bond between the compound and Ser6.55 is the key for 5-HT$_7$/5-HT$_{1A}$ selectivity in this family of ligands. In particular, ligand UCM-3307 (HYD$_1$ = B; spacer = $(CH_2)_4$; HYD$_2$ + HYD$_3$ = 1,2,3,4-tetrahydroisoquinoline) exhibits high 5-HT$_7$R affinity and selectivity over 5-HT$_{1A}$R (5-HT$_7$: K_i = 23 nM; 5-HT$_{1A}$: K_i = 219 nM), and is being characterized for functional behaviour. The hypothesis proposed herein for 5-HT$_7$/5-HT$_{1A}$ selectivity represents a rational approach that should help in the development of new specific 5-HT$_7$R ligands.

This work was supported by Ministerio de Ciencia y Tecnología (SAF2004-07103-C02-01) and Comunidad Autónoma de Madrid (SAL-0249/2006). R. A. Medina is also grateful to Ministerio de Educación y Ciencia for a F.P.U. predoctoral grant.

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P-15

SEARCH FOR PROTEIN-PROTEIN MODULATORS: DISULFIDE-BRIDGED VEGF AND VAMMIN DERIVED PEPTIDES

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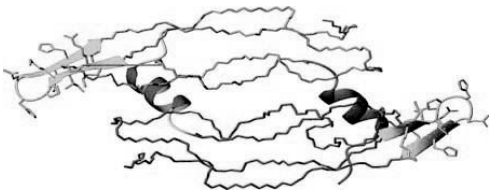
Angiogenesis is crucial in tumor development and metastasis, and as a result the anti-angiogenic therapy constitutes a valuable strategy in cancer treatment. Vascular Endothelial Growth Factor, VEGF, is one of the most important proangiogenic factors, able to regulate multiple biological functions through its interaction with membrane specific receptors, VEGFR-1 (Flt-1), VEGFR-2 (KDR, Flk-1) and VEGFR-3 (Flt-4). High levels of KDR have been observed during tumor angiogenesis, and VEGF is over-expressed in all examples of pathologic angiogenesis (cancer, cardiovascular diseases and diabetes). Therefore, one approach to novel anti-angiogenic agents could be the search for inhibitors of the protein-protein interactions involved in the molecular recognition between VEGF and its KDR receptor. Directed mutagenesis studies have allowed the identification of a surface of the VEGF molecule implicated in the recognition by KDR. Residues Arg^{82}, Lys^{84} and His^{86}, located in a β–hairpin of loop 3 (region 81-91 of VEGF), have been identified as important for the interaction with domain 2 of the receptor.[1,2]

Starting from this VEGF fragment, and the same peptide region in Vammin, a new VEGF isolated from snake venom with high affinity for the KDR receptor, two disulfide-bridged analogues were designed to preserve the β–hairpin structure of these fragments in the corresponding native proteins.This communication describes the NMR structural studies of these linear and disulfide-bridged peptides. β-Hairpin formation was analyzed on the basis of several NMR parameters, NOE, ^{1}H and ^{13}C chemical shifts. The ability of these peptides to adopt the native VEGF or Vammin β-hairpin structures will be compared with their anti-angiogenic activities.



VEGF-A_{81-91}: MRIKPHQGQHI

MRCKPHQGCHI
S—S

Vammin$_{69-80}$: MRVNPRTQSSKM

MRCNPRTQSCKM
S—S

Acknowledgements: Supported by CSIC (Proyecto Intramurales 200580F0161).

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DESIGN AND SYNTHESIS OF NEW DUAL COMPOUNDS WITH AFFINITY TOWARDS 5-HT TRANSPORTER (SERT) AND 5-HT$_7$ RECEPTOR AS POTENTIAL ANTIDEPRESSANT AGENTS

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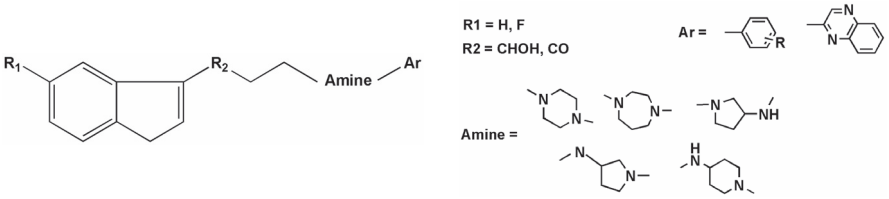
The role of serotonin (5-HT) in depression disorders has been well investigated generating very interesting therapies. Disturbances in central serotonin system have been associated with the pathogenesis of depression and the antidepressant effect of the selective 5-HT reuptake inhibitors (SSRIs) is believed to be due to an enhancement of postsynaptic 5-HT levels.[1,2]

Years ago, our group synthesized dual compounds: 5-HT reuptake inhibitors and postsynaptic 5-HT$_{1A}$ antagonists, obtaining wonderful results.[3]

Hypotheses driving current research indicate that the 5-HT$_7$ receptor might be involved in mood regulation, suggesting that this receptor is a putative target in the treatment of depression[2].

Nowadays our work consists on the synthesis of new multiple compounds, 5-HT reuptake inhibitors and with affinity towards 5-HT$_7$ receptors. In this way se have synthesized series according the structure:



Results of receptor binding studies performed on rat brain tissue with these new compounds will be presented along with molecular modelling studies combining *state of art* softwares and homology modelling with the additional aim to investigate the 5-HT$_7$ *vs.* 5-HT$_{1A}$ binging.

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P-17

CONFORMATIONAL NMR STUDIES ON 7-METHYL-1,5'-*O*-DIBENZYLINOSINES: A POSSIBLE STABILIZATION BY AN INTRAMOLECULAR CATION-PI INTERACTION?

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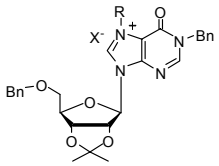
[a] Instituto de Química Médica (CSIC),Juan de la Cierva 3, 28006 Madrid, Spain. [b] Centro de Química Orgánica Manuel Lora-Tamayo (CSIC), Juan de la Cierva 3, 28006 Madrid, Spain

In the course of our studies on 5´-*O*-tritylinosine analogues as allosteric inhibitors of the enzyme thymidine phosphorylase,[1] we have undertaken the synthesis of 1,5'-*O*-dibenzylinosine derivatives. There are some previous reports on reaction of inosines with benzyl bromide to obtain 5'-*O*-benzylinosines.[2,3]



1 R= Bn
2 R= Me

However, in our hands, this reaction requires strictly controlled conditions. Thus, by increasing either the reaction time or the temperature, the major compound was the 1,7,5'-*O*-tribenzylinosine derivative (**1**). It is well documented the ease of N7 functionalization of guanosine derivatives,[4] but there are almost no examples on inosines. Similarly, reaction of the 1,5'-*O*-dibenzylinosine precursor with methyl iodide afforded the 7-methyl-1,5'-*O*-dibenzylderivative (**2**).

Interestingly, the ^{1}H-NMR spectra of **1** and **2** showed peculiar chemical shifts for geminal protons (H5´and H5´´ of the ribose, and the CH_2 of the benzyl groups). Detailed mono- and bidimensional NMR studies (gCOSY, gHSQC, gHMBC) have been performed with compound **2**, including high and low temperature experiments. Moreover, NOESY and ROESY experiments were carried out to obtain information about the conformational properties. On the basis of the available NMR restraints, the 3D-structure of the molecule was constructed and submitted to energy minimization. The results obtained point towards the predominant existence of restricted conformers that are stabilized by an electrostatic interaction between the positively charged imidazole of the base moiety and the high electron density of the 5'-benzyl substituent, suggesting a possible stabilization by an intramolecular cation-Pi interaction.

Acknowledgements. E. Casanova acknowledges the Comunidad de Madrid and the FSE for a predoctoral grant. L. Aguado acknowledges the Spanish MEC for a FPU grant. This work has been supported by the Spanish MEC (SAF2006-12713-C02-01).

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SEARCHING FOR AN ALLOSTERIC SITE IN THE ANGIOGENIC ENZYME THYMIDINE PHOSPHORYLASE

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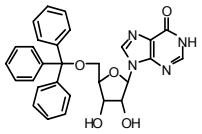
Thymidine Phosphorylase (TPase) catalyzes the reversible phosphorolysis of thymidine and analogues. Interest in TPase inhibitors has been renewed in recent years due to the implication of this enzyme in angiogenesis, tumor progression and metastasis.[1] To date, most TPase inhibitors are uracil derivatives that bind within the active site. Our research groups have recently described 5´-*O*-tritylinosine (KIN59) as the first allosteric inhibitor of human TPase.[2] In addition, KIN59 is very active in inhibiting TPase-induced angiogenesis in *in vivo* assays.[2]



KIN59

hTPase IC_{50}: 30 ± 9 μM

In order to characterize the KIN59 binding site to TPase, cocrystallization studies have been carried out.[3] Interestingly, the presence of the allosteric inhibitor was mandatory to obtain new well-ordered crystals of human TPase, but the inhibitor could not be solved in the electron density map. These results led us to address this problem with the aid of computational methods, taking into account the flexibility of the protein and the ligand. Normal mode analysis (NMA)[4] was applied to the enzyme in order to generate additional conformers that were probed for ligand binding with the automated docking program Autodock 3.0.[5] A cavity next to the hinge region of TPase was selected as a putative binding site. Two possible binding modes for KIN59 were found inside this cavity that were further explored by molecular dynamics simulations of the ensuing complexes. As a result, a proposal is made that the binding site for KIN59 in TPase lies in a relatively dynamic domain of the enzyme where the trityl and base part of the ligand establish a number of key interactions with the side chains of highly conserved amino acids.

Acknowledgements. A predoctoral fellowship to L. Aguado and research grants SAF2003-07219-C02-01 and SAF2006-12713-C02-01 from the Spanish Ministerio de Educación y Ciencia are gratefully acknowledged. Parts of the present work were conducted within the BIPEDD-CM platform (S-BIO/0214/2006) sponsored by Comunidad de Madrid.

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[5] http://www.scripps.edu/pub/olson-web/dock/autodock

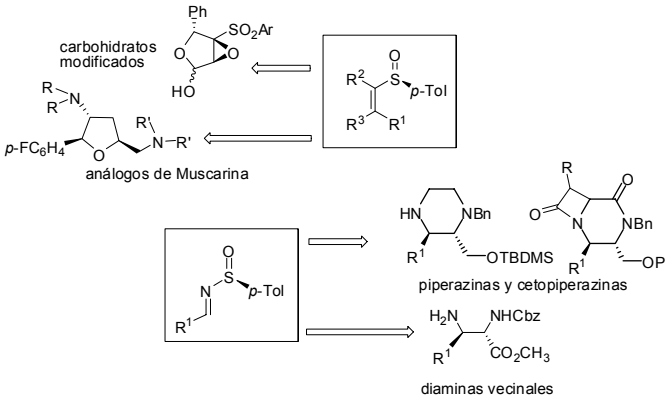
P-19

DESARROLLO DE METODOLOGÍA CON SULFÓXIDOS Y SULFINAMIDAS APLICADA A LA SÍNTESIS ASIMÉTRICA DE PRODUCTOS BIOACTIVOS

Roberto Fernández de la Pradilla, Alma Viso, Nadia Lwoff, Mercedes Ureña, Esther Castellanos, Miguel Ángel del Águila, Aida Flores, Alejandro Castellanos, Iñaki Osante, Mateo Sánchez, Ignacio Colomer.

Instituto de Química Orgánica General, Consejo Superior de Investigaciones Científicas, c/ Juan de la Cierva 3, 28006 Madrid

El grupo de Síntesis Asimétrica con Sulfóxidos del IQOG trabaja en el ámbito de la **Síntesis Orgánica** y de la **Química Médica**, procurando enlazar el desarrollo de metodología sintética con la aplicación a productos biológicamente activos y estructuralmente complejos. Nuestras contribuciones en Síntesis Orgánica se han dirigido al **control de regio- estereo- y enantioselectividad** en las reacciones, la **síntesis asimétrica** de productos enantiopuros utilizando **auxiliares de azufre** y los métodos de funcionalización de **moléculas nitrogenadas**. En esta comunicación presentaremos una visión general de las estrategias sintéticas que se desarrollan en la actualidad en nuestro grupo de investigación[1].



Agradecimientos: DGI MEC por los proyectos BQU2003-0292, CTQ2005-04632/BQU y CTQ2006-04522/BQU). JANSSEN-CILAG por la financiación adicional de nuestro grupo. CSIC, CM y MEC por las becas de NL, MU, EC, MA, AF, AC, IO, IC.

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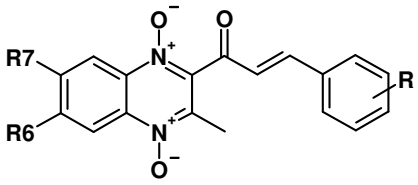
SYNTHESIS OF NEW RING SUBSTITUTED 3-PHENYL-1-(1,4-DI-*N*-OXIDE QUINOXALIN-2-YL)-2-PROPEN-1-ONE DERIVATIVES WITH ANTICANCER PROPERTIES.

Asunción Burguete, Beatriz Solano, Raquel Villar, Esther Vicente, Saioa Ancizu, Silvia Pérez-Silanes, Ignacio Aldana, Antonio Monge

Unidad en Investigación y Desarrollo de Medicamentos, Centro de Investigación en Farmacobiología Aplicada (CIFA), Universidad de Navarra, C/ Irunlarrea s/n, 31080 Pamplona, Spain.

As a continuation of our research in quinoxaline 1,4-di-*N*-oxide[1] and with the aim of obtaining new anticancer agents, which can improve the current chemotherapeutic treatments, new series of ring substituted 3-phenyl-1-(1,4-di-*N*-oxide quinoxalin-2-yl)-2-propen-1-one derivatives (**1**) have been synthesized and tested for their in vitro anticancer activity.



1

The synthesis of these compounds was carried out by a base-catalyzed Claisen-Schmidt condensation. The conditions of temperature used by other authors[2] should be modified, establishing a required temperature of –10ºC in order to obtain the desired compounds.

Synthesized compounds were evaluated at the National Cancer Institute (NCI, Bethesda, USA) against 60 human tumor cell lines at a single dose of 100 µM. Some of the compounds, which exhibit significant growth inhibition, are being evaluated against the 60 cell panel at five concentration levels.

Acknowledgements: This work has been carried out thanks to the financial support of the FIS project (1051005, October 2005) and we want to express our gratitude to the National Cancer Institute (NCI, Bethesda, USA) for the evaluation of the anticancer activity. A. Burguete. was awarded a PhD scholarship supported by the "Gobierno de Navarra".

[1] Zarranz, B.; Jaso, A.; Aldana, I.; Monge, A. *Bioorg. Med. Chem.* **2004**, *12*, 3711-3721
[2] Nielsen, S. F.; Boesen, T.; Larsen, M.; Schonning, K.; Kromann, H. *Bioorg. Med. Chem.* **2004**, *12*, 3047-3054.

P-21

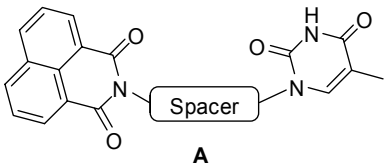
ACYCLIC NUCLEOSIDE ANALOGUES AS NOVEL INHIBITORS OF *MYCOBACTERIUM TUBERCULOSIS* THYMIDINE MONOPHOSPHATE KINASE

Olga Familiar[a], Hélène Munier-Lehmann[b], Dominique Douguet[c], Ana-Isabel Hernández[a], María-José Camarasa[a] and María-Jesús Pérez-Pérez[a]

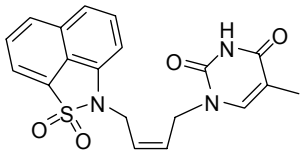
[a]Instituto de Química Médica (C.S.I.C.), Juan de la Cierva 3, E-28006 Madrid, Spain ; [b]Institut Pasteur, Unité de Chimie Organique, CNRS URA 2128, 28, Rue du Dr. Roux, 75724 Paris Cedex, France ; [c]INSERM, U554, Université Montpellier 1 et 2, CNRS, UMR5048, Centre de Biochimie Structurale, 34090-Montpellier, France

Tuberculosis (TB) remains a major cause of morbidity and mortality worldwide and numerosous targets are being explored in the development of new drugs and treatments. In the search of novel targets, *M. tuberculosis* thymidine monophosphate kinase (TMPKmt) is an attractive candidate to interfere with the replication of the pathogen.[1] TMPK catalyses the γ-phosphate transfer from ATP to thymidine monophosphate (dTMP) yielding thymidine diphosphate (dTDP) and ADP. TMPK is crucial for maintaining the thymidine triphosphate (dTTP) pools that are required for DNA synthesis in replicating organisms. Subtle differences in the active site and in the biochemical properties between the mycobacteria (TMPKmt) and the human isoenzyme (TMPKh) make the former a potential target for selective inhibition of mycobacteria *Mycobacterium tuberculosis*.[2]

We here report on the discovery of the first acyclic nucleoside analogues of general formula **A** that potently and selectively inhibit TMPKmt with Ki values in the low micromolar range. Modifications performed at the spacer and at the distal 1,8-naphthalimide group have led to an improvement in the Ki value exemplified by the napthosultam derivative **1** (Ki TMPKmt = 0.27 μM), representing the most potent TMPKmt inhibitor reported to date. Molecular modeling studies have been performed to rationalize the interaction of this new family of inhibitors with its target enzyme. The potency of the here described inhibitors against TMPKmt, as well as the novelty of their structure among TMPKmt inhibitors, make them an interesting family of compounds that deserve further exploration.



A



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Acknowledgements: OF thanks the Spanish Ministerio de Educación y Ciencia (MEC) for a predoctoral fellowship. This work has been supported by grants of the Spanish MEC (SAF programme), from the Pasteur Institute (GPH tuberculose) and INSERM

[1] Pochet, S.; Dugue, L.; Douguet, D.; Labesse, G.; Munier-Lehmann, H. *ChemBioChem* **2002***, 3*, 108

[2] Munier-Lehmann, H.; Chaffotte, A.; Pochet, S.; Labesse, G. *Protein Sci.* **2001***, 10*, 1195.

UNEXPECTED SIMILARITIES BETWEEN A HUMAN AND A MYCOBACTERIAL ENZYME THAT CATALYZE A PHOSPHORYLATION REACTION ON DIFFERENT SUBSTRATES

Ana Negri[a], Olga Familiar[b], Jan Balzarini[c], Hélène Munier-Lehmann[d], María-José Camarasa[b], Federico Gago[a], and María-Jesús Pérez-Pérez[b]

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Mycobacterium tuberculosis thymidine monophosphate kinase (TMPKmt) has been proposed as an attractive candidate to interfere with the replication of this life-threatening pathogen. TMPK catalyses the transfer of the γ- phosphate of ATP to thymidine monophosphate (dTMP) yielding thymidine diphosphate (dTDP) and ADP.[1] TMPK is crucial for maintaining the thymidine triphosphate (dTTP) pools that are required for DNA synthesis, and as such could be an important target in replicating organisms. Subtle differences in the active site and in the biochemical properties between the mycobacterial (TMPKmt) and the human isoenzyme (hTMPK) make the former a potential target for selective inhibition of mycobacteria.[2]

In our search for acyclic nucleoside analogues that could inhibit TMPKmt and thus become potential antitubercular agents, we have identified a series of compounds that selectively inhibit TMPKmt without affecting the human isoenzyme. However, when these compounds were tested against the human mitochondrial thymidine kinase (TK-2), which phosphorylates thymidine but not dTMP,[3] the Ki value was similar to that obtained against TMPKmt. Despite the low sequence identity, structural superposition[4] of the available X-ray structure of TMPKmt onto a homology-built model of TK-2 revealed an overall similar topology. Moreover, the structural determinants for the binding of the nucleoside/nucleotide (thymidine/dTMP) in the active site was found to be very similar in both enzymes, despite the fact that these two enzymes use a different substrate for the phosphorylation reaction. Nonetheless, when the binding mode of our acyclic nucleoside analogues in both enzymes was analyzed in detail we discovered some subtle differences that could be exploited for the design of selective TMPKmt compounds.

Acknowledgements: OF thanks the Spanish Ministerio de Educación y Ciencia for a predoctoral fellowship. This work has been supported by grants from the Spanish MEC (SAF2006-12713-C02) and the CAM (BIPEDD-CM).

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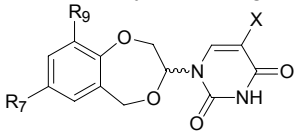
[1] Pochet, S.; Dugue, L.; Douguet, D.; Labesse, G.; Munier-Lehmann, H.*ChemBioChem* **2002***, 3*, 108-110.
[2] Munier-Lehmann, H.; Chaffotte, A.; Pochet, S.; Labesse, G. *Protein Sci.* **2001***, 10*, 1195-1205
[3] Pérez-Pérez, M. J.; Hernández, A. I.; Priego, E. M; Rodríguez-Barrios, F.; Gago F.; Camarasa, M. J.; Balzarini, J. *Curr. Top. Med. Chem.* **2005** *5*, 1205-1220.
[4] Mammoth program, URL: http://ub.cbm.uam.es/mammoth/pair/index3.php

DESIGN, SYNTHESIS AND ANTICANCER ACTIVITY OF NOVEL SUBSTITUTED-9-(2,3-DIHIDRO-1,4-BENZOXATHIIN-3-YLMETHYL)-9*H*-PURINES

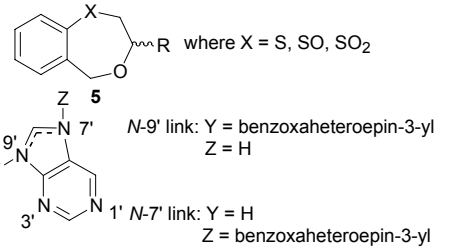
Miguel A. Gallo, Ana Conejo-García, Mónica Díaz-Gavilán, María C. Núñez, Olga Cruz-López, Antonio Espinosa, Joaquín M. Campos

Departamento de Química Farmacéutica y Orgánica, Facultad de Farmacia, c/ Campus de Cartuja s/n, 18071 Granada (Spain)

A series of pyrimidine benzo-fused seven-membered *O,N*-acetals were recently designed and synthesized.[1,2] Later on, the pyrimidine base was substituted by the purine moiety with the objective of increasing both the lipophilicity and the structural diversity of the target molecules (compound type **5**).[3]



1 $R_7 = R_9 = H$; X = F
2 R_7 = OMe; R_9 = H; X = F
3 R_7 = H; R_9 = OMe; X = F
4 $R_7 = R_9 = H$; X = H



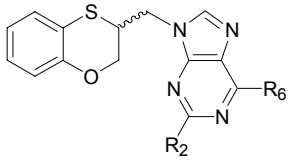
where X = S, SO, SO_2

5

N-9' link: Y = benzoxaheteroepin-3-yl, Z = H

N-7' link: Y = H, Z = benzoxaheteroepin-3-yl

If the previously described compounds are not prodrugs, it is not necessary to maintain the *O,N*-acetalic characteristic with the corresponding weakness of the baseNatom-C-O bond. Therefore, from now on we are designing molecules in which both structural entities (such as the benzoheterocyclic ring and the purine base) are linked by a heteroatom-C-C-baseNatom bond. We describe herein the design, synthesis and biological evaluation of a series of substituted-9-(2,3-dihydro-1,4-benzoxathiin-3-ylmethyl)purine derivatives **6-16**.



6 $R_2 = H$; $R_6 = Cl$
7 $R_2 = H$; $R_6 = Br$
8 $R_2 = H$; $R_6 = SMe$
9 $R_2 = H$; $R_6 = OPh$
10 $R_2 = H$; $R_6 = SPh$
11 $R_2 = H$; $R_6 = NHPh$
12 $R_2 = H$; R_6 = Allyloxy
13 $R_2 = H$; $R_6 = OBn$
14 $R_2 = H$; $R_6 = SBn$
15 $R_2 = H$; $R_6 = OCH_2C_6H_{11}$
16 $R_2 = Cl$; $R_6 = Cl$

The anticarcinogenic potential of the target molecules is reported against the MCF-7 human breast cancer cell line.

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[3] Núñez, M. C.; Rodríguez-Serrano, F.; Marchal, J. A.; Caba, O.; Aránega, A.; Gallo, M. A.; Espinosa, A.; Campos, J. M. *Tetrahedron*, **2007**, *63*, 183.

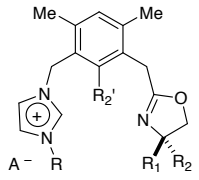
IMIDAZOLIUM SALT-OXAZOLINE/Pd(OAc)$_2$ AND BIS(IMIDAZOLIUM) SALTS/Pd(OAc)$_2$ AS CATALYST SYSTEMS

N. Mesquida, E. Alcalde, I. Dinarès and S. Rodríguez

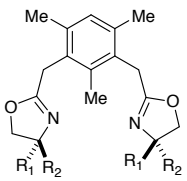
Laboratori de Química Orgànica. Facultat de Farmàcia. Universitat de Barcelona. Avd. Joan XXIII s/n. 08028-Barcelona

A broad array of imidazolium-based frameworks have been rapidly developed with advances in both *N*-heterocyclic carbenes (*NHCs*) and anion recognition chemistry, as well as room-temperature ionic liquids (*RILs*). In homogeneous catalysis, *NHCs* catalytic potential has been expanded to include an ensemble of bidentate ligands —*e.g.*, chiral oxazolinyl-*NHC*— with the aim of enhancing their catalytic activity for stereoselective transformations in organic synthesis.

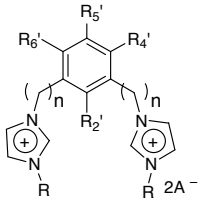
The present study focuses on several examples of the oxazolinyl-imidazolium salts, bis(oxazolines) and bis(imidazolium) salts with a variety of interannular spacers. A three step protocol for the synthesis of targeted *C*,*N* bidentate pincer precursors was examined and, new simple oxazolinyl-imidazoliun cations were conveniently prepared. On the other hand, dicationic ligand precursors were obtained following standard protocols for quaternizing *N*-substituted imidazoles.



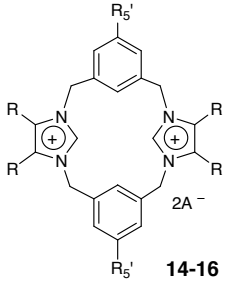
1-4, (*S*)-5, (*S*)-6



7, (*S*,*S*)-8



9-13



14-16

We selected the Suzuki-Miyaura reaction to examine the catalytic efficiency of these ligand precursors. Pd(II) catalysts should be generated *in situ* to simplify the reaction, from oxazolinyl-imidazolium cations **1**-**6** or bis(oxazoline) **7**-**8** or bis(imidazolium) salts **9**-**16** and Pd(OAc)$_2$. Notably, sterically hindered *N*-arylimidazolium cations exhibited efficiency with not only arylbromides but also arylchlorides in low catalyst system loading.

The synthetic protocol applied to these simple *C*,*N* bidentate ligand precursors should be adapted to a variety of oxazolinyl-*NHC* chiral frameworks, thereby developing their catalytic performance in asymmetric reactions.

Acknowledgments: This research was supported by the Vicerrectorat de Recerca (2006), Universitat de Barcelona and the Dirección General de Investigación (*MEC*) project CTQ2006-1182/BQU. Thanks are also due to the AGAUR, 2005SGR00158.

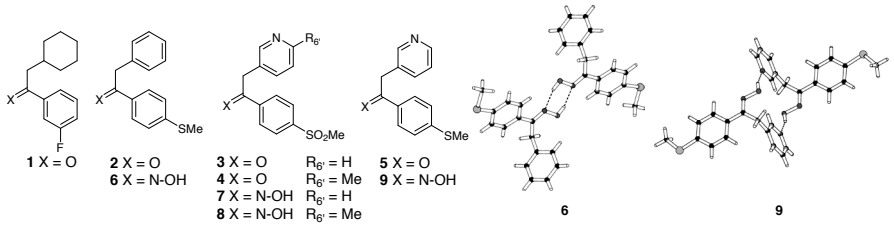
SYNTHESIS OF 1,2-DIARYL(3-PYRIDYL)ETHANONES AND DERIVATIVES. INTERMOLECULAR HYDROGEN BONDING NETWORKS OF OXIMES REVEALED BY X-RAY DIFFRACTION

Neus Mesquida,[a] Ermitas Alcalde,[a] Carmen Alvarez-Rúa,[b] Rosa Cuberes,[c] Jordi Frigola[c] and Santiago García-Granda[b]

[a]Laboratori de Química Orgànica, Facultat de Farmàcia, Universitat de Barcelona, Avda. Joan XXIII s/n, 08028 Barcelona, Spain. [b]Departamento de Química Física y Analítica, Facultat de Química, Universidad de Oviedo, 33006 Oviedo, Spain. [c]Laboratorios del Dr. Esteve, S.A., Avda. Mare de Déu de Montserrat, 221, 08041 Barcelona, Spain.

1,2-Disubstituted ethanones are valuable synthetic intermediates of a broad array of bioactive molecules, both natural and synthetic. One relevant use is in the preparation of pharmaceutically useful diaryl(heteroaryl)heterocycles, i.e. selective COX-2 inhibitors. In parallel, hydrogen bonds are the main driving forces for oxime non-covalent interactions.

The present study examines several examples of 1-aryl-2-aryl(3-pyridyl)ethanones **1**-**5** and the corresponding ketoximes **6**-**9**. Compounds **1** and **2** were directly obtained by coupling of acid chlorides with organozinc bromides in the presence of CuCN/LiBr. 1-Aryl-2-(3-pyridyl)ethanones **3**-**5** were prepared following a modified protocol of the Horner-Wittig reaction. Oximes **6**–**9** were prepared from ethanones **2**-**5** and crystallization in 96% EtOH produced crystals of **6**, **7** and **9** suitable for X-ray diffraction analysis.



1 X = O
2 X = O
6 X = N-OH
3 X = O $R_{6'}$ = H
4 X = O $R_{6'}$ = Me
7 X = N-OH $R_{6'}$ = H
8 X = N-OH $R_{6'}$ = Me
5 X = O
9 X = N-OH

6 **9**

Oximes **6**, **7** and **9** were examined in the solid state by X-ray crystallography, providing evidence of H-bonding networks: in particular, the relevance of crystal packing controlled by H-bond interactions based on homomeric intermolecular oxime···oxime interactions for **6** and oxime···N(pyridyl) interactions for **7** and **9**. Moreover, cooperative O-H···N(py) and CH/π hydrogen bonds were disclosed in crystallines **7** and **9**.

Acknowledgments: This research was supported by Laboratorios Dr. Esteve S.A., Barcelona, Spain, through project FBG2001/2002-301362, Fundació Bosch i Gimpera-Universitat de Barcelona, Spain. N.M. is grateful to Laboratorios Dr. Esteve S.A. for a post-doctoral fellowship. Thanks are also due to the DGI-MEC (CTQ2006-1182/BQU) and the AGAUR, *Grup de Recerca Consolidat* 2005SGR00158.

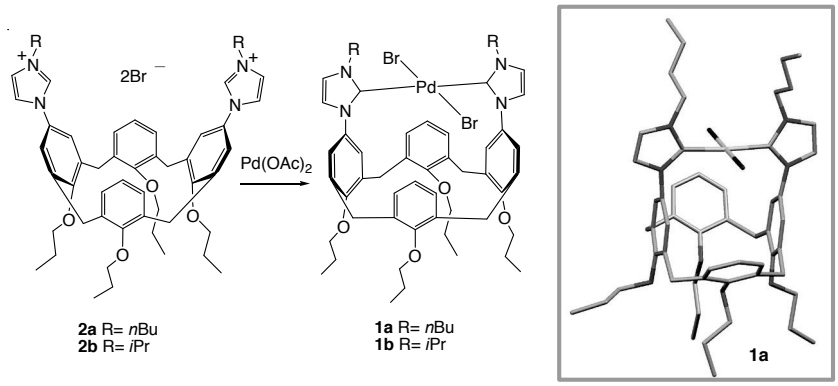
Imidazolium-Calix[4]arene Molecular Frameworks: *bis-N*-Heterocyclic Carbenes as Bidentate Ligands

Immaculada Dinarès,[a] Cristina Garcia de Miguel,[a] Mercè Font-Bardia,[b] Xavier Solans,[b] and Ermitas Alcalde[a]

[a]*Laboratori de Química Orgànica, Facultat de Farmàcia, Universitat de Barcelona, Av. Joan XXIII s/n, 08028-Barcelona, Spain.* [b]*Departament de Cristal·lografia, Mineralogia i Dipòsits Minerals, Universitat de Barcelona, C. Martí i Franquès s/n, 08028-Barcelona, Spain.*

A broad array of imidazolium-based scaffolds have been rapidly developed with advances in both *N*-heterocyclic carbenes (NHCs) and anion recognition chemistry, as well as with room temperature ionic liquids (RILs). Complexes NHCs have been of intense recent interest due to their ease of synthesis, high stability and excellent catalytic properties toward a variety of reactions. On the other hand, generic calix[4]arenes provide exceptionally useful platforms for preparing multidentate ligands with convergent binding sites. Despite the widespread applications of such multitopic ligands in supramolecular chemistry, the use of calixarenes in catalytic chemistry is only in its infancy.

As part of our ongoing research into imidazolium-based frameworks herein we report the synthesis of new bidentate palladium(II) complexes **1a,b** from *bis*-imidazolium-calixarene salts **2a,b.**



2a R= *n*Bu
2b R= *i*Pr

1a R= *n*Bu
1b R= *i*Pr

The Suzuki-Miyaura reaction was used to study their activity as catalysts, when prepared either *in situ* or from a well-defined complex.

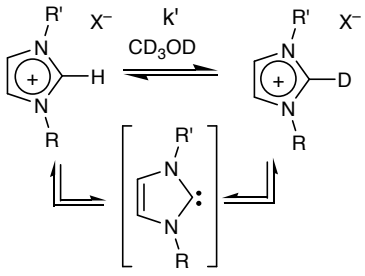
Acknoledgment. This research was supported by the Dirección General de Investigación (*Ministerio de Educación y Ciencia*) project CTQ2006-1182/BQU. Thanks are also due to the AGAUR, 2005SGR00158 (*Generalitat de Catalunya*). C.G. de M. thanks the Ministerio de Educación y Ciencia for a F.P.I. fellowship.

H/D Exchange Rates of *bis*-(Imidazolium) Dications

Immaculada Dinarès, Neus Mesquida, Sandra Rodríguez and Ermitas Alcalde.

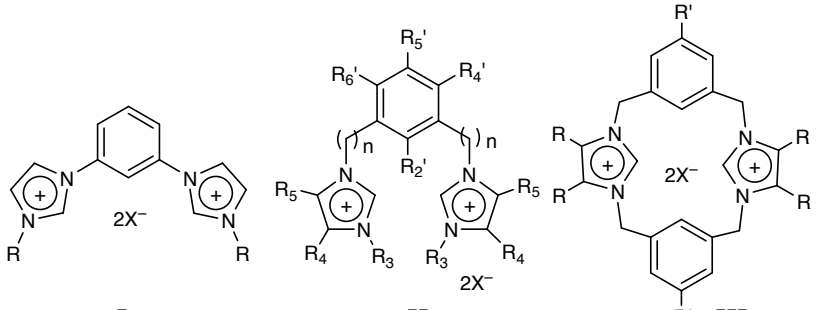
Laboratori de Química Orgànica, Facultat de Farmàcia, Universitat de Barcelona, Av. Joan XXIII s/n, 08028-Barcelona, Spain.

Imidazolium salts have been studied for more than 40 years as models of carbon acids, and for their applications as ionic liquids and *N*-heterocyclic carbene (NHC) precursors. Stable NHCs may be formed by deprotonation of the C(2)–H of the imidazolium cations, evidence of which is H/D exchange of the proton in D_2O solution. Recently, the kinetic acidity of imidazolium cations, including H/D exchange rates, carbon-proton acidity, and carbene precursor stability has been of great interest to physical and organic chemists, as the formation of NHCs is often a crucial step in catalytic organic and organometallic reactions.



The deprotonation of imidazolium salts to *N*-heterocyclic carbenes is often a decisive step in modern catalytic reactions. Because protonation of the NHC is fast compared to the formation of the NHC, the H/D exchange rates of the C(2)–H give an indirect estimate for the reaction rate of its formation.

Therefore, we studied the H/D exchange of the C(2)–H of several *bis*-(imidazolium) dications **I-III** in methanol-d_4.



I **II** **III**

The influence of the counterion, concentration and presence of D_2O has been studied. The observed exchange rates might give a rational for the suitability of the imidazolium salts as precursors of *N*-heterocyclic carbenes.

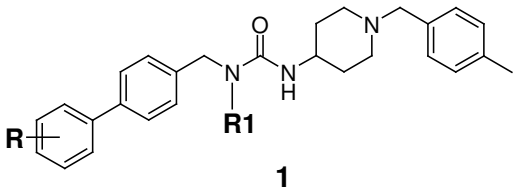
Acknoledgment. This research was supported by the Dirección General de Investigación (*Ministerio de Educación y Ciencia*) project CTQ2006-1182/BQU. Thanks are also due to the AGAUR, 2005SGR00158 (*Generalitat de Catalunya*). S. R. thanks the AGAUR (*Generalitat de Catalunya*) for a F.P.I. fellowship.

NOVEL SERIES OF SUBSTITUTED BIPHENYLMETHYL UREA DERIVATIVES AS MCH-R1 ANTAGONISTS FOR THE TREATMENT OF OBESITY

Javier Ceras[a], Nuria Cirauqui[a], Silvia Galiano[a], Silvia Pérez-Silanes [a], Ignacio Aldana[a] and Antonio Monge[a]

[a]*Unidad en Investigación y Desarrollo de Medicamentos. Centro de Investigación en Farmacobiología Aplicada (CIFA). University of Navarra. C/Irunlarrea, s/n, 31080 Pamplona. Spain.*

The use of melanin-concentrating hormone receptor antagonists (particularly MCH-R1 antagonists) as potential agents for the treatment of obesity has been widely suggested. Different reports show that icv administration of MCH stimulates feeding in rodents but not in the MCH-R1 knockout animals.[1,2] Furthermore, deletion of MCH-R1 in mice results in reduced body weight and increased leanness compared to their wild-type counterpart. Thus, antagonists of MCH-R1 may be effective in treating obesity.[3]



1

R= 4-F, 2-OMe, 4-OMe, 3-CN
R1= H, 3-hydroxy-3-methyl-2-butanone

As part of a general project with the main target of finding new MCH-R1 antagonists, we have synthesized and evaluated for in vitro binding 1R receptor of the MCH a new series of biphenylmethyl urea derivatives (structure **1**) in order to develop SAR. Prior hit-to lead efforts resulted in the identification of compounds with good affinity. We have also carried out binding assays with the hERG channel to evaluate the toxicity of the new compounds.

Acknowledgments: We wish to thank the Gobierno de Navarra for the grants given to Javier Ceras and Nuria Cirauqui.

[1] Marsh, D.J.; Weingarth, K.T.; Novi, D.E.; Chen, H.Y.; Trumbauer, M.E.; Chen, A.S.; Guan, X.M.; Jiang, M.M.; Feng, Y.; Camacho, R.E.; Shen, Z.; Frazier, E.G.; Yu, H.; Metzger, J.M.; Kuca, S.J.; Shearman, L.P.; Gopal-Truter, S.; Macneil, D.J.; Strack, A.M.; MacIntyre, D.E.; Vand der Ploeg, L.H.; Quian, S. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 3240.
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P-29

ARYLSULFONAMIDE AND ARYLAMIDE DERIVATIVES AS MCH-R1 ANTAGONISTS FOR THE TREATMENT OF OBESITY

Nuria Cirauqui[a], Silvia Galiano[a], Javier Ceras[a], Silvia Pérez-Silanes [a], Ignacio Aldana[a] and Antonio Monge[a]

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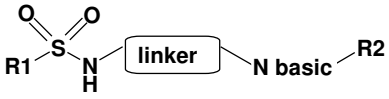
Melanin-concentrating hormone (MCH) is a 19-amino acid peptide that signals through MCH R1 found in the CNS and stimulates food intake in mammals. MCH peptide knock-out mice are hypophagic and lean,[1] while the overexpression of the MCH gene animals are hyperphagic and obese.[2] Transgenic animals devoid of MCH-R1 are resistant to diet-induced obesity and weigh less than their wild type counterparts. The anorexigenic effects of MCH-R1 antagonists molecules reported in recent years[3] support the hypothesis that blockade of MCH-R1 is a key target for efective antiobesity therapy.

As a part of a general project and with the aim of identifying new MCH-R1 antagonists, we have synthesized and evaluated for in vitro binding to 1R receptor novel series of arylsulfonamide and arylamide derivatives (**1** and **2** structures)



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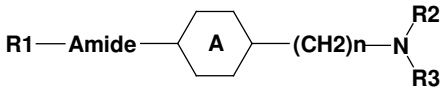

2

The structure-activity relationship studies resulted in the identification of compounds with good affinity and suggested that diphenyl substituents on the arylamide derivatives lead to better activity than biphenyl substituents.

Acknowledgements: We wish to thank the Gobierno de Navarra for the grants given to Nuria Cirauqui and Javier Ceras.

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SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW UREA DERIVATIVES AS MCH-R1 ANTAGONISTS FOR THE TREATMENT OF OBESITY

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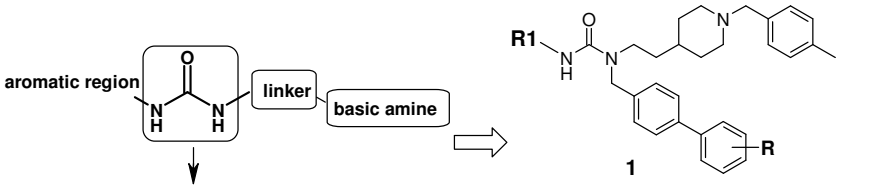
Obesity is a worldwide epidemic. The lack of efficacy of the available obesity drugs makes this disease one of the most attractive therapeutic targets. Melanin-concentrating hormone (MCH), a cyclic 19-amino acid neuropeptide, is believed to play a critical role as a regulator of feeding behaviour and energy balance based on several lines of evidence. Interestingly, mice overexpressing the MCH gene appear to give an hyperphagic and obese phenotype and display insulin-resistance, whereas transgenic.[1] MCH-R1 knockout mice are lean, resistant to diet-induced obesity and show hyperactivity.[2] Consequently, selective MCH-R1 antagonism could provide a viable treatment for obesity.

As a continuation of our research in this field and based on previous assays with an substituted biphenylmethylurea core, we have synthesized and evaluated a novel series of urea derivatives (structure **1**) with the aim of improving the MCH-R1 in vitro activity maintaining hERG affinity.[3]



R= 4-F, 2-OMe, 4-OMe, 3-CN
R1=isopropyl, 3-hydroxy-2,2-dimethylpropyl,
1,1-dihydroxyethylpropyl,
[1-(acethyloxymethyl)-1-methyl]ethyl,
(1,1-diacethyloxymethyl)propyl

SAR was explored, suggesting that optimal binding with the receptor was achieved when the biphenylmethyl group and the linker were substituted on the same nitrogen of the urea moiety. We have also carried out binding assays with the hERG channel to evaluate the toxicity of the new compounds.

---

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P-31

ACTIVIDAD ANTITUMORAL DE NUEVOS ANÁLOGOS DE SAFRAMICINA MODIFICADOS EN EL ANILLO B

Alberto López Cobeñas, Pilar López-Alvarado, Carmen Avendaño, J. Carlos Menéndez

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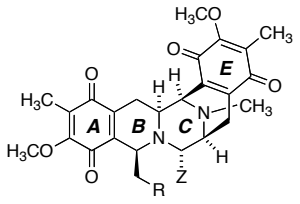
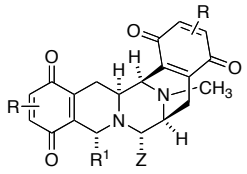
Los antibióticos antitumorales pertenecientes a la familia de las tetrahidroisoquinolinas[1] incluyen potentes agentes citotóxicos. Entre ellos, se pueden considerar ejemplos representativos las saframicinas (por ejemplo **1**-**3**), procedentes de diversas cepas de *Streptomyces lavendulae*, y una serie de compuestos de origen marino, como la jorumicina **4** y las renieramicinas (por ejemplo, **5**). En esta comunicación presentamos la síntesis y actividad antitumoral de los compuestos **6** y **7**, en los que se ha modificado el fragmento de tetrahidroisoquinolina (anillo B) en varios aspectos: sustitución, inversión de la configuración del estereocentro y apertura del anillo.



Compuesto	Z	R
Saframicina A (**1**)	CN	NH-CO-$COCH_3$
Saframicina S (**2**)	OH	NH-CO-$COCH_3$
Saframicina B (**3**)	H	NH-CO-$COCH_3$
Jorumicina (**4**)	OH	O-CO-CH_3
Renieramicina M (**5**)	CN	(*E*)- O-CO-C(CH_3)=CH-CH_3



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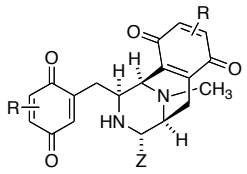

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Agradecimientos: Agradecemos la financiación del MEC (proyecto CTQ2006-10930/BQU) y CAM-UCM (grupo de investigación 920234).

[1] Revisión: Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669.

KETONE AND AMIDE DERIVATIVES OF QUINOXALINE 1,4-DI-*N*-OXIDE AS ANTI-*MYCOBACTERIUM TUBERCULOSIS* AGENTS

Raquel Villar, Esther Vicente, Saioa Ancizu, Asunción Burguete, Beatriz Solano, Silvia Pérez-Silanes, Ignacio Aldana, Antonio Monge

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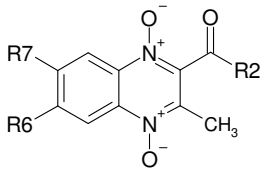
Tuberculosis (TB) is one of the leading infectious causes of death in the world and has become a growing global health problem. According to the World Health Organization, in 2003, 8.8 million new TB cases arose, and an estimated 1.7 million deaths resulting from TB occurred. One of the major problems of TB is the development of new active compounds against multidrug-resistant tuberculosis strains. In this sense several quinoxaline 1,4-di-*N*-oxide derivatives have been reported as *in vitro* anti-*Mycobacterium tuberculosis* agents.[1,2] The quinoxaline-3-methyl-2-ketone or 2-amide 1,4-dioxide derivatives (**1**-**10**), active in previous assays, were selected for the determination of MIC against different single and multiply drug resistant strains of *Mycobacterium tuberculosis* and non-replicating persistent bacteria, MBC, maximum tolerated dose, oral bioavailability, *in vivo* efficacy testing an potential for cross resistance with another bio-reduced drug.



Comp.	R6	R7	R2
1	H	H	CH_3
2	H	CH_3	CH_3
3	H	OCH_3	CH_3
4	H	F	CH_3
5	H	Cl	CH_3
6	CH_3	CH_3	CH_3
7	H	H	Ph
8	H	H	NH-Ph
9	H	H	NH-PH-(*o*)CH_3
10	H	Cl	NH-PH-(*o*)CH_3

One compound, **5**, with an MIC of 0.78 µg/mL was bactericidal with an MBC ≥2, equally active on non-replicating persistent organisms, and active on multiply drug-resistant clinical isolates. This compound was orally bioavailable and efficacious in the mouse efficacy.

Acknowledgments: Antimycobacterial data was provided by the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) through a research and development contract with the U.S. National Institute of Allergy and Infectious Diseases (NIAID). R. Villar is indebted to the Navarra Government for a grant.

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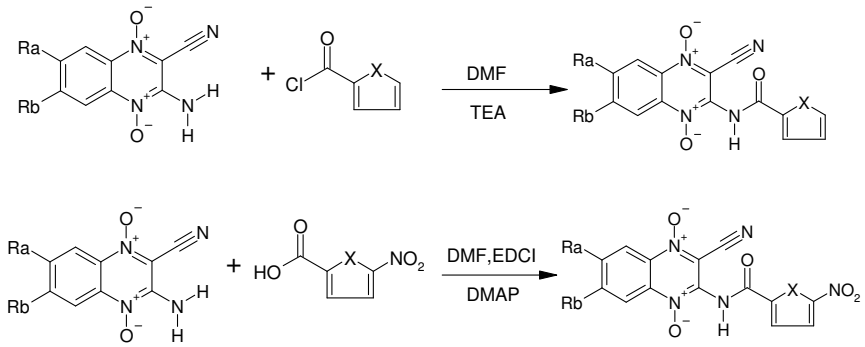
SYNTHESIS OF NEW 3-(AROYLAMINO)QUINOXALINE-2-CARBONITRILE 1,4-DI-*N*-OXIDE DERIVATIVES AS ANTI-MYCOBACTERIUM TUBERCULOSIS AGENTS

Beatriz Solano, Raquel Villar, Esther Vicente, Saioa Ancizu, Asunción Burguete, Silvia Pérez-Silanes, Ignacio Aldana, Antonio Monge

Unidad en Investigación y Desarrollo de Medicamentos, Centro de Investigación en Farmacobiología Aplicada (CIFA), Universidad de Navarra, C/ Irunlarrea s/n, 31080 Pamplona, Spain.

Tuberculosis (TB), an infection of *Mycobacterium tuberculosis*, still remains the leading cause of worldwide death among infectious diseases. The statistics indicate that 3 million people throughout the world die annually from TB. Due to this data and continuing the line of investigation of our research group[1], 40 new compounds with antituberculosis activity have been synthesized. The synthesis of these compounds have been carried out according to the scheme below:[2,3]



Ra,Rb= H; CH_3; Cl; CH_3O; F; CF_3. X= O;S.

All of these derivatives are also being tested as anti-*Mycobacterium tuberculosis* agents by the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) and some of them showed MIC values less than 6.25 µg/mL.

Acknowledgements: Antimycobacterial data was provided by the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) through a research and development contract with the U.S. National Institute of Allergy and Infectious Diseases (NIAID).

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IN VITRO ANTIMYCOBACTERIAL ACTIVITIES OF ETHYL 3-PHENYLQUINOXALINE-2-CARBOXYLATE 1,4-DI-*N*-OXIDE DERIVATIVES

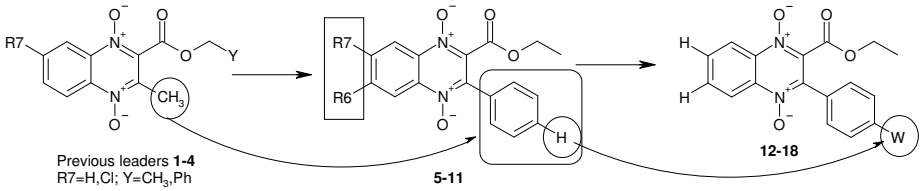
Saioa Ancizu, Esther Vicente, Asunción Burguete, Beatriz Solano, Raquel Villar, Silvia Pérez-Silanes, Ignacio Aldana, Antonio Monge.

Unidad en Investigación y Desarrollo de Medicamentos, Centro de Investigación en Farmacobiología Aplicada (CIFA), Universidad de Navarra, C/ Irunlarrea s/n, 31080 Pamplona, Spain.

One-third of the population is infected with *Mycobacterium tuberculosis* and the World Health Organization (WHO) estimates that within the next 20 years about 30 million people will be infected with the bacillus.[1]

As a result of the anti-tuberculosis research project, antimycobacterial activity of 3-methylquinoxaline-2-carboxylate 1,4-di-*N*-oxide derivatives was described.[2] The potency, selectivity, and low cytotoxicity of these compounds made them valid leads for synthesizing new compounds that possess better activity.

In a continuing effort to identify new active compounds against *M. tuberculosis*,[3,4] our research group has synthesized 14 new ethyl 3-phenylquinoxaline-2-carboxylate 1,4-di-*N*-oxide derivatives (**5-18**) by applying rational structural modifications from our previous lead-compounds. This novel series of derivatives was evaluated against H37Rv strain of *M. tuberculosis* and certain parameters of cytotoxicity and selectivity were established, following the TAACF program. All of the compounds were active in preliminary assays, with 100% of Growth Inhibition at 6.25 µg/mL. Eleven of them showed a MIC≤1.56 µg/mL; six of the thirteen derivatives tested for cytotoxicity demonstrated good selectivity and are now being more thoroughly studied.



Acknowledgements: Antimycobacterial data were provided by the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) through a research and development contract with the U.S. National Institute of Allergy and Infectious Diseases (NIAID). S. Ancizu is indebted to the Navarra Government for a grant.

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P-35

SINTESIS Y EVALUACION BIOLOGICA DE NUEVOS SISTEMAS BICÍCLICOS [4,1,0] COMO INHIBIDORES DE iNOS

Irene Suarez del Villar,[a] Ana Gradillas,[a] Ricardo Martinez-Murillo,[b] Alfredo Martinez Serrano,[b] y Javier Pérez-Castells[a]*

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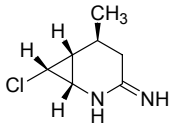
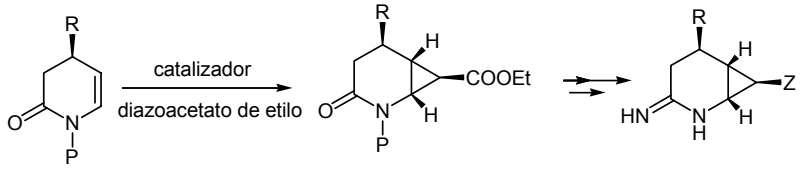
A finales de los noventa se describió el derivado amidínico cíclico denominado ONO-1714 como novedoso inhibidor selectivo de la isoforma iNOS humana que juega un papel importante en diversos trastornos tales como el choque séptico, la artritis reumatoide o la enfermedad inflamatoria intestinal. También se ha demostrado su implicación en enfermedades como el Parkinson o el cáncer.



ONO-1714

Al tratarse de un compuesto de reciente descubrimiento y poseer una estructura muy diferente a la de los otros iNOS conocidos, hasta ahora existen pocos derivados descritos y apenas se han efectuado estudios de Relación Estructura Actividad con inhibidores de esta enzima.
Para conocer nuevos aspectos acerca de la actividad inhibitoria frente a las diferentes isoformas de NOS, recientemente hemos puesto ha punto una reacción de ciclopropanación estereoselectiva como base para la síntesis de nuevos sistemas bicíclicos potencialmente activos. La aproximación sintética es novedosa y permite el acceso a una amplia familia de derivados.



R = H, CH_3
P = grupo protector

En la presente comunicación se describe la síntesis de nuevos derivados de ONO-1714 y los primeros datos de actividad inhibitoria frente a la isoforma iNOS y datos de actividad antiproliferativa frente a diferentes líneas tumorales. Los valores obtenidos permitirán en un futuro explorar los requisitos estructurales mínimos necesarios para esta familia de inhibidores de iNOS.

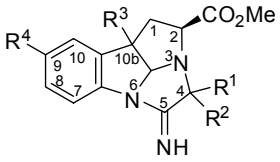
Agradecimientos: Financiación de este proyecto por el MEC (proyecto CTQ2006-00601/BQU). ISV. agradece a la FUSP-CEU una beca predoctoral.

SÍNTESIS Y EVALUACIÓN ANTITUMORAL DE ANÁLOGOS DE ALCALOIDES INDÓLICOS DERIVADOS DE HEXAHIDROPIRROLO[1',2',3':1,9a,9]IMIDAZO[1,2-*a*]INDOL

Pilar Ventosa-Andrés, Juan A. González-Vera, M. Teresa García López, Rosario Herranz

Instituto de Química Médica (CSIC), Juan de la Cierva 3, 28006 Madrid

En el curso de investigaciones orientadas hacia el estudio del potencial sintético de α-aminonitrilos derivados de aminoácidos en la generación de diversos esqueletos heterocíclicos de interés terapéutico, hemos obtenido compuestos portadores del nuevo sistema de 1,2,4,5,10b,10c-hexahidropirrolo[1'2'3':1,9a,9]-imidazo[1,2-*a*]indol (**1**), para el cual no encontramos precedentes en la bibliografía[1]. Sin embargo, este nuevo sistema heterocíclico podría considerarse híbrido entre la estructura de 1,2,3,3a,8,8a-hexahidropirrolo[2,3-*b*]indol y la de 2,3,9,9a-tetrahidroimidazo-[1,2-*a*]indol, ambos presentes en alcaloides indólicos con diversas actividades biológicas. Así por ejemplo, el esqueleto de hexahidropirrolo[2,3-*b*]indol está presente, entre otros, en el inhibidor de acetilcolinesterasa fisostigmina, en los antibacterianos flustraminas, en las ardeeminas, compuestos que revierten la resistencia múltiple a fármacos, y en diversos péptidos que contienen residuos de triptófano modificado. Por otra parte, el esqueleto de tetrahidroimidazo[1,2-*a*]indol está presente en las asperlicinas, antagonistas de los receptores de colecistoquinina CCK_1, en los antifúngicos fumiquinazolinas, y en las fiscalinas, antagonistas de la sustancia P. El interés de estos alcaloides, junto con la novedad estructural del esqueleto tetraheterocíclico de pirroloimidazoindol nos ha impulsado a estudiar, y comunicar aquí, la síntesis y evaluación antitumoral de compuestos análogos de fórmula general **2**, sustituidos en la posición 10b.



1: R^3 y R^4 = H

2: R^3 = Br, allyl, prenyl, OH, CH_3
R^4 = H, Br

Agradecimientos: Pharma Mar, S. A. por la evaluación antitumoral; CSIC por las becas I3P a P. Ventosa-Andrés y a J. A. González-Vera; CICYT por la financiación (SAF2006-01205).

[1] (a) González-Vera, J. A.; García-López, M. T.; Herranz, R. *Org. Lett.* **2004**, *6*, 2641-2644. (b) González-Vera, J. A.; García-López, M. T.; Herranz, R. *J. Org. Chem.* **2005**, *70*, 8971-8976.

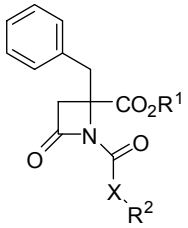
P-37

SYNTHESIS AND ANTI-HCMV EVALUATION OF NEW AZETIDINE DERIVATIVES

Paula Pérez Faginas[a], M. Teresa García López[a], Graciela Andrei[b], Robert Snoeck[b], Jan Balzarini[b] and Rosario González Muñiz[a]

[a]Instituto de Química Médica (CSIC), Juan de la Cierva 3, 28006, Madrid, Spain. [b]Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium.

Human cytomegalovirus (HCMV) is a member of the β-herpes virus family and causes severe infections in inmunocompromised individuals. The HCMV pathogen encodes a serine protease essential for capsid assembly and viral maturation[1]. Due to its critical role this enzyme has become an attractive target for the development of anti-HCMV drugs. In a previous work, we described two series of compounds, azetidinones (**1**) and azetidines (**2**) derived from amino acids, acting as covalent and non-covalent HCMV inhibitors, respectively[2]. Taking compound **3** as prototype, we have synthesized a series of structural analogues (**4**) to try to improve their inhibitory properties. Since we have previously observed that an increase in the hydrophobic character at *C*-terminus is followed by an enhancement of the activity, we have decided to replace the Ala residue at this position by other aliphatic and aromatic moieties. We have also prepared derivatives from polar amino acids as negative controls.



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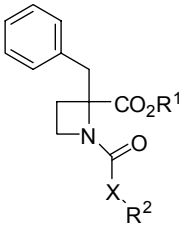

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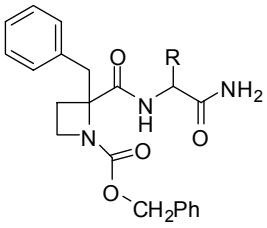

3 R= Me
4 R= CH_2Phe
$CH_2CH(CH_3)_2$, $CH(CH_3)_2$
$(CH_2)_4NH_2$, $(CH_2)_2CO_2H$

This communication deals with the synthesis and evaluation against HCMV in cell cultures of this new family of azetidines derived from amino acids.

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CONSTRAINED PEPTIDE ANALOGUES OF LOOPS 2 AND 4 OF BRAIN-DERIVED NEUROTROPHIC FACTOR.

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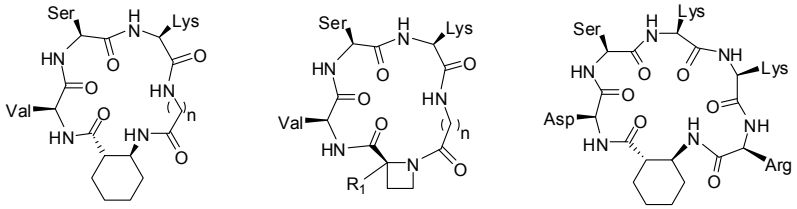
Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of neurotrophic factors, dimeric molecules which drive to receptor dimerization and activation upon binding.[1] BDNF promotes the survival of various neuronal populations showing potential in the treatment of neurodegenerative diseases. In addition, antagonists of BDNF receptors might be of utility in the treatment of BDNF-dependent malignancies. Several studies have involved solvent-exposed loops (1, 2 and 4) of the BDNF dimer in the binding and activation of its trkB receptor.[2] In this sense, we have used loop 2 (Val-Ser-Lys-Gly) and loop 4 (Asp-Ser-Lys-Lys-Arg) as templates for the design of small monocyclic peptides. Molecular modelling studies, based on the three-dimensional structure of BDNF,[3] have shown that 2-carboxy-azetidines and 1-amino-2-carboxycyclohexane are suitable linkers to bring together the *C* and *N*-termini of loop 2 and 4 sequences, while maintaining the overall three-dimensional structure of these loops. This has led us to the design of constrained peptides **1**-**6** as mimetics of the β-turn structure of loop 2, and the cyclic hexapeptide **7**, as mimetic of loop 4 (Figure 1).



1 n=1
2 n=2

3 n=1, R=H **5** n=1, R=CH_3
4 n=2, R=H **6** n=2, R=CH_3

7

Figure 1

This communication addresses the solid-phase synthesis, molecular modelling, NMR studies and preliminary biological results of compounds **1**-**7**.

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P-39

SÍNTESIS DE NUEVOS CARBANUCLEÓSIDOS TIOFENOCONDENSADOS

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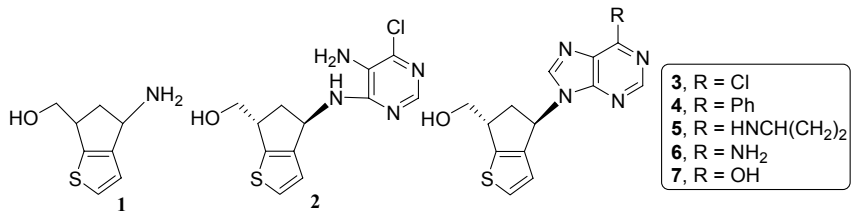
Fármacos no tóxicos que actúen frente al virus de la inmunodeficiencia humana (VIH) o al virus del herpes, por ejemplo, por inhibición selectiva de quinasas y polimerasas, han sido objeto de investigación durante las últimas décadas[1]. Además la aparición de cepas de VIH resistentes a los fármacos anti-VIH aprobados por la FDA, estimuló el desarrollo de nuevos análogos nucleosídicos capaces de superar dichas resistencias[2]. En concreto, la actividad anti-VIH del carbovir y de su derivado el abacavir[3] (introducido en clínica) atrajo el interés hacia los carbanucleósidos derivados de ciclopenteno.

En nuestro laboratorio venimos trabajando desde hace unos años en la síntesis y estudio de la actividad biológica de nuevos heterocarbanucleósidos en los que el anillo de ciclopenteno ha sido integrado en un anillo de tiofeno.

En esta comunicación se presenta la síntesis de una nueva serie de heterocarbanucleósidos tiofeno-condensados **3-7**, vía el intermedio cloropirimidínico *trans*-**2**. A este intermedio se accede al hacer reaccionar una mezcla 1:1 de los aminoalcoholes precursores *cis/trans*-**1**, obtenida previamente por nosotros[4], con 5-amino-4,6-dicloropirimidina en *n*-BuOH a reflujo; el producto *trans*-**2**, se obtuvo con buen rendimiento, previa separación por cromatografía flash de su isómero *cis*.



Agradecimientos: Los autores agradecen la financiación del proyecto a la *Xunta de Galicia PGIDIT02BTF20305PR*.

[1] Mahony, W. B.; Domin, B. A.; Daluge, S. M.; Zimmerman, T. P. *Biochemical Pharmacology* **2004**, *68*, 1797.
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SYNTHESIS OF BICYCLIC ALKALOIDS FROM CARBOHYDRATES

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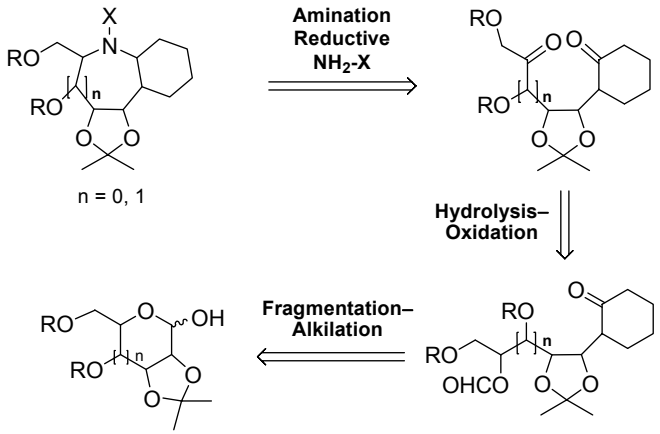
Many bicyclic alkaloids containing quinoline and azepine systems, have shown significant biological activities.[1] Therefore, many efforts have been devoted to develop stereocontrolled synthesis of this class of compounds.[2] In this communication a versatile methodology to obtain functionalized bicyclic alkaloids from readily available carbohydrates is described.



Acknowledgments: This work was supported by the Investigation Program PPQ2003-01379 (Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica, Ministerios de Ciencia y Tecnología y Educación y Ciencia, Spain). We also acknowledge financial support from FEDER funds. Dácil Hernández thanks the Ministerio de Educación y Ciencia for an FPU fellowship.

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ONE-POT SYNTHESIS OF AZANUCLEOSIDES FROM AMINO ACIDS

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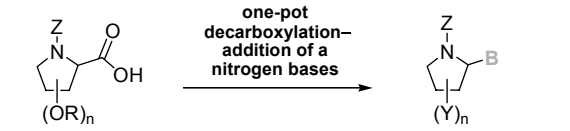
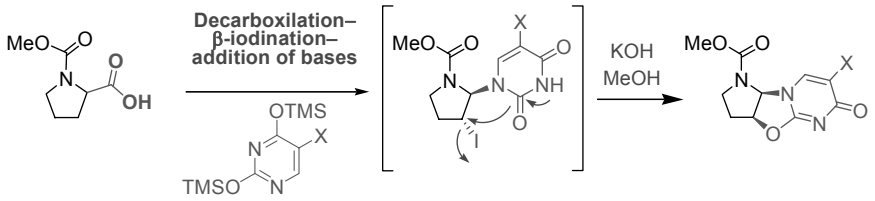
The development of new methodologies to obtain bioactive products has arisen much interest, since some of these compounds have shown potential antitumoral, antifungal or antiviral activity. In this communication we describe a new process to prepare azanucleosides from amino acids.



Z = acyl, carbamate
R = H, alkyl, acyl

B = nitrogen bases (thymine, uracil, etc)

A modification of this reaction is the tandem decarboxylation-β-iodination-addition of nitrogen bases. This reaction allows the synthesis of β-iodo-derivates and their later conversion into tricyclic azanucleosides. Some of these compounds have shown a promising antifungal activity.[1]



Acknowledgments: This work was supported by the Investigation Programs and CTQ/PPQ2006-14260 (Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica, Ministerios de Ciencia y Tecnología y Educación y Ciencia, Spain). We also acknowledge financial support from FEDER funds. Dácil Hernández thanks the Ministerio de Educación y Ciencia an FPU fellowship.

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RNAs INHIBIDORES DIRIGIDOS FRENTE AL IRES DEL HCV

Raquel Díaz-González, Cristina Romero-López, David Paul y Alfredo Berzal-Herranz

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La infección causada por el virus de la hepatitis C (HCV), en la mayoría de los casos, progresa a hepatitis crónica, cirrosis y carcinoma hepatocelular. El tratamiento actual consiste en la acción combinada de PEG-interferón y ribavirina, efectivo sólo en el 50% de los pacientes que toleran la terapia. Sin embargo, actualmente no existen agentes antivirales específicos del HCV aprobados para el tratamiento de la infección. Uno de los mayores problemas en el desarrollo de dichos agentes es la elevada variabilidad genética que presenta el virus. El genoma del HCV es una hebra de RNA lineal de polaridad positiva que presenta en la región 5´ UTR un dominio altamente conservado y estructurado (IRES) que dirige el inicio de la síntesis de la poliproteína viral por un mecanismo independiente de cap. Estas propiedades lo convierten en una excelente diana terapéutica. En nuestro laboratorio se ha aplicado un método de selección molecular *in vitro* con el que se ha obtenido una colección de moléculas de RNA, compuestas por un dominio catalítico tipo hammerhead que procesa el genoma viral en la posición 363 y un aptámero de 25 nucleótidos seleccionado por su capacidad de unión al IRES. Hemos comprobado *in vitro* que estas moléculas inhiben eficientemente la traducción mediada por el IRES sin afectar la traducción dependiente de cap, con inhibiciones de hasta un 90%. Tras el análisis de todas ellas, hemos centrado nuestra atención en aquellas que tienen una inhibición más potente para realizar un análisis más exhaustivo. Estudios *ex vivo* confirman su potencial inhibidor y su utilidad como herramientas terapéuticas con inhibiciones cercanas al 60%.

P-43

ACTIVIDAD ANTIPROLIFERATIVA Y PROAPOPTÓTICA DE COMPUESTOS ORGANOSELÉNICOS EN CÁNCER DE PRÓSTATA

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Numerosos estudios en modelos animales y más recientemente en humanos han demostrado la eficacia anticarcinogénica y quimiopreventiva de distintos compuestos que contienen selenio[1]. Entre los mecanismos de acción implicados en estas actividades la inducción de apoptosis[2] y la participación en procesos relacionados con el estrés oxidativo se encuentran entre los más representativos. Trabajos recientes han demostrado que el tratamiento con compuestos selenados en líneas tumorales de cáncer de próstata produce una disminución muy significativa del crecimiento celular[3].

Con el objetivo de obtener nuevos agentes activos en cáncer de próstata se han diseñado estructuras que responden a un núcleo central de alquilisoselenourea unido mediante grupos amida a diversas terminaciones arílicas o heteroarílicas. Se ha realizado un estudio de relación estructura química-actividad biológica así como un análisis comparativo con derivados homólogos conteniendo azufre. Los compuestos de mayor actividad antiproliferativa se han ensayado en cuanto a inductores de apoptosis y se ha determinado la acumulación de caspasa-3 como punto de confluencia de las rutas apoptóticas.

Ocho de los compuestos evaluados mostraron interesante actividad citotóxica frente a la línea tumoral prostática PC-3, presentando uno de ellos un valor de IC_{50} tres veces inferior al patrón utilizado como referencia, etopósido, el cual es empleado actualmente en clínica.

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NUEVOS DERIVADOS ORGANOSELÉNICOS COMO AGENTES ANTIPROLIFERATIVOS

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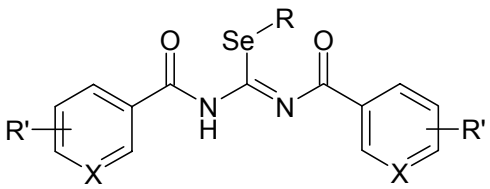
Como continuación de nuestro trabajo dirigido a la obtención de nuevos agentes citotóxicos[1,2] se presenta la síntesis y evaluación biológica preliminar de nuevos imidoselenocarbamatos con estructura general:



En el diseño de estas estructuras se ha pretendido reunir algunos fragmentos estructurales de reconocida eficacia en el tratamiento del cáncer, el factor simetría[3] y la presencia de selenio[4]. El selenio es un elemento traza que se ha identificado como posible agente quimioprotector contra el cáncer y otras patologías relacionadas con el estrés oxidativo.

De todos los compuestos sintetizados se ha valorado su actividad citotóxica en cuatro líneas celulares tumorales (leucemia, colon, mama, pulmón), determinando en cada uno de ellos los siguientes parámetros: IC_{50}, TGI, DL_{50} y GI_{50}. Algunos de estos derivados han presentado una interesante actividad antiproliferativa.

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[3] Sanmartín, C.; Font, M.; Palop, J.A. *Mini-Rev. Med. Chem.* **2006**, *6*, 639-650.

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P-45

FAST MICROWAVE PREPARATION OF LOSARTAN

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Losartan, chemically defined as 2-butyl-4-chloro-5-(hydroxymethyl)-l-{[2'-(lH-tetrazol-5-yl) biphenyl-4-yl] methyl} imidazole, is an effective Angiotensin II competitive antagonist and is therefore widely used in the treatment of hypertension, renal failure, glaucoma and related diseases and conditions. Because of its mechanism of action, the product avoids the side-effects of calcium antagonists and thus, has been the origin of a whole family of analogs, "the sartans".[1]

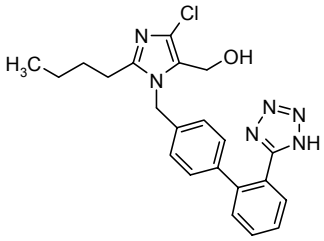
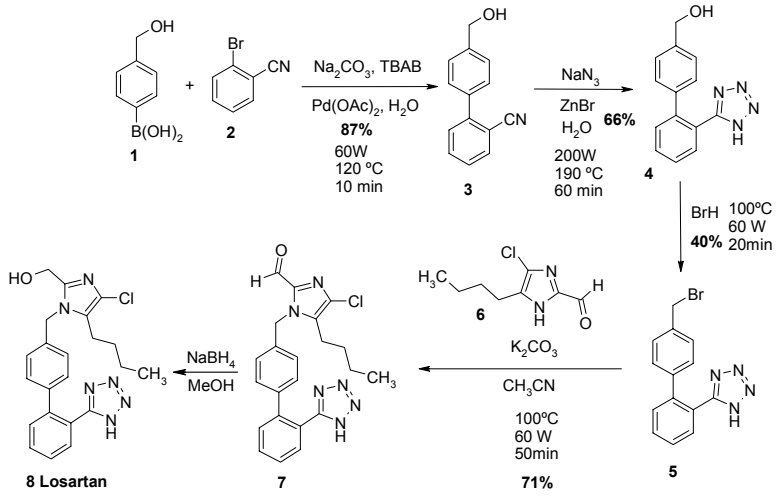


Figure 1

Water is a cheap, readily available nontoxic solvent for use in chemistry. There are, however, problems with the use of water, such as the solubility of substrates. With its high dielectric constant, water is also a potentially useful solvent for microwave-mediated synthesis. As well as benefiting from the rate enhancement effects found when using microwave heating, when water is heated well above its boiling point in sealed vessels, organic substrates can become partially soluble.[2] We have prepared Losartan using this technique in most of the steps.[3,4,5] The synthetic strategy has been redesigned in relation with the conventional preparation methods, to prevent the use of protecting groups, thus simplifying the whole procedure.



(2-{2-[3-(2-DIMETHYLAMINO-ETHYL 1)-1H-INDOL-5-YLMETHYL]-2-METHANESULFONYLMETHYL-1H-INDOL-3-YL}ETHYL) DIMETHYLAMINE, THE MAIN SUMATRIPTAN IMPURITY

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Alcalá de Henares. Madrid.

Among the many serotonin-like compounds studied, the discovery of the anti-migraine drug sumatriptan **1** stimulated the development of other 5-HT_{1D} receptor agonists.[1] From the chemical point of view, several of them (sumatriptan **1**,[2] avitriptan **2**,[3] and almotriptan **3**[4]) have the common feature of possessing a sulfamoylmethyl group attached, through a methylene bridge, to the position 5 of indole nucleus (Figure 1).

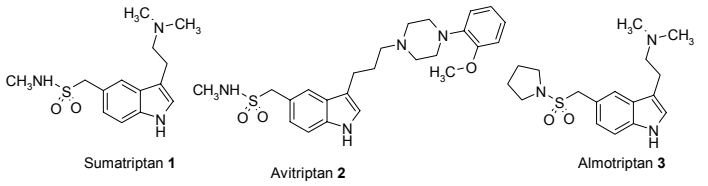
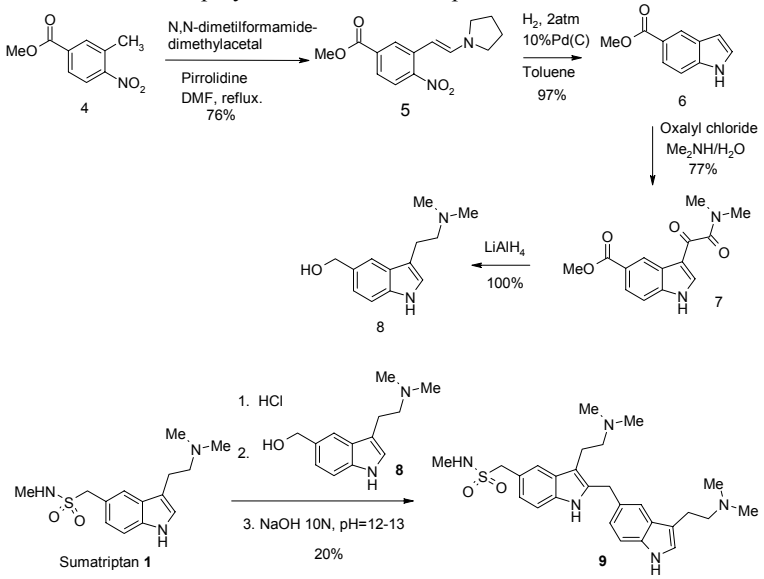


Figure 1

In the present work, the compound **9** has been synthesized**,** being the main impurity detected in Sumatriptan[5]. The method employed to obtain this compound is indicated in the scheme 1.



Scheme 1

[1] Hopkins S.J., *Drugs Today,* 28, 155 (1992)
[2] Relevant patents: Dowle, M. D. and Coates, I. H., GB 2 124 210 (1983). Dowle, M. D. and Coates US Patent 4, 816 470 (1989). Oxford, A. W., GB 2 162 522 (1984)
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ACCESS TO FULLY ORTHOGONALLY PROTECTED *anti,anti*-4-AMINO-PIPERIDINE-3,5-DIOLS THROUGH CHEMOSELECTIVE REDUCTION OF β-LACTAM CYANOHYDRIN HYBRIDS

B. Alcaide,*[a] P. Almendros,[b] G. Cabrero[a] and M. P. Ruiz[a]

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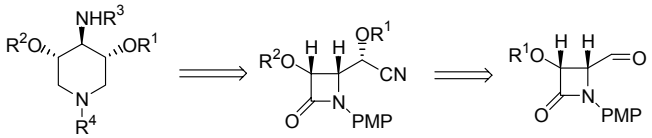
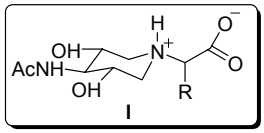
Polyhydroxylated piperidines, also called azasugars or iminosugars, and their synthetic analogues have attracted a great deal of attention due to their ability to mimic sugars and selectively inhibit glycosidases and glycoprotein-processing enzymes.[1] Therefore, a continuous interest exists in the development of new methodologies for asymmetric synthesis of these compounds. On the other hand, selective bond cleavage of the 2-azetidinone ring coupled with further synthetic transformations renders these fascinating molecules powerful synthetic building blocks in the stereocontrolled synthesis of a wide variety of nitrogen-containing compounds.[2]

We now report two short, complementary β-lactam-cyanohydrin–based routes to orthogonally protected enantiopure *anti,anti*-4-amino-3,5-piperidine diols, by a strategy that allows stereocontrolled construction of all three contiguous stereocenters (Scheme 1).



Scheme 1

Specifically, the utility of this novel reaction sequence has been demonstrated by the synthesis of fully orthogonally protected sialidase inhibitor analogues (type I).



I

Acknowledgments. We would like to thank the DGI-MEC (Project CTQ2006-10292) and CAM-UCM (Grant GR69/06) for financial support. G. C. thanks the MEC for a predoctoral grant.

[1] See, for example: (a) Afarinkia, K.; Bahar, A. *Tetrahedron:Asymmetry* **2005**, *16*, 1239. (b) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Chem. Rev.* **2000**, *100*, 4683.

[2] See, for example: (a) Alcaide, B.; Almendros; Aragoncillo, C. *Chem. Rev.* **2007**, in press. (b) Alcaide, B.; Almendros, P. *Curr. Med. Chem.* **2004**, *11*, 1921. (c) Alcaide, B.; Almendros, P. *Synlett* **2002**, 381. (d) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Synlett* **2001**, 1813.

SYNTHESIS OF ALL FOUR STEREOISOMERS OF β-PHENYLPROLINE

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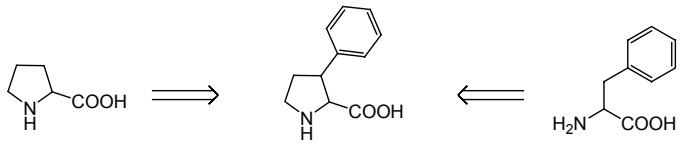
The incorporation of constrained α-amino acids into bioactive peptides is an important approach to study their conformational requirements for biological activity. Because of motional restrictions inherent to the pirrolidine ring, proline is well known for its ability to induce conformational constraints in peptides. During the last years, several β-substituted prolines have been synthesised to serve as amino acid chimeras in which the functional groups of the amino acid side-chain are combined with the conformational restrictions characteristic of proline. Replacement of the natural residue in peptides with such proline-α-amino acid chimeras has provided additional information about receptor recognition requirements and affinity.

Among these proline derivatives, we are interested in the synthesis of β-phenylproline, a chimeric amino acid that includes the structure of both proline and phenylalanine (Figure 1).



proline β-phenylproline phenylalanine

Figure 1

Although some methods reported so far can provide optically pure final products, our main objective is the development of a versatile approach to the synthesis of all four possible stereoisomers of β-phenylproline, *i.e.* two *cis* enantiomers and two *trans* enantiomers, in a multigram scale and enantiomerically pure form. To this end, we have applied a strategy to the synthesis of rac-*cis* and rac-*trans* compounds that, followed by a highly efficient resolution method using chiral HPLC, has allowed us the isolation of all four stereoisomers of β-phenylproline in optically pure form.

P-49

SÍNTESIS DE ANÁLOGOS BICÍCLICOS DE PROLINA

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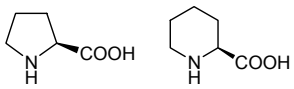
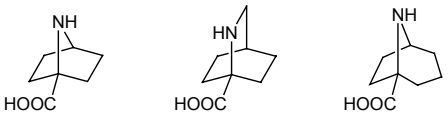
Dada su naturaleza cíclica, la prolina presenta propiedades conformacionales únicas entre los aminoácidos proteicos. Esta singularidad la convierte en un residuo clave tanto para la estructura como para la función de péptidos y proteínas. Por este motivo, existe un gran interés por sintetizar derivados de prolina, así como de su homólogo superior, el ácido pipecólico (Figura 1). Una estrategia muy interesante para modificar la estructura de estas moléculas es la unión de dos átomos del ciclo para dar lugar a la formación de estructuras bicíclicas.

Estas estructuras resultan muy interesantes ya que permiten, de una forma muy clara, capturar una conformación determinada de una molécula e incluso modular el grado de libertad en función del tamaño del puente de unión.



prolina ác. pipecólico

Figura 1. Estructuras de prolina y de ácido pipecólico



azabiciclo [2.2.1] azabiciclo [2.2.2] azabiciclo [3.2.1]

Figura 2. Estructura de los análogos de prolina y ácido pipecólico sintetizados

Tomando como base la amplia experiencia que nuestro grupo de investigación posee en la síntesis de aminoácidos restringidos, nos planteamos el desarrollo de metodologías que permitiesen el acceso a diversos análogos bicíclicos de prolina y ácido pipecólico. En esta comunicación, se presenta la síntesis[1] de tres derivados en los que los átomos de carbono de las posiciones 2 y 5 se encuentran unidos mediante un puente carbonado de longitud variable (Figura 2). Uno de ellos es análogo de prolina (azabiciclo [2.2.1]), otro, es un derivado del ácido pipecólico (azabiciclo [2.2.2]) y el tercero (azabiciclo [3.2.1]) resulta ser un aminoácido quimera, que contiene al mismo tiempo las estructuras de la prolina y el ácido pipecólico.

[1] (a) Avenoza, A.; Cativiela, C.; Busto, J. H.; Fernández-Recio, M. A.; Peregrina, J. M.; Rodríguez, F. *Tetrahedron* **2001**, *57*, 545-548; (b) Casabona, D.; Cativiela, C. *Tetrahedron* **2006**, *62*, 10000-10004; (c) Casabona, D.; Jiménez, A. I.; Cativiela, C. *Tetrahedron* **2007**, *63*, 5056-5061.

INHIBIDORES DE PROLILOLIGOPEPTIDASA CON NUEVOS SUSTITUYENTES EN LAS POSICIONES P1 y P2

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La prolioligopeptidasa (POP) es una serin-proteasa citosólica que hidroliza pequeños péptidos que contienen prolina por el extremo carboxilo terminal de los residuos de prolina.[1,2] Muchos de ellos son péptidos bioactivos tales como la sustancia P, vasopresina y β-endorfina, implicados en procesos de aprendizaje o desarrollo de la memoria. Debido a ello, en los últimos años, la POP ha ido ganando importancia como diana en el tratamiento de enfermedades como la esquizofrenia, el Alzheimer o el desorden bipolar.[3] Se han descrito muchos inhibidores de bajo peso molecular de estructura general acil-L-prolil-pirrolidina, siendo el más estudiado el Z-L-prolil-L-prolinal.[4] Estas moléculas poseen tres zonas de interacción P1, P2 y P3 que interaccionan con las regiones S1, S2 y S3 del sitio activo del enzima (Fig.1).

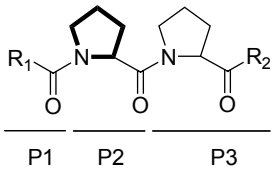

Figura 1. Estructura general de los inhibidores de POP

En la presente comunicación se muestra la síntesis de una quimioteca de inhibidores basados en la estructura anterior, en la cual se han modificado las posiciones P1, P2 y el extremo acilo de la posición P3 así como los resultados preliminares de su evaluación sobre la POP humana.

[1] Polgar, L. *Cell Mol. Life Sci.* **2002**, *59*, 349-362.
[2] Polgar, L. *Curr. Med. Chem.* **2002**, *2*, 251-257.
[3] Komatsu, Y. *J. Neurosci.* **1996**, *16*, 6342-6352.
[4] Wilk, S.; Orlowski, M. *J. Neurochem.* **1983**, *41*, 69-75.

P-51

SÍNTESIS DE NUEVOS DERIVADOS DE RASAGILINA COMO POTENCIALES FÁRMACOS NEUROPROTECTORES

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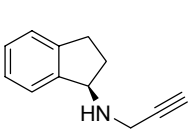
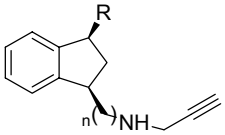
Las disfunciones en el catabolismo de neurotransmisores como dopamina y acetilcolina son un importante factor en la fisiología de patologías neurodegenerativas como la enfermedad de Parkinson (EP) y de Alzheimer (EA). Los niveles de dichos transmisores están modulados por enzimas como *MAO* (*MAO_A* y *MAO_B*) y *acetilcolinesterasa*, cuya inhibición representa una de las estrategias usadas para corregir los síntomas de los pacientes que sufren dichas patologías, por lo que en los últimos años se han desarrollado nuevos inhibidores de *MAO* y *acetilcolinesterasa* como agentes neuroprotectores.[1]

La Rasagilina [*N*-propargil-1(*R*)-aminoindano, **I**][2] es un nuevo fármaco de uso en la EP tanto en monoterapia como en combinación con levodopa. Es un potente, selectivo e irreversible inhibidor de *MAO_B*, que previene la degradación de dopamina, mensajero químico responsable de transmitir determinadas señales entre la sustancia negra y el cuerpo estriado encargadas de realizar el control de los movimientos. En la actualidad se llevan a cabo estudios acerca de la capacidad neuroprotectora en la EA de la rasagilina y otros compuestos relacionados, con la idea de que la coexistencia en una misma molécula de dos farmacóforos responsables, respectivamente, de la capacidad inhibitoria frente a *MAO* y *acetilcolinesterasa* y de la actividad neuroprotectora puede representar una interesante y completa aproximación al tratamiento de una enfermedad tan compleja como la EA.

Por todo ello hemos iniciado la preparación de una serie de derivados de la rasagilina (**II**) diferentemente sustituidos en la posición 3 del anillo indánico, los cuales presentan el agrupamiento propargilamino enlazado directamente, o a través de un puente metileno, al sistema bicíclico de la misma, al objeto de evaluar su utilidad en el tratamiento de las enfermedades de Parkinson y Alzheimer.



Rasagilina
I



II
n = 0, 1

R = OR, NR'R'', CO_2R', CH_2OR', CONR'R'', alquilo, arilo o heteroarilo

[1] Shih, J. C. et al. *Annu. Rev. Neurosci.* **1999**, *22*, 197.
[2] Youdim, M. B. et al. *J. Med. Chem.* **2002**, *45*, 5260.

SÍNTESIS DE DERIVADOS DE *S*-PROLINA SUSTITUIDOS DE INTERÉS COMO PROLINA-MIMÉTICOS

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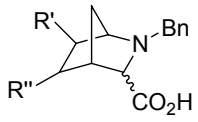
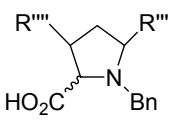
Los neuropéptidos del sistema nervioso central (SNC) **PLG** (*L*-prolil-*L*-leucil-glicinamida)[1] y **GPE** (glicina-prolina-glutámico)[2] desempeñan un importante papel neuromodulador en el SNC, por lo que se ha propuesto que dichos péptidos o análogos de los mismos puedan generar un nuevo grupo de agentes farmacológicos para el tratamiento de patologías de tipo neurodegenerativo, como las enfermedades de Alzheimer, Parkinson o Huntington.

Al objeto de contribuir a la preparación de análogos de PLG y GPE modificados en el residuo de prolina, dada la importancia de dicho residuo en el papel biológico de ambos neuropéptidos, hemos iniciado una línea de investigación destinada a preparar análogos de PLG y GPE que sustituyan la prolina presente en los mismos por diferentes compuestos prolina-miméticos.

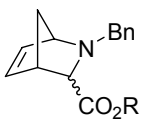
En la presente comunicación describimos los procesos sintéticos de preparación de diferentes derivados prolina-miméticos, tipo **I** y **II**, a partir de los aductos, tipo **III**, obtenidos en la reacción de aza-Diels Alder entre ciclopentadieno e iminas, quirales o aquirales,[3] con el objetivo de investigar la influencia de las modificaciones realizadas en el residuo de prolina en la actividad biológica de PLG y GPE y de sus análogos.



I



II



III

Agradecimientos: Los autores agradecen a la Xunta de Galicia la ayuda financiera concedida para la realización del presente proyecto (PGIDIT05PXIB20301PR).

[1] Mishra, R.K., Chiu, S., Chiu, P., Mishra, C.P. *Methods Find. Exp. Clin. Pharmacol.* **1983**, *5*, 203.
[2] Yamamoto, H., Murphy, L.J. *J. Endocrinol.* **1995**, *146*, 141.
[3] Rodríguez-Borges, J. E., García-Mera, X., Fernández, F., Lopes, V. H.C., Magalhães, A. L. and Cordeiro, M. N. D. S. *Tetrahedron* **2005**, *61 (46)*, 10951.

P-53

SÍNTESIS DE ÁCIDOS HIDROXÁMICOS CON POTENCIAL EFECTO ANTIMALÁRICO

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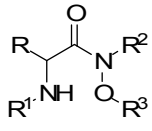
En 2002 Hanada y col. publicaron que el enzima fosfolipasa C de *Plasmodium falciparum* (*Pf*PLC) podría ser una buena diana en la síntesis de fármacos antimaláricos[1]. Este dato nos hizo estudiar el efecto de una pequeña familia de ácidos hidroxámicos sintetizados en nuestro grupo y que poseían la capacidad de inhibir la fosfolipasa C de *Bacillus cereus*.



Estudios sobre el efecto de esta familia sobre *P. falciparum* mostraron que, efectivamente, varios de los compuestos probados inhibían el crecimiento *in vitro* del parásito con valores de IC_{50} iguales o menores de 1 µM.

Se eligieron los dos mejores inhibidores y se estudió principalmente el efecto que podrían tener sobre el metabolismo de lípidos ya que, originalmente, habían sido sintetizados como inhibidores lipídicos y exhibían una cierta similitud con el alquilfosfolípido miltefosina, compuesto que bloquea el crecimiento del parásito en la etapa de trofozoíto y que inhibe un enzima implicado en el metabolismo de fosfatidilcolina y fosfatidiletanolamina[2].

Los ácidos hidroxámicos estudiados no mostraron capacidad para inhibir *in vitro* *Pf*PLC pero bloquearon el crecimiento del parásito en la etapa de trofozoíto, cuando se incrementa el metabolismo lipídico y, en su presencia, se apreció una disminución de la síntesis de fosfatidilcolina pero no así de la de fosfatidiletanolamina. Esto, unido al hecho de que no inhibieran en enzima fosfocolinametil transferasa, que une ambas rutas sintéticas nos hace pensar que el efecto que tienen sobre *P. falciparum* es debido a la inhibición de las dos últimas etapas de la síntesis de fosfatidilcolina.

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SPHINGOLIPID ANALOGOUS: SEARCHING NEW DRUGS AGAINST COPD

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Chronic obstructive pulmonary disease (COPD) is characterised by chronic inflammation of the airways and progressive destruction of lung parenchyma, a process that in most cases is initiated by cigarette smoking. Among the several mechanisms postulated to be involved in the pathogenesis of COPD, disruption of the balance between apoptosis and replenishment of structural cells in the lung has been recently reviewed[1]. There is an increase in apoptotic alveolar epithelial and endothelial cells in the lungs of COPD patients. Moreover, Petrache et al reported increased lung ceramide levels in emphysema patients, suggesting that ceramide upregulation might be an important pathogenetic element in the development of emphysema[2].

The putative apoptotic activity of D-erythro-dihydroceramides (DHC's) is a matter of controversy. Thus, it has been published that exogenously added short chain DHC's do not exhibit apoptotic activity in different cell. lines[3, 4], while L-threo-N-acetyl-sphinganine causes cell death in HL-60 cells[3]. Additionally, accumulation of natural DHC's, but not ceramides, along with cell death occurs in human leukaemia cells treated with gamma-tocopherol, as well as in prostate cancer cells[5]. Finally, a recent report describes that both long and short chain erythro-DHC's do not simply lack apoptogenic activity, but counteract the apoptotic effect of ceramide by inhibiting Cer channel formation in mitochondria in early apoptosis [6]. In this context, the synthesis of a small combinatorial DHC library obtained by systematic variation of both the sphingoid and aliphatic and acyl chains as well as the synthesis of cyclic ceramides (jaspines) is reported in this work. In addition, preliminary data on the activity of the synthesized compounds in A549 cells, a human alveolar epithelial cell line used in COPD studies, are also presented.

[1] Demedts IK, et al., *Respir Res.* , **2006**,7, 53.
[2] Petrache I, et al., *Nat Med.*, **2005**, *11*, 471.
[3] Bielawska A, et al., *J Biol Chem.*, **1993**, *268*, 26226.
[4] Ogretmen B, et al., *J Biol Chem.*, **2001**, *276*, 32506.
[5] Jiang Q, et al., *Proc. Natl Acad. Sci USA*, **2004**, *101*, 17825.
[6] Stiban J, et al. *Apoptosis*, **2006**, *11*, 773.

ENANTIOMERICALLY PURE 4-SUBSTITUTED D-PIPECOLIC ACIDS WITH INTERESTING PHARMACOLOGICAL PROPERTIES

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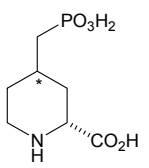
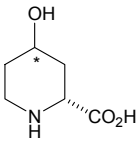
Pipecolic acid derivatives are widely used in therapeutic chemistry because of their significant and various biological activities. In particular, 4-substituted derivatives can act as anaesthetics, antitumorals, antibiotics, anticoagulants, NMDA receptor agonists or antagonists, immunosuppressants and enzyme inhibitors. The design and study of novel drugs with central nervous system activity containing 4-substituted pipecolic acids requires the development of new methodologies to synthesize them stereoselectively.[1]

In this regard, taking advantage of our previous methodology to build the piperidine ring[2] and with the aim of design new potential chemotherapeutic agents, we have optimized the asymmetric synthesis of seven important 4-substituted D-pipecolic acids starting from the same chiral 4-piperidone. Two selective competitive antagonists of the NMDA receptor, diastereomeric *cis*- and *trans*-4-phosphonomethyl-D-pipecolic acids, *cis*-**1** (CGS-20281) and *trans*-**1**,[3] have been prepared in enantiomerically pure form. (2*R*,4*S*)- and (2*R*,4*R*)-4-hydroxypipecolic acids[4] *cis*-**2** and *trans*-**2**, two versatile chiral precursors in the preparation of biologically active molecules, have been diastereodivergently obtained.

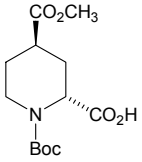
In addition, we have developed three synthetic routes directed to the obtention of conformationally constrained α-amino acid chimeras glutamic acid/pipecolic acid *trans*-**3**, lysine/pipecolic acid *trans*-**4** and ornithine/pipecolic acid *trans*-**5**, all of them in ortogonally protected form. *Trans*-**3** is a D-glutamic acid analogue with NMDA receptor agonist activity[5] and *trans*-**4** and *trans*-**5** are restricted analogues of D-lysine and D-ornithine respectively, and show interesting applications in peptidomimetics design.[6]



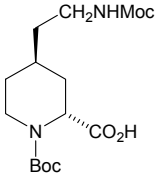
cis-**1**/*trans*-**1**



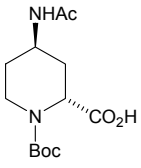
cis-**2**/*trans*-**2**



trans-**3**



trans-**4**



trans-**5**

[1] Kadouri-Puchot, C.; Comesse, S. *Amino Acids* **2005**, *29*, 101-130.
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ENANTIOMERICALLY PURE POLYSUBSTITUTED PIPERIDINES AS ANALOGUES OF BIOLOGICALLY ACTIVE COMPOUNDS

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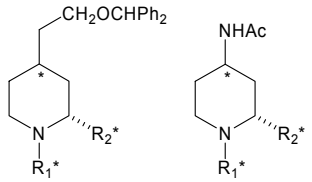
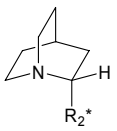
Chiral polysubstituted piperidines represent one of the most common building blocks in natural products with biological activity and have been identified as important therapeutic agents for the treatment of a range of diseases. As a consequence the stereoselective synthesis of chemically modified analogues of active substituted piperidines provides a powerful tool to further investigate the development of new drugs. In this context this work resumes our work on the asymmetric synthesis of different piperidine derivatives as close structural analogues of bioactive compounds starting from the same chiral 4-piperidone.[1]

1-Benzyl-4-[2-(diphenylmethoxy)ethyl]piperidine is one of the most potent and selective DAT inhibitors known and as such is a potent cocaine antagonist.[2] We have synthesized two structural analogues of this compound with one substituent at C_2, targets *cis*-**1** and *trans*-**1**. First pharmacological assays on the role of these compounds as serotonin transporter inhibitors using cellular model Caco-2[3] have provided very promising IC_{50} values.

On the other hand, substituted piperidines that contain an amino group at C_4 have great pharmaceutical interest because they are potent analgesics with opioid activity and selective antagonists at the MK1 receptor. Moreover these compounds show central nervous system (CNS) activity.[4] Therefore we have optimized the stereoselective synthesis of 2-substituted 4-acetamidopiperidines *cis*-**2** and *trans*-**2**. Finally, a great deal of agonists of nicotinic or muscarinic receptors with CNS activity contain a 1-azabycicle motif in their structure.[5] This biological importance has motivated the development of synthetic strategies to the preparation of 1-azabicyclo[2.2.2]octane **3** and 1-azabicyclo[2.2.1]heptanes *endo*-**4** and *exo*-**4**.



cis **1**/*trans* **1** *cis* **2**/*trans* **2**



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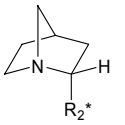
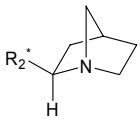


endo-**4**



exo-**4**

[1] Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron* **1999**, *55*, 7601-7612.
[2] Singh, S. *Chem. Rev.* **2000**, *100*, 925-1024 and references therein.
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NUEVOS ANÁLOGOS DEL KRN7000 CON POTENCIAL ACTIVIDAD INMUNOMODULADORA

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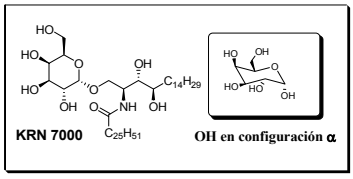
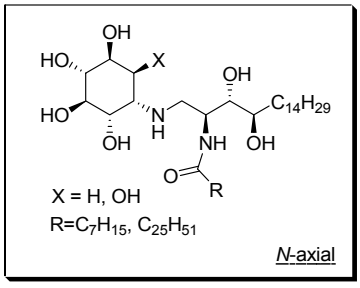
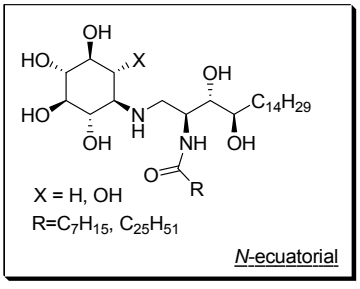


La modificación estructural de una serie de compuestos extraídos de una esponja marina, *Agelas mauritianus* ha conducido al KRN 7000 que ha revelado una fuerte actividad antitumoral[1].

La estimulación que produce en las células iNKT ha hecho evidente el potencial terapéutico del KRN 7000 en enfermedades autoinmunes y cancerosas.
El KRN 7000 es una α-galactosilceramida, perteneciente a una nueva serie de glicolípidos que se caracteriza por el tipo de enlace que une las dos partes de la molécula que es de tipo α. Se ha demostrado que esa configuración particular es la responsable de la actividad observada[2].

El objetivo de este trabajo consiste en la síntesis de nuevos análogos del KRN 7000, sustituyendo la α-galactosa por aminociclitoles cuyos enlace amino es de configuración axial o ecuatorial.





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NUEVOS ANÁLOGOS DE LA GLUCOSILCERAMIDA

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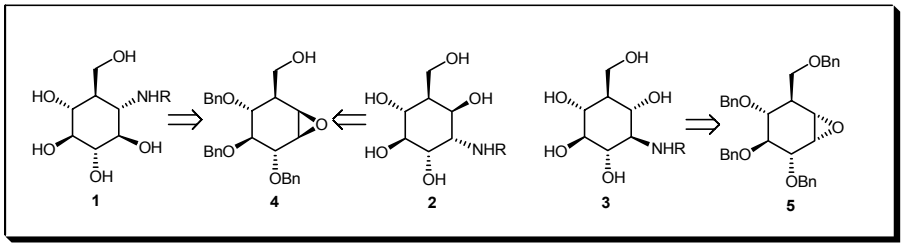
La enfermedad de Gaucher se produce por la actividad deficiente de la enzima Glucosilceramida hidrolasa lisosomal, que conduce a una incapacidad de metabolizar la Glucosilceramida, que se acumula en los lisososmas de los macrófagos impidiendo que éstos funcionen normalmente y aumentan de tamaño. El tratamiento de esta enfermedad como de las glicoesfingolipidosis en general, se centra en la recuperación total o parcial de la actividad enzimática en los lisosomas o bien en la disminución del sustrato del enzima afectado. Entre ellos se encuentra la terapia de reemplazo enzimático[1] que consiste en la administración intravenosa del enzima cuya funcionalidad está afectada y las chaperonas químicas que son moléculas de bajo peso molecular que permiten la recuperación de la funcionalidad de la proteína con defectos de plegamiento.

En la presente comunicación se describe la síntesis de derivados de tipo aminocarbazúcar (**1**-**3**), relacionados estructuralmente con el monosacárido presente en la Glucosilceramida con el objetivo de estudiar su actividad sobre las enzimas involucradas en el metabolismo de la Glucosilceramida y como chaperonas químicas de la Glucosilceramida hidrolasa lisosomal.



La síntesis de los aminociclitoles se planteó a partir de reacciones de apertura regio y estereocontroladas de epóxidos (**4-5**) promovida por un ácido de Lewis coordinante, como el $LiClO_4$.[2]

[1] Desnick, R. J. *J. Inherit. Metab. Dis.* **2004**, *27(3)*, 385-410.
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P-59

BÚSQUEDA DEL FARMACÓFORO DE ANTIBIÓTICOS ANTITUMORALES EN DERIVADOS DE PIRAZINO[1,2-*b*]ISOQUINOLINA

Irene Ortín, Juan Francisco González,
Elena de la Cuesta y Mª del Carmen Avendaño

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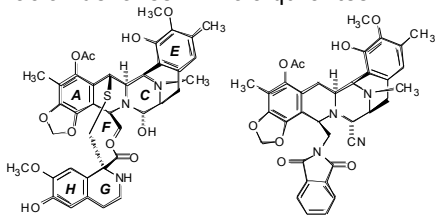
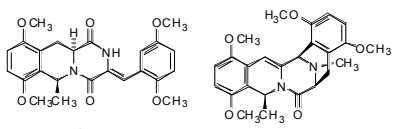
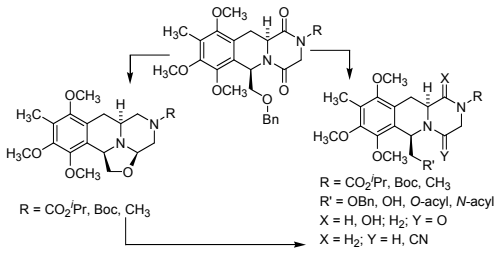
Se sabe que la actividad antitumoral de trabectedina (ET-743) se mantiene en análogos más sencillos como ftalascidina (Pt-650).[1] En nuestro grupo hemos desarrollado una estrategia sintética que, haciendo uso de la química de cationes iminio y aciliminio, permite acceder a compuestos tricíclicos, pentacíclicos y octacíclicos.[2] Cuando estudiamos la citotoxicidad de compuestos representativos, encontramos valores GI_{50} (concentración que inhibe en un 50% el crecimiento celular) de orden micromolar, tanto en compuestos tricíclios como pentacíclicos (ver por ejemplo los compuestos **1** y **2**), sin que aparentemente tenga relevancia la presencia o ausencia de un buen grupo saliente (CN, OH) que permita la formación de iones iminio alquilantes.[3]





Estos datos nos impulsaron a ampliar los estudios SAR a través de procesos de reducción quimio y diastereoselectiva en derivados de pirazino[1,2-*b*]isoquinolina-1,4-diona según el esquema.



Agradecimientos: Proyectos: CTQ2006-10930/BQU y GRUPO 920234, Beca FPI de I. Ortín y a la Empresa PharmaMar.

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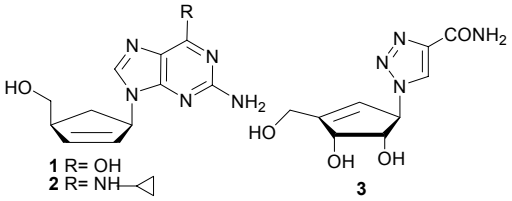
TRIAZOLOCARBANUCLEÓSIDOS. PARTE 2: SÍNTESIS Y EVALUACIÓN BIOLÓGICA DE 4-ARIL-[1,2,3]-TRIAZOLO-2',3'-DIDESOXI-2',3'-DIDESHIDROCARBANUCLEOSIDOS

Franco Fernández,[a] Isabel Pérez-Castro,[a] Olga Caamaño,[a] Carmen López,[a] Marcos D. García,[b] Erik De Clercq.[c]

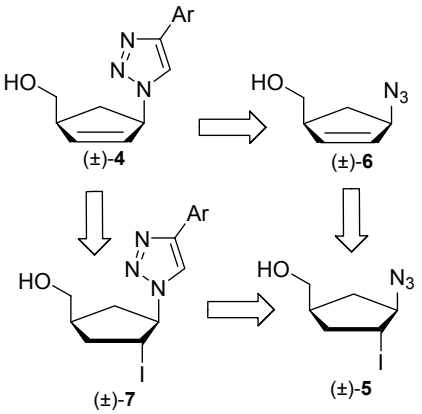
[a]*Departamento de Química Orgánica, Facultade de Farmacia, U.S.C, Campus Sur, E-15782, Santiago de Compostela.* [b]*Departamento de Química Fundamental, Facultade de Química, U.D.C., Campus da Zapateira,15071, A Coruña.* [c]*Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroedersstraat, B-3000 Leuven, Belgium*



Los carbanucleósidos, surgidos de la sustitución del oxígeno de la unidad de azúcar de los nucleósidos naturales por un grupo metileno, exhiben interesantes propiedades en el campo de la terapia antivírica. En este contexto, destacan compuestos como el carbovir (**1**) y abacavir (**2**) por su actividad anti-VIH.[1]

Como parte de nuestra linea de investigación centrada en la síntesis y evaluación biológica de nuevos 1,2,3-triazolocarbanucleósidos análogos a la ribavirina (**3**),[2] se planteó la preparación de compuestos que además de poseer el anillo triazólico como sustituto de la base heterocíclica, presenten una identidad estructural en la parte del pseudoazucar referible a la del carbovir (**1**) y abacavir (**2**).

Para la preparación de los 4-aril-[1,2,3]-triazolo-2',3'-didesoxy-2',3'-dideshidrocarbanucleosidos objetivo tipo (±)-**4**, se plantearon inicialmente dos alternativas sintéticas a partir del iodoazidociclopentilmetanol (±)-**5**. Este podría someterse a un proceso de deshidroiodación que condujese al azidoalcohol insaturado (±)-**6**, para a continuación construir la base heterocíclica mediante una cicloadición 1,3-dipolar de Huisgen catalizada por Cu (I) o, frente a esta aproximación, se construiría primero el sistema triazólico sobre la iodoazida (±)-**5** para obtener el iodotriazolilalcohol (±)-**7**, y a continuación se efectuaría el proceso de deshidroiodación.En esta comunicación se describe el desarrollo de ambas aproximaciones sintéticas, así como los resultados alcanzados en la preparación de diversos derivados de tipo (±)-**4**.



Los derivados tipo (±)-**4** han sido sometidos a ensayos *in vitro* de actividad antiviral frente a diversos virus de ADN y ARN.

[1] a) A. A. Krayevsky and K. A. Watanabe, "Modified Nucleosides as Anti-AIDS Drugs: Current Status and Perspectives"*;* Bioinform, Moscow, 1993. b) S. Thomas, J. E. McDowall, V. Cheah, A. Bye and M. B. Segal, "The Entry of Abacavir into the Guinea-pig Brain: Comparison with Other Reverse Transcriptase Inhibitors". Presented at the 12th World AIDS Conference, Geneva, 1998.

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P-61

ONE-POT MODIFICATION OF PEPTIDES AND AMINO ACIDS

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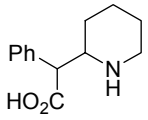
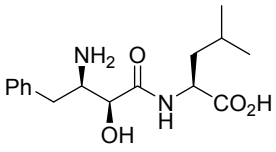
The synthesis of modified amino acids and peptides has allowed to obtain new drugs, or to increase the bioactivity, biodisponibility or hydrolytic stability of existing ones.[1a] For instante, the β-amino acid Ritalin is clinically used to treat hyperactivity in children,[1b] and the dipeptide bestatin is a potent inhibitor of aminopeptidase B.[1c]

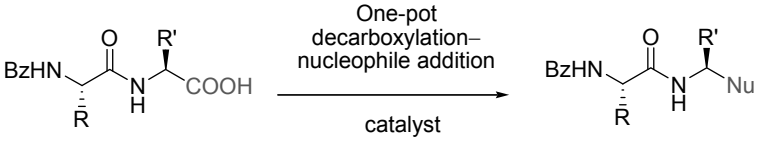


Ritalin



Bestatin

In order to modify bioactive peptides, and to study structure–activity relationships with their derivatives, we have developed a tandem decarboxylation–nucleophile addition reaction. The reaction takes place in moderate to good yields under mild, catalytic conditions.



Acknowledgments. This work was supported by the Investigation Programs PPQ2003-01379 y CTQ2006-14260/PPQ (Plan Nacional de I+D, MEC). We also acknowledge financial support from FEDER funds. C.J.S. thanks CSIC for an I3P contract.

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NEW S-NITROSOTHIOLS DERIVED FROM SNAP AND GSNO WITH POTENT PLATELET ANTI-AGGREGANT ACTIVITY

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INTRODUCTION

S-Nitrosothiols were considered chemicaly unstable products until the room temperature stable SNAP was obtained and reported in 1978[1]. The unstability of nitrosothiols in solution adds serious difficulties to its development as therapeutic drugs. Several factors affect its decomposition in solution including the exposure to light, temperature, pH conditions and the presence of transition metal ions.[2]

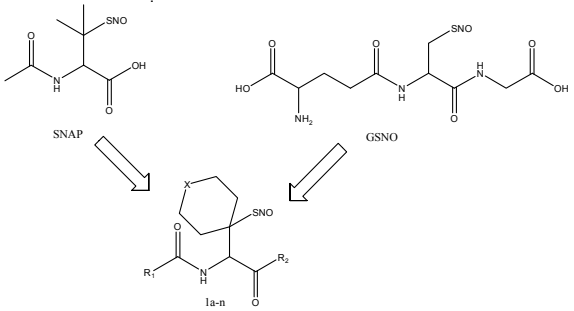
Nitric oxide released from nitrosothiols, is an ubiquitous signaling molecule in mammalian biology that is involved in several physiological pathways related with cGMP cascade, endotelium relaxation and it is a known inhibitor of platelet aggregation process [3,4].

OBJECTIVE

Our objective was to obtain new S-nitrosothiols as potential anti-aggregating agents with higher stability than the reference compounds SNAP and GSNO.

RESULTS

Starting from the structures of SNAP and GSNO several new compounds have been synthesised. In general, tertiary nitrosothiols are more stable than secondary, primary or aryl nitrosothiols[1].



Platelet aggregation was measured *in vitro* in human platelet rich plasma (PRP) using a luminometric method with ADP as aggregant agent. Effect on the expression of IIb-IIIa platelet receptors was determined by flow cytometry using PAC-1 and in both cases the IC_{50} (nM) was calculated and compared with values obtained with the reference compounds.

CONCLUSION

Compound 1b (R_1=CH_3, R_2=OH) with a better pharmacological profile than reference compounds (IC_{50} 0,31 and 0,19 nM respectively) was selected as a lead compound for optimization.

1.-Lin et al Tetrahedron (2006); 62; 8410-8418
2.-Singh et al. J Biol Chem (1996); 271; 18596
3.-Moncada et al. Pharmacol Rev. (1991); 43; 109-142
4.-Casadei et al. Prog. Biophys. Mol. Biol. (2003); 82; 67-80

P-63

A NOVEL ORAC (OXYGEN RADICAL ABSORBANCE CAPACITY) METHOD USING A UV-vis MICROPLATE READER. A GENERAL EXPERIMENTAL PROTOCOL

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Oxidative stress has been associated with the development of many chronic and degenerative illnesses, including cancer, cardiovascular failures, and neuronal degeneration such as Alzheimer's disease.[1] In fact, epidemiological studies have established an inverse correlation between the occurrence of these diseases and the intake of high amounts of fruits and vegetables that are rich in antioxidants.

In the last years, several *in vitro* methods have been developed for assaying the antioxidant activity of natural and synthetic products. One of the most widely used is the fluorometric oxygen radical absorbance capacity assay (ORAC-FL)[2] that measures the capacity of the tested sample to compete against a target molecule in the capture of free oxygen radicals. The ORAC-FL assay involves the use of a microplate fluorescence reader, more expensive than a microplate optical reader. For this reason, the development of methodologies that could use UV-vis spectroscopy instead of fluorometry could be of interest in small laboratories from public research institutions and from pharmaceutical and food industries.

Results are usually expressed with reference to a well-known antioxidant (trolox) as ORAC units. Although the ORAC scale pursuits to correct differences among laboratories results, a literature research reveals serious discrepancies in the ORAC values for a given pure product. For example, for the well-known antioxidant quercetin the following ORAC-FL values could be found in the recent scientific literature: 10.5,[3] 7.28,[4] and 6.50.[5]

In this work we adapted the ORAC assay to a conventional microplate visible reader and proposed a general experimental protocol that provided accurate ORAC-UV values.

Acknowledgments: The authors gratefully acknowledge the financial support of Ministerio de Educación y Ciencia (SAF2006-01249) and Comunidad de Madrid (Programa de I+D para Grupos de Investigación en Biociencias S-SAL/0275/2006), and the Contracts in Practices to V. Gálvez and B. López-Iglesias from CSIC (I3P program).

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Resveratrol and coumarins – New hybrid compounds

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Resveratrol or 3,4',5-trihydroxy-*trans*-stilbene (**fig.1**) is a natural compound found in grapes and certain other plants. This phytoalexin exhibits a variety of useful biological properties as antileukemic, antibacterial, antifungical, antiplatelet aggregation, anti-inflammatory, antioxidative and coronary vasodilator activities. This compound has been showing possible cancer chemopreventive properties on the basis of inhibitory effects on tumor initiation, promotion and progression.[1]

Coumarins or benzopyrones (**fig.2**) are a large family of compounds of natural or synthetic origin – this structural diversity remains to a numerous biological activities. They are known antimicrobial, antiviral, anti-inflammatory, enzimal inhibition, antioxidative, anticoagulant and anticancer proprieties.[2]

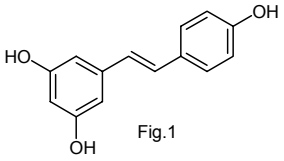

Fig.1

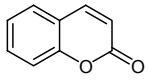

Fig.2

Due to these coincident properties, we thought that could be interesting to design and synthesize hybrids that incorporate the skeleton of these two molecules (**fig.3**). In these compounds the resveratrol nuclei is blocked, in its *trans* conformation, by the coumarin ring. Series of these molecules, with different number and position of the hydroxyl group on the benzenic nucleus, were designed, synthesized and evaluated as cardio-protective agents and I-MAO inhibitors. Another modification that we are studying is to substitute the benzene ring, in the tree position of the coumarin, for other different hetero aromatic rings, to see how these changes can contribute to the biological activity of these molecules.

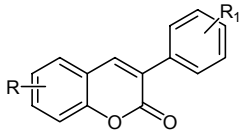

Fig.3

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P-65

BINDING PROPERTIES OF NEW GLYCOMIMETICS: A 3D VIEW BY NMR

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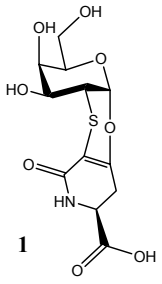
Glycomimetics are used for rational drug design. Obviously, it is necessary to take into account the shape of the receptor binding site and the conformation and dynamic nature of the natural ligand. In this work we have investigated, by using NMR and molecular dynamics, the conformational behaviours of three new glycomimetics and their consequences for binding to receptors.

The conformational analysis of ligand **1** showed an equilibrium between two conformers where the lactam moiety shows partial mobility; the galactose instead is present in the chair conformation. Different NMR experiments were used to evaluate the affinity of this ligand for the protein Viscumin (VAA), a galactose-binding: saturation transfer difference (STD) underlined finally the specific binding using the galactose moiety in an exclusive manner.

Morphine-6-*O*-β-D-glucuronide (M6G) **2** is a natural metabolite of morphine in humans and animals; its properties[1] and its capacity to penetrate the blood-brain barrier have been extensively studied[2]; morphine-6-*O*-α-D-mannose (M6M) **3** was synthesised in the attempt to reproduce the analgesic effect of M6G and to avoid the collateral effects of the opioids. The conformational study has been also performed by using NMR and molecular dynamics, underlining a significant difference between the two ligands: M6G is present as an equilibrium between a folded and an extended conformation, whereas M6M shows only the extended one. DOSY and NOESY experiments conducted in presence of an excess of the surfactant sodium dodecyl sulfate (SDS) permitted to detect the conformational behaviour in a membrane-like environment for **3** and **2**.



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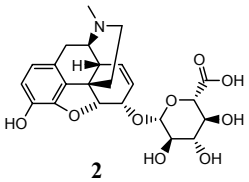

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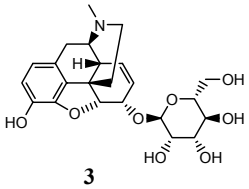

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SÍNTESIS Y EVALUACIÓN BIOLÓGICA DE COMPUESTOS HÍBRIDOS DERIVADOS DEL SISTEMA BENZOFUROXANO Y 1,3-DIÓXIDO DE BENZIMIDAZOL

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En estudios previos en nuestro grupo de trabajo se encontró que compuestos híbridos conteniendo semicarbazonas, guanilhidrazonas, tiosemicarbazonas y el sistema benzofuroxano presentaban actividad *in vitro* frente a diferentes cepas de *Trypanosoma cruzi*[1]. Además, estos compuestos son inhibidores moderados de Cruzaína, principal cisteín proteasa de *T. cruzi*[2]. A fin de encontrar compuestos más activos en el presente trabajo se amplia la serie de feniloximetilbenzofuroxanos sustituidos en posición *para* utilizando tiosemicarbazidas 4-sustituidas, sintetizándose también los correspondientes derivados *orto* sustituidos (**1-10**, Figura 1). Los benzofuroxanos se convierten en *N,N'*-dióxido de benzimidazol utilizando 2-nitroalcanos adecuadamente sustituidos (**11-20)**. Por otra parte, se prepara una serie de derivados conteniendo en posición *para* distintas *bis*alquilaminoguanidinas (**21-22**).

Los nuevos compuestos sintetizados se evalúan *in vitro* contra la forma epimastigota de *T. cruzi* (cepas Tulahuen, Brener e Y) y se estudia la capacidad de los mismos de inhibir la enzima Cruzaína.

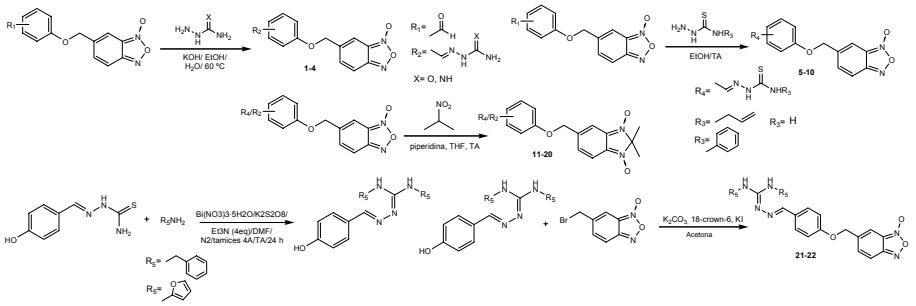

Figura 1. Síntesis de los nuevos compuestos híbridos desarrollados

Agradecimiento: PEDECIBA

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P-67

ESCALADO DE 5-(FENILETENIL)BENZOFUROXANOS CON ACTIVIDAD ANTICHAGÁSICA

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Nuestro grupo de trabajo encontró que los derivados **1-6** (Figuras 1 y 2) presentan una excelente actividad *in vitro* frente a diferentes cepas de *T. cruzi*[1]. Estos compuestos fueron preparados por una ruta, en escala de 100 mg, que implica una reacción de Wittig seguida de la formación del sistema heterocíclico.

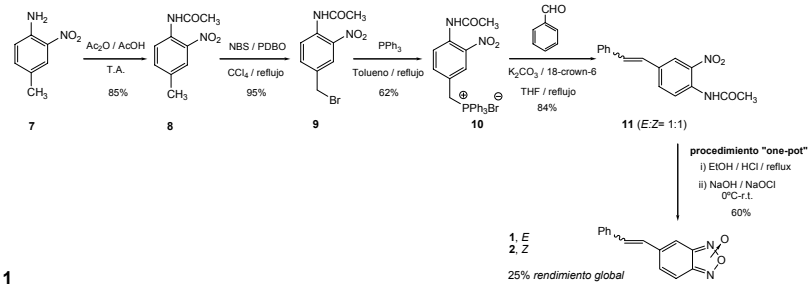

Figura 1

Con el fin de realizar el estudio pre-clínico de **1-6**, se diseñó un procedimiento sintético a escala de 10 g, seguro, ambientalmente adecuado y con mínima presencia de productos secundarios. Para ello se propuso un escalado que invirtiese las etapas de síntesis, una reacción de Wittig en condiciones de Boden con un aldehído derivado del sistema heterocíclico (Figura 2). Los estudios de HPLC indicaron que los productos secundarios $\mathbf{1}_{deox}$-$\mathbf{6}_{deox}$ se generan en menos del 3 %, mientras que por este procedimiento los compuestos de interés se obtienen con mejores rendimientos y en adecuadas proporciones isoméricas. Se discutirán las variables estudiadas para el escalado de los compuestos **1-6**.

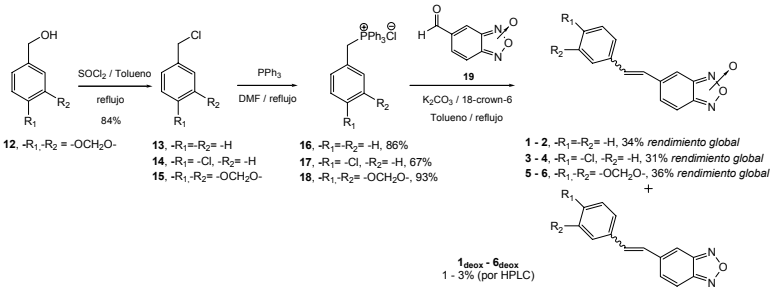

Figura 2

Agradecimientos: ***Drugs for Neglected Diseases initiative***

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ESTUDIOS DE METABOLIZACIÓN DE AGENTES ANTICHAGÁSICOS DERIVADOS DE 5-(FENILETENIL)BENZOFUROXANOS

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En la búsqueda de agentes quimioterapéuticos para el tratamiento de la enfermedad de Chagas, nuestro grupo de investigación ha preparado y evaluado más de quinientos derivados de *N*- óxido de aminas heterocíclicas aromáticas. En este estudio se han identificado derivados del heterociclo benzofuroxano con muy buena actividad tanto *in vitro* como *in vivo* frente a distintas cepas de *T. cruzi*. Especialmente los derivados 5-feniletenilbenzofuroxano fueron los que presentaron mejores actividades biológicas[1]. Es así que se decide el desarrollo preclínico de estos productos, en este sentido se someten, entre otros, a estudios metobolización *in vitro* usando como modelo biloógico la fracción microsomal de hepatocitos de rata y *T. cruzi*. La metabolización se estudia usando cromatografía líquida de alta performance en fase C18 y con el fin de identificar inequívocamente los productos de metobalización se sintetizan los potenciales metabolitos. Estudios previos han demostrado que el sistema benzofuroxano se metaboliza a la *o*-dioxima de benzoquinona y 2,3-diaminofenazina[2] En la Figura 1 se muestran las estructuras de los compuestos líderes y los metabolitos diseñados y sintetizados. Se comparan los correspondientes cromatogramas encontrándose que los metabolitos principales resultan ser los 2-nitroamino derivados.

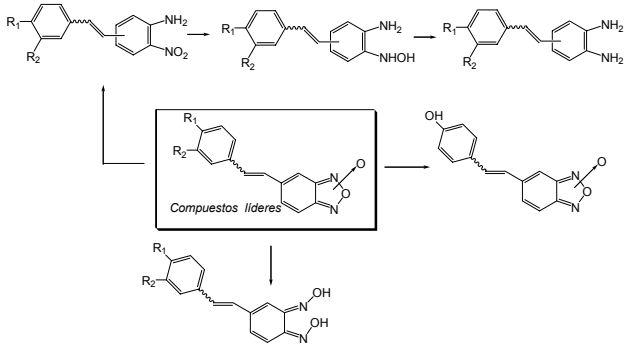

Figura 1. Estructura de los compuestos líderes y sus potenciales metabolitos

Agradecimiento: Drugs for Neglected Diseases initiative

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P-69

FLAVONOIDES SINTÉTICOS: ANÁLISIS DE SU POTENCIAL COMO AGENTES ANTITUMORALES Y QUIMIOPREVENTIVOS PARA EL CÁNCER.

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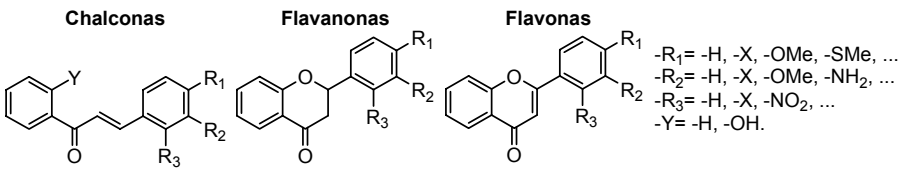
La quimioprevención del cáncer involucra la prevención, retraso o reversión de los procesos de carcinogénesis a través de la ingesta de alimentos o agentes farmacéuticos. Uno de los mecanismos de protección contra la carcinogénesis es la inducción de enzimas involucradas en el metabolismo de carcinógenos, particularmente enzimas detoxificantes de fase II como glutatión *S*-transferasa (GST) y quinona reductasa (QR). La quimioprevención también se puede conseguir mediante la inhibición de la familia de enzimas citocromo P450 (CYP450), ya que éstas tienen la capacidad de activar compuestos procarcinógenos volviéndolos dañinos para las células. Se han encontrado diversos compuestos naturales y sintéticos que son capaces de inducir en distinto grado las enzimas de fase II. [1]

En este trabajo se han sintetizado y evaluado en cuanto a su capacidad inductora, nuevos compuestos de la familia de los flavonoides que podrían actuar como agentes quimiopreventivos. Se estudiaron chalconas, flavonas y flavanonas con diferentes sustituyentes en posición 2, 3, 4, 5 o 2', 4' o ambas, abarcando un amplio rango de propiedades fisicoquímicas. Se estudió el efecto de la administración intragástrica de estos compuestos a ratas Sprague Dawley sobre la actividad de las enzimas GST, QR y CYP hepáticas. [2]

Además se analizó su citotoxicidad frente a tres líneas celulares tumorales: MCF-7 (derivada de adenocarcinoma de mama humano), TK-10 (derivada de carcinoma de riñón humano) y HT-29 (derivada de adenocarcinoma de colon humano).[2]

Considerando los productos evaluados, las chalconas fueron las que presentaron mejor perfil como potenciales agentes quimiopreventivos para el cáncer y dentro de estas aquellas con sustitución 2'-OH.



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[2] Presentado, en parte, en el *3rd Brazilian Symposium on Medicinal Chemistry.* **2006,** S2-069

MACROCYCLIC LACTAMS AS NOVEL GLYCOGEN SYNTHASE KINASE-3β INHIBITORS

Mª Ángeles Expósito[a], Diana Alonso[a], Javier López[a], Esther Martín-Aparicio[a], Ana Fuertes[a], Mª José Pérez-Puerto[a], Ana Castro[a], Miguel Medina[a], Ana Martínez[a].

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Glycogen synthase kinase 3 (GSK-3) is a serine-threonine protein kinase which plays an important regulatory role in several signaling pathways of cellular processes. Disorders in many of these regulatory pathways are involved in several human diseases, such as Parkinson's Disease, Alzheimer's Disease (AD), type II diabetes, bipolar disorders, schizophrenia, chronic inflammatory disorders or prion-induced neurodegeneration. Therefore, the discovery of new GSK3 inhibitors could provide new therapeutic approaches to treat these diseases[1].

Focusing on the study of AD, the presence of neurofibrillary tangles in neurons of cerebral cortex is one of the abnormalities observed in the brain of AD patients, and hyperphosporylated tau protein seems to be a main component of these neuronal deposits. GSK3-β is thought to be one of the most relevant enzymes involved in tau phosphorylation, hence its inhibition could play an important role in the treatment of this disease.

The ocean is considered to be a great source of potential drugs and it is interesting to point out the prominent role that marine invertebrates have played in the generation of novel GSK3-β inhibitors including hymenialdisine, meridianines and indirubines isolated from sponges, ascidians and molluscs[2].

As part of our research, based in the isolation of new lead compounds from marine origin with potential for the treatment of AD, we have found that the isopropanolic extract from the mediterranean bryozoan *Myriapora truncata* showed inhibitory activity against GSK3-β. Fractionation and purification of active components from this extract, guided by *in vitro* enzyme inhibition assays, resulted in the isolation and identification of **Clausenlactama**, previously only isolated from terrestrial sources, the tree *Clausena excavata*[3].

In order to confirm the structure of the isolated compound and fully explore the potential of this kind of structures as novel inhibitors of the enzyme, a program to produce synthetic analogues have been carried out and all the compounds have been tested in our biological assays.

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P-71

SYNTHESIS AND BIOLOGICAL EVALUATION OF THIOXOQUINAZOLINE DERIVATIVES AS DUAL PDE 7/4 INHIBITORS

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Phosphodiesterases (PDE) are the enzymes responsible for the hydrolysis of intracellular cyclic adenosine (cAMP) and guanosine monophosphate and their activity is associated with a wide variety of diseases, such as those affecting central nervous system function (e.g. depression), cardiovascular function, cell adhesion, metabolic processes and inflammatory cells/immune system.[1] From the large PDE family, PDEs 3, 4 and 7 are predominant in immune cells,[2] and among them, T cells appear to rely on PDE7 for regulation of cAMP levels. Thus, an intense effort toward the development of PDE7 inhibitors has been generated for the last years because inhibition of this enzyme could be an approach to treating T cell dependent disorders.[3]

Regarding our contribution to this field, new thioxoquinazoline derivatives were identified as PDE7 inhibitors. From these results, new related compounds have been synthesized and evaluated biologically, showing interesting results.

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A NOVEL NEURAL NETWORK APPROACH TO PREDICT THE INHIBITION OF NITRIC OXIDE SYNTHASE

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A supervised artificial neural network model has been developed for the prediction of inhibition of Nitric Oxide Synthase. A diverse set of chemicals was chosen in this study and the definition of the molecules was achieved from a not supervised neural network using a home made program named CODES®. This program codifies each structure from a topological point of view, in a set of numerical parameters with the only knowledge of its SMILES code and consequently of its chemical structure. Using this methodology, two models have been obtained for the prediction of inhibition of nNOS and iNOS.

P-73

OPTIMIZATION OF A MATHEMATICAL TOPOLOGICAL PATTERN FOR THE PREDICTION OF ANTIBACTERIAL ACTIVITY

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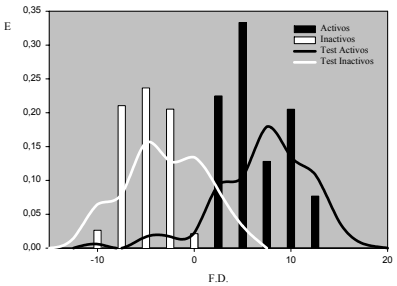
El objetivo del presente trabajo es la aplicación de la topología molecular al diseño de nuevas estructuras con actividad antibacteriana. Para ello se ha realizado un estudio de propiedades fisico-químicas, farmacológicas y microbiológicas de un grupo de 29 quinolonas[1] con el fin de obtener funciones de conectividad que relacionen la estructura química con la actividad.

Asimismo, se han seleccionado 51 quinolonas con probada actividad antibacteriana[2] y 51 quinolonas que carecen de dicha actividad. Se les han calculado 134 descriptores topológicos mediante el programa Molconn y con ambos grupos se ha realizado un análisis lineal discriminante con el programa estadístico BMDP, obteniéndose una función capaz de clasificar un compuesto como activo o inactivo.

Una vez seleccionadas las funciones de conectividad y las funciones discriminantes se han realizado los diagramas de actividad farmacológica (F.D.) de todas ellas, y se ha establecido un modelo topológico matemático capaz de seleccionar aquellas estructuras que presenten la actividad deseada.



El modelo topológico diseñado, se ha aplicado a un grupo test, formado por 100 antibacterianos y 100 no antibacterianos, con el fin de validar la calidad del modelo, obteniéndose elevados porcentajes de clasificación correcta, lo que permite confirmar que la topología molecular constituye una herramienta potente y eficaz para la búsqueda de nuevos compuestos con actividad antibacteriana.

Agradecimientos: este trabajo ha sido realizado gracias a la financiación de la Universidad CEU Cardenal Herrera (PRUCHB06/11 and PRUCH06/39)

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PREDICTION OF BIOLOGICAL PROPERTIES FOR ANTIFUNGICAL BY CONNECTIVITY FUNCTIONS

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Recently, the opportunistic fungal infections have risen dramatically. One of the biggest problems facing nowadays the antifungal therapy is the arising of drugs resistance strains for most of the drugs currently used in clinic practice. Therefore, it is important to find new antifungal candidate compounds, particularly new leads, able to become the basis for developing new drugs.[1]

We have developed a mathematical-topological equation with a multilinear regression analysis[2] to predict minimum inhibitory concentration (MIC) versus two microorganisms *Microsporum gypseum* and.*Trichophyton mentagrophytes var. interdigitale*. The structural description has been achieved through topological indices. The results obtained clearly reveal the high efficiency of molecular topology for the prediction of these properties. Randomization and cross-validation by use of leave-one-out test were also performed in order to assess the stability and the prediction ability of the connectivity functions selected.

Microsporum gypseum

$LogMIC_{M.gypseum} = 0.017 + 0.070\ S^T(\text{-}OH) - 16.916\ G^v{}_5 + 0.267\ G^v{}_2 + 280.42\ J^v{}_5 - 6.367\ J_2 + 4.932\ {}^9X_p$

N=33; SEE=0,289; SEE(vc)=0,375; r^2=0.75;

Trichophyton mentagrophytes var. interdigitale.

$LogMIC_{T.m.interd.} = -30.730 - 0.776\ {}^4\chi^v{}_{pc} - 0.015\ TTD(4) + 6.282\ S_9 - 0.511\ S^T(>C=) + 0.090\ S^T(\text{-}OH) + 0.054\ S^T(\text{-}F)$

N=33; SEE=0,284; SEE(vc)=0.296; r^2=0.76;

The obtained results demonstrate that the molecular topology is a very useful tool in the prediction of microbiological properties.

Acknowledgement: Financial support of this work was by the Universidad CEU Cardenal Herrera (PRUCHB06/11 and PRUCH06/39).

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P-75

THE DESIGN AND SYNTHESIS OF NEW 2-AMINOBENZIMIDAZOLES N-ALKYL SUBSTITUTED AS POTENT p38 MAP KINASE INHIBITORS

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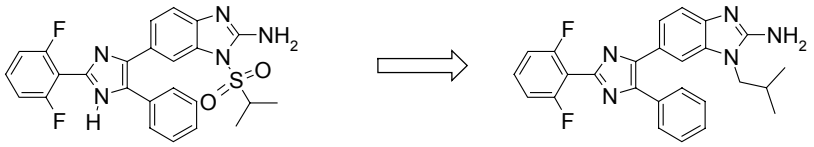
p38 MAP Kinase is currently one of the most attractive targets for pharmaceutical industry[1] as well as for the medicinal chemistry community[2]. A unique combination of well established pharmacology, clinical efficacy and the opportunity to employ structure-based drug design has converted it a highly attractive target for therapeutic intervention. It is well-known that the p38 MAP Kinase signaling pathway plays an important role in inflammation and other physiological processes.

We have previously reported the design and discovery of a 2-aminobenzimidazole based series as potent p38 MAPK inhibitors[3]. Our initial lead compound **1,** had low nanomolar activity in both ATP competitive enzyme binding assay and in the inhibition of TNFa release in macrophages. We developed an extensive SAR around this lead molecule and identified new benzimidazole derivatives. As a result, we found that the sulfonyl group in the N-3 imine nitrogen, plays a key role for the activity. This labile moiety could be replaced by an alkyl group and led to new inhibitors which showed good activity both *in vitro* and *in vivo* **(2)**.

The synthesis and biological activities of these compounds will be described.



1 **2**

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OBTENTION OF MINIMUM INHIBITORY CONCENTRATION PREDICTION EQUATIONS FOR A GROUP OF ANTIBACTERIAL QUINOLONES

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In this work a multilinear regression analysis has been carried out in order to look for a connectivity functions capable to accurately predict biological propertires of a group of quinolones.[1] The studied properties were: the minimum inhibitory concentration 50 (MIC_{50}) and 90 (MIC_{90}) versus two microorganisms *Escherichia Coli* and *Streptococcus pyogenes*,[2] widely used nowadays because of their broad spectrum of activity, well tolerance profile and advantaged pharmacokinetic properties. The structural description has been achieved through topological indices. The results obtained clearly reveal the high efficiency of molecular topology for the prediction of these properties. Randomization and cross-validation by use of leave-one-out test were also performed in order to assess the stability and the prediction ability of the connectivity functions selected.

Streptococcus pyogenes	
MIC_{50}: 213,48 + 2,46 $^{5}\chi_{P}^{v}$ + 1,06 $^{2}\kappa$ - *24,44* S^{T} *(-OH)*	N=13; SEE=0,431; SEE(vc)=0,578; r^2=0.951; r^2(cv)=0,913
MIC_{90}: - 5,34 + 7,39 $^{7}\chi_{P}$ + 12,86 $\Delta^{1}\chi$ – *3.07* V_4	N=12; SEE=0,698; SEE(vc)=1,102; r^2=0.939; r^2(cv)=0,848
Escherichia coli	
MIC_{50}= 0,571 - 0,035 S^{T}*(-CH_3)* – 2,42 J_4 – 0.021 V_4	N=17; SEE=0,027; SEE(vc)=0,031; r^2=0,854; r^2(cv)=0,764
MIC_{90}= 0,228 - 0,091 S^{T}*(-Cl)* – 0.144 G_{4}^{v} + 6,29 J_5	N=14; SEE=0,073; SEE(vc)=0,093; r^2=0,925; r^2(cv)=0,876

The obtained results demonstrate that the molecular topology is a very useful tool in the prediction of microbiological properties.

Acknowledgement: Financial support of this work was by the Universidad CEU Cardenal Herrera (PRUCHB06/11 and PRUCH06/39).

[1] Mut-Ronda, S. et al., *Bioorg. Med. Chem. Let.*, **2003**,*13*, 2699.
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P-77

TOPOLOGICAL PREDICTION EQUATIONS OF VOLUME OF DISTRIBUTION AND MEAN RESIDENT TIME FOR A GROUP OF ANTIBACTERIAL QUINOLONES

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The search of new molecules with therapeutic activity is a laborious process with an elevated economic cost. The main target of our work is the search of new molecules with possible antimicrobial activity and appropriate farmacokinetic properties derived from the therapeutic group of quinolones that are safe, effective and of quality[1].

We have developed a topological QSAR equation[2] to predict:

Volume of Distribution (Vd):

$$Vd = 10{,}12 + 0{,}704\ S^T\ (\text{-}NH_2) - 0{,}613\ S^T\ (\text{-}Cl) - 0{,}615\ G_2$$

N=16; SEE=0,694; SEE(vc)=0,906; r^2=0,858; r^2(vc)=0,823

Mean Resident Time oral administration (MRTpo)

$$MRTpo = -79{,}33 + 4534.4\ {}^4X^v_{CH} + 13{,}69\ {}^2Ka - 2{,}21\ S^T\ (\text{-}o\text{-})$$

N=12; SEE=0,008; SEE(vc)=0,013; r^2=0,890; r^2(cv)=0,849

The obtained results demonstrate that the molecular topology is a very useful tool in the prediction of pharmacokinetics properties.

Acknowledgement: Financial support of this work was by the Universidad CEU Cardenal Herrera (PRUCHB06/11 and PRUCH06/39).

[1] Mut-Ronda, S. et al., *Bioorg. Med. Chem. Let.*, **2003**,*13*, 2699.
[2] Calabuig, C. et al., *Int. J. Pharm.*, **2004**, *278*,111.

NUEVOS DERIVADOS DE 6-BENZO[*b*]TIOFENOCARBOXAMIDA 1,1-DIOXIDO COMO INDUCTORES SELECTIVOS DE APOPTOSIS EN CÉLULAS TUMORALES

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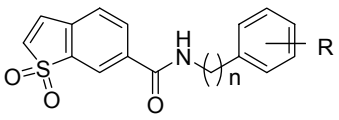
Los derivados de benzo[*b*]tiofenosulfonamida 1,1-dioxido (BTS) son potentes agentes citotóxicos[1]. que inducen apoptosis por una sobreproducción de radicales libres de oxígeno (ROS) en células tumorales[2]. Una serie de derivados de benzo[*b*]tiofenocarboxamida 1,1-dióxido (BTC) estructuralmente relacionados, ha mostrado alta actividad citotóxica frente a diferentes líneas de células tumorales[3]. Uno de los compuestos sintetizados ha sido elegido para el estudio del efecto apoptótico y producción de ROS sobre la línea celular de leucemia aguda T linfoblástica humana CCRF-CEM. El efecto citotóxico sobre CCRF-CEM está mediado por la acumulación de ROS, como lo revela la prevención de apoptosis por la adición de N-acetilcisteína.

Adicionalmente, para el estudio de selectividad sobre células tumorales, se ha evaluado la actividad de BTC sobre linfocitos T aislados a partir de sangre periférica de individuos sanos. Tras 4 horas de incubación, BTC induce apoptosis en células de leucemia, pero no en linfocitos T no tumorales. Los estudios revelan que las células CCRF-CEM incubadas con BTC sufren un incremento en los niveles intracelulares de ROS, significativamente mayor que el observado en linfocitos T



BTC

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P-79

SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW BENZO[B]THIOPHENE DERIVATIVES AS ANTIMALARIAL AGENTS

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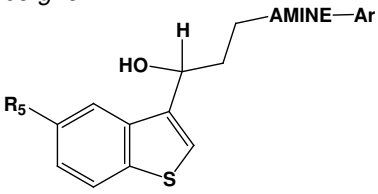
[1] Unidad en Investigación y Desarrollo de Medicamentos, Centro de Investigación en Farmacobiología Aplicada (CIFA), Universidad de Navarra, 31080, Pamplona. Spain
[2] Departamento de parasitología, Facultad de Farmacia, Universidad Complutense de Madrid.

Malaria is one of the most dangerous diseases affecting primarily poor people of tropical and subtropical regions. The search for novel drugs against specific parasites is an important goal for antimalarial drug discovery.

The increasing resistance of the malaria parasite *Plasmodium falciparum* to currently available drugs and especially to chloroquine demands a continuous effort to develop new effective therapeutic options. Identification of new molecular scaffolds structurally unrelated to existing antimalarial agents represents a valuable strategy to bypass resistance phenomena.

Accordingly, a serie of benzothiopehene derivatives recently published as antidepressants[1], was evaluated *in vitro* against a chlorosquine-sensitive strain (3D7) of *P. falciparum*[2] and Ferriprotoporphyrin IX biomineralisation inhibition test (FIBT)[3]. The most active compounds are being evaluating *in vivo* against *P. berghei* [4].



R_5 = H, F

Amine = piperazine, 4-aminopiperidine

Ar = Variable

[1] Orus L., Pérez-Silanes S., Oficialdegui A., Martinez J., Del Castillo J.C., Mourelle M. (2002). Synthesis and molecular modeling of new 1-aryl-3-[4-arylpiperazin-1-yl]-1-propane derivatives with high affinity at the serotonin transporter and at 5-HT_{1A} receptors. J. Med. Chem. 45 (19): 4128-4139.

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QSAR AND COMPLEX NETWORK APPROACH TO THE DESIGN OF MAO INHIBITORS: PREDICTION, SYNTHESIS AND BIOLOGICAL ASSAY OF NOVEL COUMARINS

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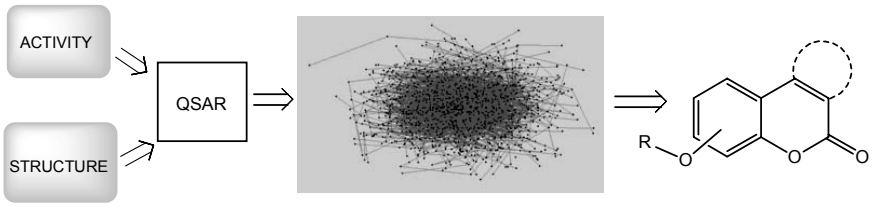
In recent years, efforts have been focused on the development of new theoretical approach to explain in an unified framework the structure-activity relationships of MAO A and/or B inhibitors. In this sense, we combined the Complex Networks Analysis with the QSAR methodology called MARCH-INSIDE to carry out an unified analysis for a very large database of heterogeneous compounds.

Initially, a Markov model was used to calculate molecular descriptors and fit a classification function based on dataset Principal Components derived with 94.5% of accuracy (3222 out of 3408 inputs). Next, the values of the PCA scores were used to calculate Complex Network of MAO inhibitors.

This combined analysis was used for the design of a novel generation of coumarin-scaffold based MAO inhibitors.



A set of 31 coumarin derivatives was evaluated by the model and subsequently synthesized and assayed as MAO inhibitors in order to corroborate the predicted biological activity. The model classifies correctly 26 compounds (83,87% of accuracy) consequently, this methodology represents a useful tool for the *in silico* screening of MAO activity.

P-81

SYNTHESIS AND BINDING AFFINITY OF NEW PYRAZOLE AND ISOXAZOLE DERIVATIVES AS POTENTIAL ATYPICAL ANTIPSYCHOTICS

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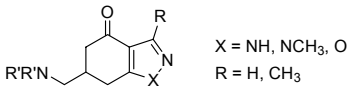
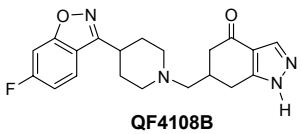
The newer generation of treatments for schizophrenia, referred to as atypical antipsychotics, add to the blockade of dopamine receptors, a potent activity at serotonin receptors. It is thought that 5-HT_{2A} antagonism together with relatively weaker dopamine antagonism are principal features that differentiate the side-effect profile of atypical antipsychotics, such as clozapine, from the first generation of treatments.[1] Although the newer atypical antipsychotics olanzapine, risperidone, and quetiapine have brought about improvements in toleration and negative symptomatology, chronic treatment may lead to unwanted weight gain, blood dyscrasias, and motor dysfunctions, such as extra-pyramidal side effects (EPS) and tardive dyskinesia (TD). These side effects may be linked to drug-dependent affinity for other receptors. The search in our group continues for new atypical antipsychotics that are more efficacious and have fewer side effects than currently available treatments.[2]

In this communication, we will describe our recent efforts to discover novel templates in the area of selective dual 5-HT_{2A}/D_2 antagonists for potential use as treatments for schizophrenia. A typical bioisosteric replacement of the benzene in the aminobutyrophenone pharmacophore by a pyrazole or an isoxazole ring has been applied to afford indazolone and benzisoxazolone cores (I), respectively. From this work, compound **QF4108B** has emerged as a new lead because of its favourable pharmacological profile.



I



QF4108B

Acknowledgment: We thank the MEC (Ref SAF2005-08025-C03) for the financial support. M. B. thanks the Spanish Ministerio de Educación y Cultura for a predoctoral Fellowship.

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4-ARYLPIPERAZINYLALQUIL BENZOLACTAMS AS POTENTIAL DOPAMINE D_3 RECEPTOR ANTAGONISTS.

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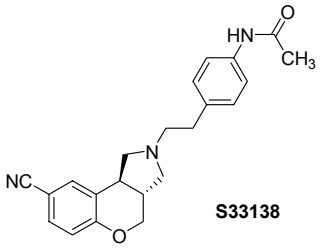
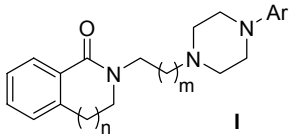
Schizophrenia is a chronic, severe, and disabling neurodevelopmental disorder that affects about 1% of the world population. Recent studies[1] have suggested that the dopamine D_3 receptor subtype, since it is selectively located in the limbic brain areas known to be associated with cognitive and emotional functions, might be a promising rational target for development of new drugs for the treatment of this pathology.

Major progress in D_3 receptor drug development would allow us to a better understanding of this illness and to improve its treatment, as compounds with dopamine D_3 antagonist profile may give rise to beneficial antipsychotic activity avoiding extra-pyramidal side effects of the actual therapy.[2] Thus, compound S33138, a selective D_3 antagonist, is now in Phase II trials for the treatment of schizophrenia.[3]



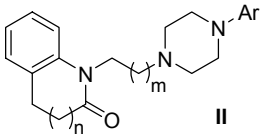
S33138

In this communication we will report the synthesis and binding affinity of two new series D_3 antagonists (**I** and **II**) based on a benzolactam scaffold, which maintain three characteristic elements of many dopamine D_3 receptor antagonist: 1) an amine moiety, 2) a spacer, usually a linear alkyl chain, and 3) a hydrophobic residue, often connected through an amide bond.[4] These new compounds will allow us to evaluate some of the structural requirements for high affinity and selectivity binding at the D_3 receptor.



I

m = 2, 3
n = 1, 2, 3



II

Acknowledgment: We thank the Xunta de Galicia (Ref PGIDIT06 PXIB203173PR) for the financial support.

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P-83

SYNTHESIS, BINDING AFFINITY AND SAR OF NEW BENZOFURANONE DERIVATIVES AS POTENTIAL ANTIPSYCHOTICS

Reyes Aranda,[a] Karen Villalba,[a] Christian F. Masaguer,[a] Filipe Miguel Areias,[b] María Isabel Loza[b]

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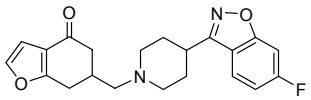
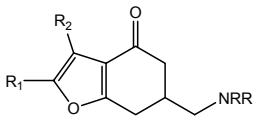
Atypical antipsychotic agents offer improved treatment of schizophrenia by combining efficacy with less propensity to cause harmful CNS side effects. Recent attention in this field has been focused on the development of compounds that act both dopamine and serotonin receptors.

Over the last few years, we have been working on the synthesis of series of atypical antipsychotic agents based on the modulation of the butirophenone system with the aim of combining the antagonism at the 5-HT_2 family and the D_2 receptors in a single molecule.[1] In this field, we have reported the synthesis, pharmacology and 3D-QSAR analysis of a number of aminoalkylbenzo[b]furanones as potential antipsychotics;[2] it is worth of mention compound **QF1004B** because of its interesting pharmacological profile.



QF1004B

As part of this study, we have investigated whether the receptor affinities of these compounds are associated with absolute stereochemistry. For this purpose, we have prepared benzofuranone **QF1004B** as single enantiomers and determined their binding affinities on D_2, 5-HT_{2A} and 5-HT_{2C} receptors. Also in this communication, we will report the synthesis, binding affinity and structure-activity relationships of novel aminoalkylbenzo[b]furanones (**I**) bearing different substituents in the furan ring.



I

Acknowledgment: We thank the *Xunta de Galicia* (Ref PGIDIT04 BTF203004PR) for the financial support.

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[1] Raviña, E.; Masaguer, C. F.; *Curr. Med. Chem.: CNS Agents* **2001***, 1,* 43.

[2] (a) Raviña, E.; Casariego, I.; Masaguer, C. F.; Fontenla, J. A.; Montenegro, G. Y.; Rivas, M. E.; Loza, M. I.; Enguix, M. J.; Villazon, M.; Cadavid, M. I.; Demontis, G. C. *J. Med. Chem.* **2000**, 43, 4678. (b) Brea, J.; Rodrigo, J.; Carrieri, A.; Sanz, F.; Cadavid, M. I.; Enguix, M. J.; Villazón, M.; Mengod, G.; Caro, Y.; Masaguer, C. F.; Raviña, E.; Centeno, N. B.; Carotti, A.; Loza, M. I. *J. Med. Chem.* **2002**, *45*, 54. (c) Dezi, C.; Brea, J.; Alvarado, M.; Raviña, E.; Masaguer, C. F.; Loza, M. I.; Sanz, F.; Pastor, M. *J. Med. Chem.* **2007**, *50 (in press).*

SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW FATTY ACID SYNTHASE (FASN) INHIBITORS

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Silvia Ortega-Gutiérrez,[a] Gemma Casals,[b] Joan Brunet,[b]
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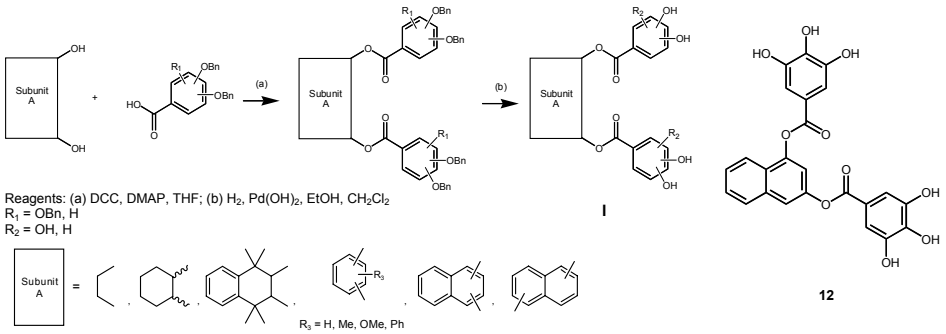
Cancer is a leading cause of death worldwide.[1] Fatty acid synthase (FASN) has been recently validated as a therapeutic target for the treatment of cancer, since inhibition of this enzyme induces apoptosis of the tumour cells without producing damages in the surrounding healthy tissue.[2]

In a project aimed at the development of new FASN inhibitors, we have designed, synthesized and characterized a new series of polyphenolic derivatives **I** that display high cytotoxic capacity (8 – 125 μM) in several tumour breast cancer cell lines (SK-Br3, MCF-7 and MDA-MB-231), and do not induce cytotoxicity in normal fibroblasts. In addition, they inhibit FASN activity confirming that their cytotoxicity is mediated by direct inhibition of this enzyme. In particular, compound **12** has shown the best properties of cytotoxicity (IC_{50} = 21 μM in SK-Br3 cells) and FASN inhibition (90%).[3]



Therefore, the new polyphenolic derivatives presented herein could constitute a novel therapeutic strategy for the treatment of cancer, one of the most widespread diseases in the world nowadays.

Acknowledgements: This work has been supported by MEC predoctoral (CT) and Juan de la Cierva (TP) fellowships, and grants SAF-2004/07103-C02-01, SAF-2007/67008-C02-01 and FIS-PI04/1417.

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P-85

ALZHEIMER'S DISEASE: THIOPHENE DERIVATIVES WITH NEUROPROTECTIVE PROPERTIES

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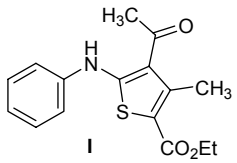
Alzheimer's disease (AD), the most widely spread senile dementia, is a neurodegenerative disorder of the central nervous system (CNS). Although its etiology remains still unclear, AD is well-known as a multifaceted disease whose main hallmarks are a deficit of cholinergic transmission, oxidative cellular damage and deposits of aberrant structures: amyloid plaques and neurofibrillar tangles.

Sporadic AD (that is, non-familial, about 97% of all the patients) is a disease of aging. Since the aging process is associated with an increase of the production of reactive oxygen species (ROS), scavengers of ROS or, in general, antioxidants, can be considerer as potentially useful compounds for the treatment of AD and other neurodegenerative diseases associated with aging.

Since more than a decade, our group is devoted to the design and synthesis of new molecules that could be useful for the treatment of AD. A series of thiophene derivatives were synthesised and evaluated as inhibitors of GSK-3β,[1] the enzyme responsible of the formation of the tangles. Then, one of them (**I**) was also checked as a neuroprotective agent against toxic insult related to oxidative stress in cell cultures of human neuroblastoma SH-SY5Y



I

In this initial screening, we found that compound **I** protected the neurons against mitochondrial free radicals. More compounds of the original series and newly synthesised analogues of that new lead compound are going to be evaluated in a near future in the same pharmacological test

Acknowledgments: The authors gratefully acknowledge the financial support of Ministerio de Educación y Ciencia (SAF2006-01249) and Comunidad de Madrid (Programa de I+D para Grupos de Investigación en Biociencias S-SAL/0275/2006), the Predoctoral Fellowship to G. C. González from CSIC (I3P program), and the Contracts in Practices to V. Gálvez and B. López-Iglesias from CSIC (I3P program).

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VIRTUAL SCREENIG OF PAMP AGAINST THE NCI DIVERSITY SET TO IDENTIFY POTENTIAL PAMP MODULATORS

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Proadrenomedullin N-Terminal 20 Peptide (PAMP) is an extremely potent angiogenic factor, able to induce neovascularization in animal models at concentrations six orders of magnitude lower than classic proangiogenic factors such as vascular endothelial growth factor (VEGF) and adrenomedullin, which makes it an attractive molecular target for angiogenesis based antitumor therapies.[1]

Its 3D structure has been recently determined in a helix-inducing trifluoroethanol and water (TFE/H_2O) solution, and in a membrane-mimetic sodium dodecylsulfate-d25 (SDS) micellar solution and deposited in the PDB with code 2FLY.[2]

Virtual Screening of PAMP by use of Autodock against the NCI diversity set, a library of compounds with nonredundant pharmacophore profiles. 32 were selected as potential modulators of PAMP activity. (**Figure 1**)

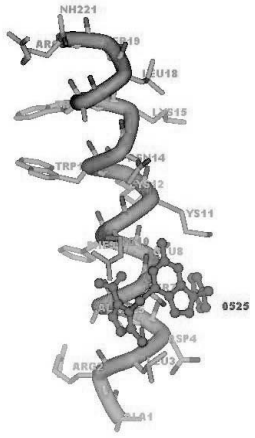

Figure 1. Compound 0525 docked into PAMP

These compounds were requested from the NCI and are currently being tested.

A competition experiment with a PAMP specific antibody in order to determine the affinity of these compounds for PAMP has been developed and all compounds have been evaluated. Five of them have demonstrated to be able to compete with PAMP antibody and are therefore potential candidates to modulate PAMP activity.

Their efficacy as antiangiogenic compounds is currently being tested in a chick aortic ring angiogenesis assay.[3]

Acknowledgment: We thank the NCI for providing us the 32 compounds. This research was supported by MEC (SAF2005-02608).

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P-87

PREDICCIÓN DEL ACLARAMIENTO DE FÁRMACOS EN HUMANOS MEDIANTE MÉTODOS QSPR

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El aclaramiento de un fármaco es un parámetro farmacocinético que aporta información sobre la capacidad del organismo para eliminar dicho fármaco. Tradicionalmente, el valor del aclaramiento de un fármaco en estudio se obtiene tras su síntesis, mediante estudios in vitro e in vivo, que son largos y con un coste económico elevado. No obstante, el aclaramiento del fármaco en humanos no se conoce hasta después de realizar el primer ensayo clínico.

El objetivo de este trabajo es la obtención de una función de conectividad capaz de predecir el valor del aclaramiento de cualquier fármaco en humanos, mediante la aplicación de la topología molecular (métodos QSPR, Quantitative Structure-Property Relationship)

En el presente trabajo se ha utilizado un grupo de 125 fármacos cuyo valor de aclaramiento se ha obtenido de la bibliografía[1,2] y cuya estructura se ha caracterizado numéricamente mediante descriptores topológicos (índices de Kier y Hall, electrotopológicos, etc). Se ha realizado una regresión multilineal (MLRA) con el 80 % de los fármacos, mediante el programa estadístico BMDP donde los descriptores topológicos se relacionan con el aclaramiento del fármaco en humanos. El 20 % se restante se utiliza para validar la capacidad predictiva del mismo. El modelo de predicción se ha seleccionado atendiendo a parámetros estadísticos tales como el r^2, SE (standar error), p y Cp de Mallow.

Los resultados muestran una función con 8 índices topológicos y un coeficiente de correlación de 0.92. La validación de dicha función se realizó mediante estudios de estabilidad (cross validation (cv)) obteniéndose un r^2_{cv} de 0.8. y estudios de aleatoriedad, obteniéndose en todos los casos un r^2_{cv} inferior a 0.5 lo que indica que la función es estable y no aleatoria. Por tanto podemos concluir que la topología molecular es una herramienta muy útil en la predicción de propiedades farmacocinéticas como el aclaramiento de fármacos en humanos.

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IDENTIFICACIÓN DE NUEVOS COMPUESTOS ACTIVOS FRENTE A S.AUREUS RESISTENTE A METICILINA MEDIANTE LA APLICACIÓN DE MÉTODOS QSAR

María José Duart[a], Julia Uroz-Cervantes[a], Sara Costa-Piles,[b], Pedro A. Alemán- Lopez,[b] Luís Lahuerta Zamora,[b] Rafael V. Martin-Algarra,[b] and Gerardo M. Antón-Fos[b] (email: mjduart@umh.es)

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El *Staphylococcus aureus* resistente a la meticilina (SARM), es causa importante de infecciones comunitarias y hospitalarias, y representa un problema clínico relevante para la salud pública debido a las reducidas opciones de tratamiento[1].

El objetivo de este trabajo es diseñar un modelo topológico capaz de identificar nuevos compuestos con actividad antibiótica frente a SARM mediante métodos QSAR (Quantitative Structure Activity Relationship).

Se han seleccionado dos grupos, uno de 34 compuestos activos y otro de 30 compuestos inactivos frente a SARM[2]. A cada compuesto se le han calculado 134 descriptores topológicos, entre los que se incluyen índices de Kier y Hall, índices de carga e índices electrotopológicos[3], entre otros. Se ha realizado un análisis discriminante entre ambos grupos, mediante el programa BMDP, obteniéndose varias funciones capaces de identificar compuestos con actividad antibiótica frente a SARM. Con cada función se ha dibujado el diagrama de actividad farmacológica para establecer los límites donde la probabilidad de encontrar un activo es máxima y en base a ello se ha establecido el modelo topológico matemático.

El modelo topológico matemático diseñado permite seleccionar compuestos activos frente a SARM con una probabilidad de acierto superior al 80%. Mediante este modelo, solo aquellos compuestos que se seleccionen como potenciales activos serían sintetizados y sometidos a ensayos para poner de manifiesto dicha actividad, lo que supondría un ahorro económico y de tiempo.

Agradecimientos: este trabajo ha sido realizado gracias a la financiación de la Universidad CEU Cardenal Herrera (PRUCHB06/11 and PRUCH06/39)

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[3] Kier L.B.; Hall L.H. J. Chem. Inf. Comput. Sci, **1997**, 37, 548.

P-89

Optimized synthesis of aminooxy-peptides as glycoprobe precursors for interaction studies

Carmen Jiménez-Castells[a], Beatriz G. de la Torre[a], Ricardo Gutiérrez-Gallego[a,b] and David Andreu[a]

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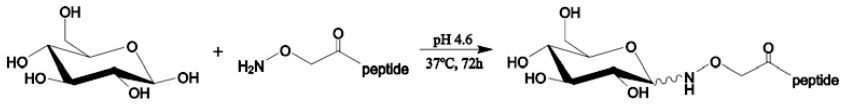
Glycosylation, the most abundant posttranslational modification of proteins, plays a key role in multiple biological recognition events, including pathogen-cell interaction. Considerable interest exists in finding reliable tools to study sugar-protein interactions, and the role of drugs interfering with such mechanisms.

Surface plasmon resonance (SPR) is one of the most powerful tools for studying sugar-protein interactions. In this technique, one of the interacting entities (protein or sugar) is immobilized onto a sensor chip surface, the other one is flown across and the resulting read-out enables both quantitation and kinetic analysis of the interaction. Of the two immobilization options, the sugar-on-chip has demonstrable advantages. We have designed an approach whereby the sugar (1) is immobilized via a peptide module (2) on the sensor surface[1]. The required glycopeptide module (3) is prepared by chemospecific oxime ligation between the reducing end of the sugar and an aminooxyacetic acid (Aoa) residue at the peptide *N*-terminus (Scheme 1).



1 **2** **3**

Scheme 1: Oxime ligation between an *N*-terminal Aoa-containing peptide and a carbohydrate ligand[1].

In this presentation we will describe an optimized synthesis of the Aoa peptide which circumvents overacylation of the NH-O nitrogen leading to undesired heterogeneity[2]. By avoiding base-containing activation mixtures which cause overacylation, our method[3] practically suppresses the unwanted side reaction and leads to near-quantitative yields of highly homogeneous Aoa-peptides, useful as glycoprobe precursors in glycomic studies.

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OBTENCIÓN DE POLIOXACICLOS POR OXIDACIÓN DEL FURANO

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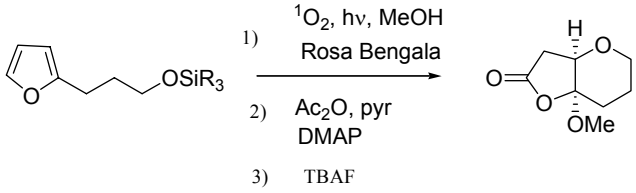
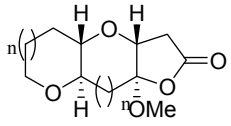
Nuestro grupo de investigación ha desarrollado una metodología sintética de formación de éteres cíclicos, que se basa en la oxidación del furano por el oxigeno singlete y posterior ciclación por adición de Michael intramolecular.[1]



Se han determinado los aspectos estereoquímicos del método así como sus limitaciones en cuanto al tamaño del anillo formado.[2]

En esta comunicación se describe la aplicación de esta metodología a la síntesis de los polioxaciclos **I** y **II**, precursores de un gran número de compuestos biológicamente activos.



I n = 1

II n = 2

Agradecimientos: Al Ministerio de Educación y Ciencia por la concesión del proyecto CTQ2007-61788 y a la Xunta de Galicia (PGIDIT04BTF301031PR)

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P-91

PREPARACION DE LIQUIDOS IONICOS Y SU APLICACIÓN EN SINTESIS ORGANICA

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Los líquidos iónicos (LIs)[1] están constituídos por sales que contienen al menos un componente orgánico y presentan un punto de fusión inferior a 100 ºC. Las sales más habituales contienen un catión 1,3-dialquilimidazolio, aunque también abundan los cationes alquilamonio, alquilfosfonio, N-alquilpiridinio o N,N-dialquilpirrolidinio entre otros . Generalmente, el empleo de los LIs como disolventes aumenta la velocidad de reacción y la selectividad. Además, se pueden reutilizar, abaratando así los costes y pueden sustituir a los disolventes orgánicos tradicionales que son volátiles y muy contaminantes. Por otra parte, los líquidos iónicos quirales que hicieron su aparición hace unos cinco años, descubrieron un campo totalmente nuevo en la síntesis asimétrica de compuestos con potencial actividad biológica.

El gran interés que los LIs han despertado en la comunidad científica queda reflejado en el aumento exponencial de artículos aparecidos durante los últimos diez años en revistas especializadas; menos de 50 en 1995 y más de 1500 artículos sobre LIs en el año 2004 (**Fig. 1**).

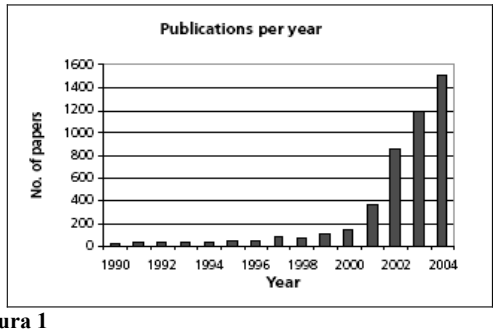

Figura 1

En esta comunicación presentamos los últimos resultados obtenidos por nuestro grupo de investigación en el uso de los líquidos iónicos como disolventes, catalizadores de reacciones o como soporte de reactivos.

Agradecimientos: Al Ministerio de Educación y Ciencia por la concesión del proyecto CTQ2007-61788 y a la empresa Green Solutions Chemicals, S.L. por el suministro de líquidos iónicos.

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Novel Multipotent Tacrine-Dihydropyridine Hybrids with Improved Acetylcholinesterase Inhibitory and Neuroprotective Activities as Potential Drugs for the Treatment of Alzheimer's Disease

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[b]*Instituto Teófilo Hernando, Departamento de Farmacología y Terapéutica, Facultad de Medicina, UniVersidad Autónoma de Madrid, C/Arzobispo Morcillo 4, 28029 Madrid, Spain,*
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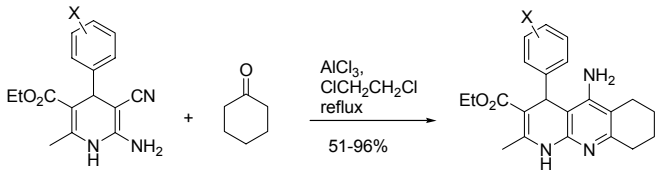
Alzheimer's disease (AD) is an age-related neurodegenerative disease characterized by progressive memory loss, decline in language skills, and other cognitive impairments. Although the etiology of AD is not well-known, there are diverse factors such as amyloid-β (Aβ) deposits, β-protein aggregation, oxidative stress, and low levels of acetylcholine (ACh) that are thought to play significant roles in the disease.

The cholinergic theory of AD suggests that the selective loss of cholinergic neurons in AD results in a deficit of ACh in specific regions of the brain that mediate learning and memory functions. The primary approach for treating AD has therefore focused on increasing the levels of acetylcholine in the brain by using acetylcholinesterase inhibitors (AChEI) such as tacrine, donepezil, galantamine, and rivastigmine. On the other hand, it is well-known that Ca^{2+} overload is the main factor initiating the processes leading to cell death. Several lines of evidence show that calcium dysfunction, involved in the pathogeny of AD, augments Aβ formation and τ hyperphosphorylation. Ca^{2+} entry through L channels causes calcium overload and mitochondrial disruption, which lead to the activation of the apoptotic cascade and cell death. Hence, blocking the entrance of Ca^{2+} through this specific subtype of Ca^{2+} channel could be a good strategy to prevent cell death.

Scheme 1. Synthesis of New Tacrine-DHP Hybrids.



(X= H, 4-F, 2-NO_2, 3-NO_2, 4-NO_2, 4-Me, 2-OMe, 3-OMe, 4-OMe)

In this work we describe the synthesis and biological evaluation of the tacrine-1,4-dihydropyridine (DHP) hybrids (**3**-**11**). These multipotent molecules are the result of the juxtaposition of an acetylcholinesterase inhibitor (AChEI) such as tacrine (**1**) and a 1,4-DHP such as nimodipine (**2**). Compounds **3**-**11** are very selective and potent AChEIs and show an excellent neuprotective profile and a moderate Ca2+ channel blockade effect.

Consequently, these molecules are new potential drugs for the treatment of Alzheimer's disease.

SINTESIS Y EVALUACION BIOLOGICA DE NUEVOS SISTEMAS [4,1,0] COMO INHIBIDORES DE iNOS

Irene Suarez del Villar,[a] Ana Gradillas,[a] Ricardo Martinez-Murillo,[b] Alfredo Martinez Serrano,[b] and Javier Pérez-Castells[a]*

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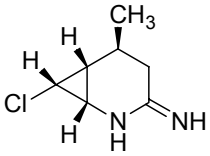
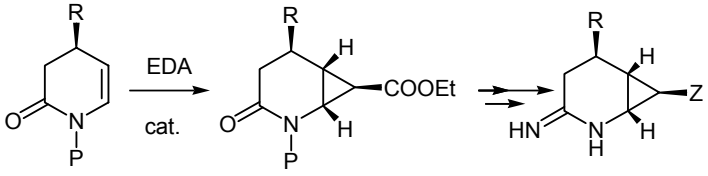
A finales de los noventa se describió el derivado amidínico cíclico denominado ONO-1714 como novedoso inhibidor selectivo de la isoforma iNOS humana que juega un papel importante en diversos trastornos tales como el choque séptico, la artritis reumatoide o la enfermedad inflamatoria intestinal. También se ha demostrado su implicación en enfermedades como el Parkinson o el cáncer.



ONO-1714

Al tratarse de un compuesto de reciente descubrimiento y poseer una estructura muy diferente a la de los otros iNOS conocidos, hasta ahora existen pocos derivados descritos y apenas se han efectuado estudios de Relación Estructura Actividad con inhibidores de esta enzima.

Para conocer nuevos aspectos acerca de la actividad inhibitoria frente a las diferentes isoformas de NOS, recientemente hemos puesto ha punto una reacción de ciclopropanación estereoselectiva como base para la síntesis de nuevos sistemas bicíclicos potencialmente activos. La aproximación sintética es novedosa y permite el acceso a una amplia familia de derivados.



En la presente comunicación se describe la síntesis de nuevos derivados de ONO-1714 y los primeros datos de actividad inhibitoria frente a la isoforma inducible iNOS y datos de actividad antiproliferativa frente a diferentes líneas tumorales. Los valores obtenidos permitirán en un futuro explorar los requisitos estructurales mínimos necesarios para esta familia de inhibidores de iNOS.

Agradecimientos: Financiación de este proyecto por el MEC (proyecto CTQ2006-00601/BQU). ISV. agradece a la FUSP-CEU una beca predoctoral.

COPPER COMPLEXES OF AZAPIRIDOPHANES AS SOD MIMICS

Enrique García-España,[a] Belen Abarca,[b] Raquel Belda,[a] Begoña Verdejo,[a] Conxa Soriano,[b] Salvador Blasco,[a] Jorge González,[a] José Miguel Llinares,[a] Carmen Terencio.[c]

a) Departament de Química Inorgànica, Instituto de Ciencia Molecular, Facultat de Química,Universitat de València. b) Departament de Química Orgànica, Facultat de Farmàcia, Universitat de València. c) Departament de Farmacología, Facultat de Farmàcia, Universitat de València

Aerobic organisms use atmospheric oxygen as metabolic oxidant to produce energy for their living processes. However the reduction of O_2 to water originates reactive radical species as intermediates. Living organisms need to develop defence mechanisms to remove these radical species or to convert them into useful chemicals for metabolic purposes.

Superoxide dismutase enzyme (SOD) has the role to protect cells from the damage caused by superoxide radical. Under normal conditions in organisms, free radicals are trapped by SOD present in mitochondria, blood, or in the extracellular space, but when there is overproduction of radicals the defence control mechanisms becomes problematic.

The use of SOD in therapy is limited by its short plasma half-life and inability to penetrate cell membranes. Low molecular mass mimics of SOD are therefore of much interest as potential pharmaceuticals.[1234]

We have prepared a series of cyclic polyaminepyridine compounds and their complexes of Cu(II), Zn(II) with imidazolate bridge, and we have studied their behaviour as SOD mimics. We should like to report our results here.

SOD like activity has been determined by the nitroblue tetrazolium (NTB) method, and calculated the IC_{50}. Assays in vitro have been performed with PMA-stimulated polymorphonuclear leucocytes (PMNL). SOD like activity is determined by the luminol enhaced lumuniscence inhibition.

Acknowledgements: Financial support from Ministerio de Educación y Ciencia (projets BQU2003-09215-CO1 and BQU2003-09215-C03) is gratefully acknowledged.

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P-95

NUEVA ACTIVIDAD ANTI-H1 DE LA VITAMINA D2

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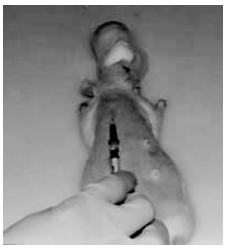
Nuestro grupo de investigación diseñó un modelo topológico-matemático capaz de predecir la actividad antihistamínica de un compuesto.[1] Este modelo, se obtuvo utilizando el análisis lineal discriminante y funciones de conectividad en las que se incluyen diferentes descriptores topológicos, y ha demostrado su eficacia en la búsqueda de nuevos compuestos con actividad antihistamínica[2].

En la búsqueda de esta propiedad sobre compuestos conocidos, el ergocalciferol (vitamina D_2) apareció como potencial antihistamínico. El papel que juega la vitamina D en el metabolismo es complejo, y esta actividad antihistamínica H1 no ha sido descrita hasta el momento, por lo que se decidió realizar los correspondientes ensayos farmacologicos *in vivo* para evaluarla.

Para estudiar la actividad anti-H1 se siguió el procedimiento de Watanabe y col, optimizado por nuestro grupo de investigación.[1,3] Se utilizaron ratas albinas hembra de raza Wistar, con peso comprendido entre 190-220 g. Los productos se prepararon en atmósfera inerte y se administraron vía oral mediante sonda esofágica, utilizando como vehículo metilcelulosa en disolución acuosa al 0.5 % y por vía intravenosa albúmina marcada con fluoresceína (F-BSA). Posteriormente se administró vía intradérmica histamina en el dorso del animal y 30 minutos después se procede al sacrificio del animal, para recortar las zonas edematosas y medir utilizando un fluorímetro la cantidad de albúmina-fluoresceína extravasada. Se eligió como fármaco de referencia terfenadina, según se describe en la bibliografía.



En la presente comunicación se muestra que la vitamina D tiene una actividad antihistamínica H1 comparable a terfenadina.

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SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIP OF 3-FURYL AND 3-THIENYLQUINOXALINE-2-CARBONITRILE 1,4-DI-*N*-OXIDE DERIVATIVES AGAINST *PLASMODIUM FALCIPARUM*

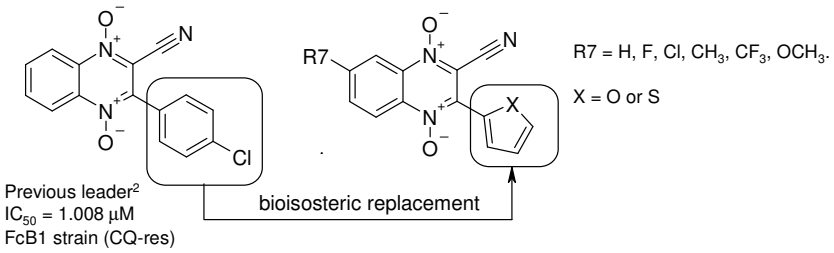
Esther Vicente[a,b], Saioa Ancizu[a], Asunción Burguete[a], Beatriz Solano[a], Raquel Villar[a], Emily Bongard[b], Sarah Charnaud[b], Silvia Pérez-Silanes[a], Ignacio Aldana[a], Livia Vivas[b] and Antonio Monge[a]

[a] *Unidad en Investigación y Desarrollo de Medicamentos, Centro de Investigación en Farmacobiología Aplicada (CIFA), Universidad de Navarra, 31080, Pamplona. Spain.* [b] *Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine (LSHTM), Keppel Street, London WC1E 7HT, United Kingdom*

Malaria is by far the world's most important tropical parasitic disease. Mortality, currently estimated at over a million people per year, has risen in recent years, probably due to increasing resistance to antimalarial medicines. [1]

As a continuation of our research in 3-phenylquinoxaline 1,4-di-*N*-oxide[2] and with the aim of obtaining new antimalarial agents which can improve the currently available treatments, new series of 3-(2-furyl) and 3-(2-thienyl)quinoxaline-2-carbonitrile 1,4-di-*N*-oxide derivatives have been synthesized following the classical Beirut reaction. Antiplasmodial activity was evaluated *in vitro* against *Plasmodium falciparum* (chloroquine-sensitive, 3D7, and chloroquine-resistant, K1, strains) by the incorporation of [^{3}H]-hypoxanthine. Cytotoxicity was tested in KB cells using the Alamar Blue assay.

Twelve compounds were synthesized and evaluated for antimalarial activity. Eight of them showed a IC_{50} lower than 1 μM against both 3D7 and K1 strains. Six of the eight products tested for cytotoxicity demonstrated good selectivity and are now in more advanced studies. Their potency and selectivity make them valid leads for synthesizing new compounds that possess better activity.



Acknowledgements: We wish to thank the Ministerio de Educación y Ciencia (Grant AP2003-2175 to Esther Vicente) and the University of Navarra (PiUNA project).

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P-97

CHIRAL OXIRANES FROM CARBOHYDRATE DERIVATIVES AS PRECURSORS: STEREOSELECTIVE SYNTHESIS OF ISOSERINE ANALOGUES

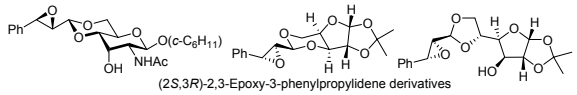
Felipe Alcudia González, Fernando Iglesias-Guerra, Margarita Vega Holm, Mª Luisa Martínez Gómez, Ignacio Periñán Domínguez, José M. Vega-Pérez

Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, c/ Profesor García González, nº 2. 41002 Sevilla, Spain. falcudia@us.es

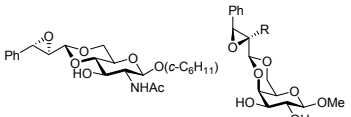
Isoserine derivatives constitute the essential fragment in natural products of high therapeutic value, such as taxol (an anti-cancer agent), bestatin (a dipeptide modifier of the immune response), and the kinostatins (potent inhibitors of the HIV-1 protease). Due to the β-aminoalcohol properties of these compounds, one procedure for their synthesis is regio- and stereoselective opening of chiral oxiranes with amines.

Our group has been using carbohydrate derivatives as chiral templates in the stereoselective synthesis of different compounds. Recently we have developed a method for the stereoselective epoxidation of olefins. The aim was to obtain the chiral oxiranes on a skeleton that could be transformed easily into modified isoserines. The olefinic chain was joined to the sugar moiety via an acetalic bond in order to be easily separated from the chiral inductor.

Cinnamal acetals from different carbohydrate derivatives were epoxidized with *m*-CPBA. High diastereoisomeric excess were obtained. The major oxirane configuration obtained depends on the sugar moiety used as chiral inductor in each case.

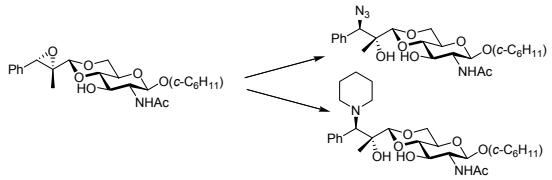


(2*S*,3*R*)-2,3-Epoxy-3-phenylpropylidene derivatives



(2*R*,3*S*)-2,3-Epoxy-3-phenylpropylidene derivatives

The ring-opening reaction of these oxiranes with different nitrogen nucleophiles gave compounds (in good yields and diastereoisomeric excesses) with an α-hydroxy-β-aminoacetal structure, and can be used as precursors of phenylisoserine analogues.



We are also developing epoxidation reactions employing chiral dioxiranes generated *in situ* from different sugar derivatived ketones and Oxone®. To test their abilitiy as chiral catalysts we performed the reaction of non chiral alkenes with these ketones. Good enantiomeric excesses were obtained. The following step is the application of this methodology on different cinnamal acetals (sugar and hydrobenzoin derivatives). We hope that double asymmetric induction generated improves the diastereoisomeric excesses first reported.

ANALYSIS OF MOE´S ABILITY TO REPRODUCE THE BIOACTIVE CONFORMATION OF PROTEIN-BOUND LIGANDS

Jessica Opacic, Leonardo Pardo, Mercedes Campillo

Laboratori de Medicina Computacional, Unitat de Bioestadística, Facultat de Medicina, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain

A pharmacophore definition is known as the first essential step toward understanding the interaction between a receptor and a ligand and is clearly established as one of the successful computational tools in rational drug design. A critical step in pharmacophore generation is the correct conformational analysis of the ligand that must include the bioactive conformation, which is the geometry adopted by the ligand when it binds the receptor.

The aim of this work is to evaluate the ability of MOE (Molecular Operating Environment) to reproduce the conformation of protein-bound ligands. The stochastic search, systematic search and conformational import procedures of MOE with five recommended forcefields for small ligands (MMFF94, MMFF94s, MMFF94x, OPLSAA, and TAFF) and three different solvation models (born, gas phase and distance) were tested. In addition, the ability to generate conformation ensembles in MOE was compared to other programs (Catalyst and OMEGA). We have followed the approach developed previously by others[1]. Thus, the generated conformation ensembles were superimposed on X-ray crystallographic ligands from protein-ligand complexes extracted from the Protein Data Bank. Root mean square deviation was used as a measure of the likeness. All methods gave reasonable results but the systematic search was the best one. On the other hand the systematic search generates enormous amount of conformations which can be very time consuming when using them further in other analyses. Furthermore, MOE proved to be dependent on the input conformation and had difficulties generating the bioactive conformation when the number of rotatable bonds increased.

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P-99

SYNTHESIS AND LARVICIDAL ACTIVITY OF NAPHTHOQUINONES AGAINST *AEDES AEGYPTI*

María Teresa Molina[a*], Eulogio López-Montero[a], Karlos A. L. Ribeiro[b], Antônio Euzébio G. Santana[b], Marília O. F. Goulart[b*]

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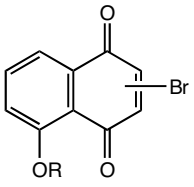
[b]*Instituto de Química e Biotecnologia, Universidade Federal de Alagoas, Maceió, Alagoas, 57072-970, Brazil*

Mosquitoes are responsible for the spread of more diseases than any other group of arthropods. Of particular interest is *Aedes aegypti* because of its role as a vector for the arboviruses responsible for yellow fever and dengue fever, both of which are endemic to Central and South America, Asia and Africa[1].
Quinones have been extensively studied due to their biological activity (especially antitumoral) and some anthraquinones such as emodin have displayed larvicidal activity against three mosquito species[2]
In this work we have examined the larvicidal activity against *Aedes aegypti* of two series of naphthoquinones: halonaphthoquinones (I), prepared in several steps from juglone, and lapachol derivatives (II).



I

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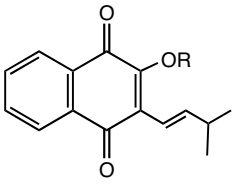

II

R = H, Li, Ac

Several synthetic naphthoquinones were significantly active larvicides (LD_{50} < 5 ppm and < 10mM). The most active compounds proved to be the bromo derivatives of juglone.
The present results reinforce the potential use of substituted hydroxyquinones and halogenated quinones as very promising leads against 4th instar larves of *Aedes aegypti*, the vector of dengue.

Acknowledgements: We thank DGICYT (Spain), grant BQU2003-00813, CSIC-CNPq (2005BR0046), and CAPES (Brazil)

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CHIRAL SULFINAMIDES AS ORGANOCATALYSTS IN THE ALLYLATION OF ACYL HYDRAZONES.

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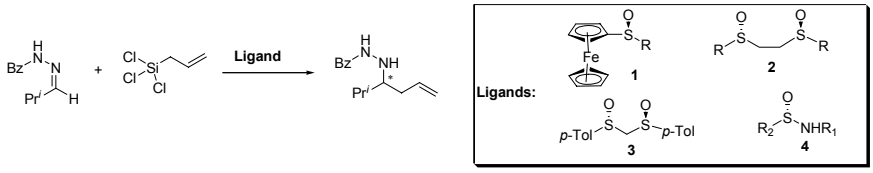
The development of efficient methods for the synthesis of chiral sulfoxides at the beginning of the nineties has broadened their application to new processes of carbon-carbon, and carbon-heteroatom processes.[1] Recent interesting applications include *inter alia* the utilization of sulfoxides as chiral ligands or ligands precursors in metal catalyzed asymmetric reactions, in coordination chemistry and as Lewis base in organocatalysis. On the other hand, due to the importance of chiral amines which account for the 75% of the total drugs or drug candidates, their preparation has been a standing area of interest in the last decades. Our group has recently shown that chiral sulfoxides are excellent organocatalysts in the allylation of hydrazones with trichloroallyl silane *en route* to allyl amines.[2] Accordingly, excellent enantioselectivities were obtained in the allylation of benzoyl hydrazones using simple sulfoxides, though up to 3 equivalents of the organocatalysts were necessary. In order to determine the mechanism of the reaction and to develop a catalytic approximation of the process, we have recently applied as ligands a range of sterically and electronically diverse monodentate and bidentate sulfoxides obtained by the DAG method. Opportunely, using C_2-symmetric bis-sulfoxide **2**, excellent enantioselectivities were obtained in the presence of only 1 equivalent of the ligand.[3]



In the present communication we present our preliminary results on the enantioselective allylation of hydrazones, using enantiomerically pure sulfinamides **4** as organocatalysts. Taking into account the electronic feature of the S-O bond in sulfinamides, a better catalytic activity is predicted, as a consequence of an enhanced coordination between the silane an the ligand. It is worth mentioning that the modular approach developed for the synthesis of the sulfinamides, will allow a rapid optimization of the electronic and steric substituents both on the sulfur and on the amide function.

Acknowledgements: We thank the Dirección General de Investigación Científica y Técnica (Grant No. CTQ2006-15515-CO2-01 and CTQ2004-01057). V. V. and A. A. thank the CSIC and MEC for a I3P predoctoral grant and a Ramón y Cajal Contract, respectively.

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P-101

PEPTIDOMIMÉTICOS β-LACTÁMICOS COMO MODULADORES ALOSTÉRICOS DE LOS RECEPTORES DOPAMINÉRGICOS D_2

Claudio Palomo [a], Jesús M. Aizpurua [a], Azucena Jiménez [a], Raluca M. Fratila [a], Ane M. Gabilondo [b], J. Javier Meana [b]

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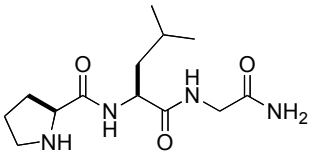
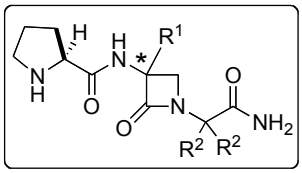
[b] *Dpto. Farmacología, Facultad de Medicina, Universidad del País Vasco, 48940 Leioa, Vizcaya.*

La L-propil-L-leucilglicinamida (PLG o melanostatina) es un tripéptido hipotalámico que actúa como modulador alostérico de los receptores dopaminérgicos D_2 facilitando su interacción con ligandos agonistas mediante la adopción de una conformación bioactiva presumiblemente β-girada[1]. Nuestro grupo ha descrito recientemente una síntesis de β-lactamas via aziridina que permite acceder a moldes ("scaffolds") mono, di- y trisustituídos que estabilizan un giro β en torno al anillo β-lactámico. [2, 3]

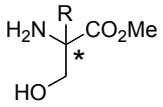
Ahora comunicamos la preparación de los nuevos compuestos β-lactámicos **1** miméticos de la PLG. La síntesis se llevó a cabo de manera totalmente estereocontrolada y con buenos rendimientos globales a partir de los serinatos α-sustituidos **2**.



PLG



1 (R^1= ^{i}Bu, Bn, CH_2-CH=CH_2); (R^2= H, Me)



2

La capacidad de estos análogos como moduladores alostéricos de receptores dopaminérgicos D_2 se evaluó mediante experimentos de competición de fijación del radioligando antagonista selectivo [^{3}H]-espiperona por el fármaco agonista (-)N-propilnorapomorfina [(-) NPA] en membranas de cerebro humano postmortem.

Tanto la PLG como algunos de los miméticos β-lactámicos incrementaron la afinidad del agonista (-)NPA por el estado de alta afinidad del receptor D_2 de 40 a 134 veces a concentración 1 μM. Los resultados obtenidos reflejan una mayor capacidad moduladora de los nuevos peptidomiméticos frente a la melanostatina, siendo el análogo **1**-(**R*), [R^1= ^{i} Bu; R^2= Me] el que mayor efecto presentó.

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LA VÍA DEL METILERITRITOL FOSFATO DE BIOSÍNTESIS DE ISOPRENOIDES COMO DIANA PARA EL DISEÑO DE NUEVOS ANTIBIÓTICOS Y ANTIMALÁRICOS

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La vía del metileritritol fosfato (MEP) de biosíntesis de isoprenoides es una de las dianas más prometedoras para el desarrollo de nuevos antibióticos y antimaláricos[1]. Esta vía metabólica está presente en la gran mayoría de las bacterias patógenas y en el agente causal de la malaria, *Plasmodium falciparum*, pero ausente en los seres humanos. El bloqueo de la vía del MEP en alguna de sus etapas por parte de un determinado compuesto podría inhibir el crecimiento bacteriano y del parásito sin afectar al organismo huésped, por lo que dicho compuesto podría presentar actividad antibiótica y antimalárica.

Hasta el momento se ha comprobado la acción quimioterapéutica de la fosmidomicina y compuestos análogos en microorganismos y *P.falciparum*. Dichos compuestos inhiben la enzima desoxixilulosa 5-fosfato reductoisomerasa que cataliza la segunda etapa de la vía del MEP. La fosmidomicina que actúa como inhibidor de la enzima DXR de microorganismos inhibe también a la enzima de *P.falciparum* y lo que es más importante actúa también sobre el parásito intacto (IC_{50}~370nM)[2].

Para proceder al diseño racional de inhibidores de una determinada etapa de la vía del MEP es necesario disponer de información estructural sobre la enzima que cataliza dicha etapa así como de métodos específicos y fiables para determinar su actividad. Actualmente se ha resuelto la estructura atómica de las cinco primeras enzimas de la vía del MEP y en nuestro grupo de investigación disponemos de métodos automatizables para la determinación de su actividad. A partir de estas herramientas estamos procediendo al diseño de inhibidores de enzimas de la vía del MEP mediante técnicas de modelización molecular y a la validación funcional de los mismos.
En esta comunicación se presentan algunos de los resultados obtenidos así como de los proyectos en fase de realización.

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LABELING OF LIGANDS FOR THE STUDY OF SEROTONIN 5-HT$_{1A}$ AND 5-HT$_6$ RECEPTORS

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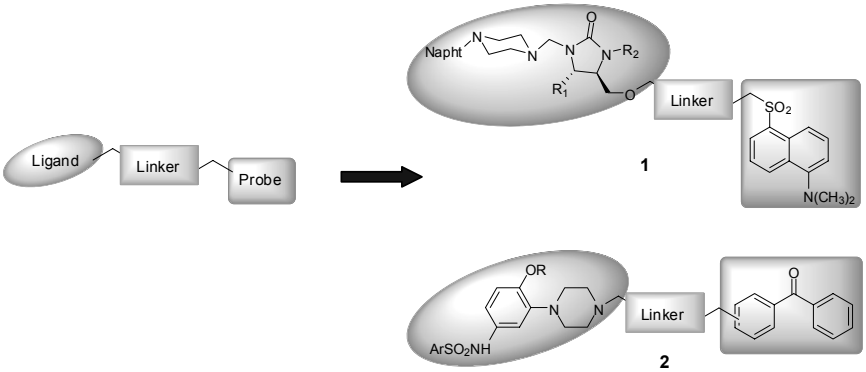
The complete sequentiation of human genome has provided an enormous amount of molecular information on the relationship between the genes and the proteins they codify. This repertoire of proteins, called the proteome, is the responsible for the correct function of the cells. Moreover, alteration of their activity is responsible for a wide range of disorders. For that reason, it is necessary to develop tools that enable the direct study of the proteome in order to discover new targets and drugs.[1]

Taking into account our experience on serotonin receptors,[2] we have started the development of 5-HT$_{1A}$ (**1**) and 5-HT$_6$ (**2**) ligands coupled with different molecular probes. The use of crosslinking and fluorescent techniques[3] of these molecular entities will allow us to obtain structural information about the receptor-ligand interaction.



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DISEÑO, SÍNTESIS Y ACTIVIDAD BIOLÓGICA DE ESPIRODERIVADOS INHIBIDORES DE RHO-KINASAS

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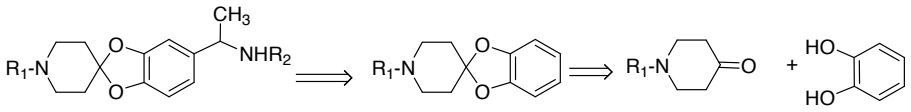
La Rho-quinasa desempeña un papel importante en la regulación de la presión arterial y en la contracción de la musculatura lisa vascular. Diversos agonistas de los receptores acoplados a la proteína G de la membrana celular como, por ejemplo, la angiotensina II activan la Rho, que acaba activando la Rho-quinasa.[1-2]

Al activarse Rho-cinasa por Rho se fosforila la fosfatasa de la cadena ligera de miosina, con lo cual esta fosfatasa es inhibida favoreciendo la contracción de las células musculares lisas vasculares, la formación de fibras de estrés y la migración celular. Así, la activación de Rho y de Rho-quinasa tiene efectos importantes en diversas enfermedades cardiovasculares.



En este trabajo se presentará la síntesis i los resultados de la actividad biológica de una serie de nuevos inhibidores de la Rho-quinasa con estructura de espirobenzodioxolo-piperidina.

Los inhibidores de esta vía son de utilidad para el tratamiento de las enfermedades cardiovasculares (y otras no cardiovasculares) entre ellas la hipertensión arterial, la hipertensión pulmonar, el espasmo cerebral y coronario y la disfunción eréctil.

Agradecimientos: A la Universidad de Barcelona por la Ayuda ACES-2006 y ACES-2007.

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P-105

HYBRIDS INDOLOQUINOLIZIDINE-PEPTIDE AS DUAL LIGANDS FOR DOPAMINE AND ADENOSINE RECEPTORS

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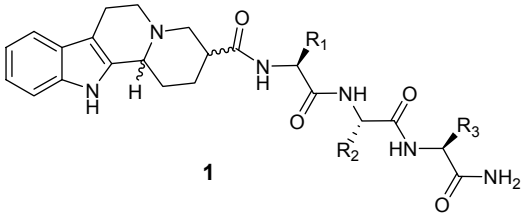
The application of a multiple ligand approach is a new trend in medicinal chemistry and it is especially true for disorders in which the alteration of a single receptor is therapeutically insufficient.[1] A relevant example is Parkinson's disease (PD), where balanced modulation of dopamine and adenosine receptors showed promising efficacy and fewer side effects than single-target dopamine treatments.[2] Previous satisfactory results based on the synthesis and evaluation of hybrids alkaloid-peptide[3] led to the design of novel indoloquinolizidine-peptide compounds (**1**) as multiple ligands for both dopamine and adenosine receptors. In the present work, we report the synthesis of indolo[2,3-*a*]quinolizidines (**2**) and its derivatization with several tripeptides. The biological evaluation of **1** revealed their capacity to interact selectively with some subtypes of dopamine (D_1 and D_2) and adenosine (A_{2A}) receptors, indicating that these molecules are useful tools to evaluate adenosine-dopamine cross-talk mechanisms and to test the potential of multiple ligands in the treatment of PD.



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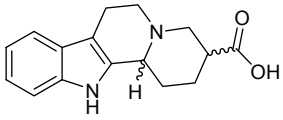

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DESIGNED MULTIPLE LIGANDS: PYRAZOLE CARBOXAMIDE DERIVATIVES WITH CB_1 CANNABINOID AND μ OPIOID PROPERTIES

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The CB1 cannabinoid and μ opiod receptors are implicated in important pharmacological responses and in several diseases like drug dependence and pain. The interactions between both systems have been studied in detail.[1] It has been shown that both receptors are co-expressed in the same cells. Moreover, there are evidences that they form heterodimers.[2]

Taking into account the state of the art, it was envisaged to design and study multiple ligands which bind to both receptors. The new synthesized compounds[3] are structurally related to the opioid fentanyl and the cannabinoid rimonabant. The two pharmacophoric parts are separated by aliphatic, cycloalkyl or aromatic linkers (Figure 1).

Even though the CB1 receptor binding affinity of these compounds lies in micromolar range, they showed potent inverse agonist activity. In [^{35}S]GTPγS binding assays on membrane of post-morten human frontal cortex they were even more potent than the reference compound rimonabant.

In vivo cannabinoid properties were characterized on the basis of behavioural effects in mice using the cannabinoid tetrad assays. They showed ability to antagonize the effects of the agonist WIN55212-2. The opioid properties were evaluated in hot plate test. They acted as μ opioid antagonists.

Opioid and cannabinoid antagonist have already shown to be of interest in drug dependence treatment. Therefore, the dual antagonism of the new compounds suggest a therapeutical application for opiate dependent patients.

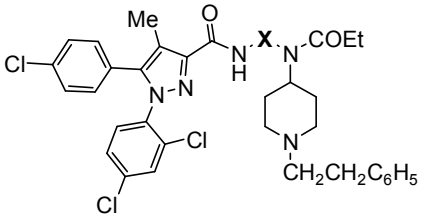

Figure 1

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P-107

ESTUDIO FARMACOLÓGICO DE LAS OXIMAS, SÍNTESIS Y CARACTERIZACIÓN DE LA 1,2-CICLOPENTANONAMONOXIMA (b) Y 1,2- CICLOPENTANODIOXIMA (c)

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Las oximas tienen actividad farmacológica de enorme interés, sustancias como la bifenilcarbaldehido oxima presenta una enorme selectividad por el receptor estrógeno (ER)[1]. Se ha probado la eficacia de Milbemicinoxima administrada en combinación con Praziquantel contra el deterioro cardiaco inducido experimentalmente en gatos infectados con Dirofilaria Immitis. Se han obtenido derivados de oximas y se ha estudiado su capacidad para inhibir la serotonina (SERT) y dopamina (DAT) transportadores especificos a nivel de la corteza de los conejos y las membranas estriadas respectivamente. Se ha realizado síntesis de dioximas por ultrasonido y transferencia de fase catalizada [2]

Esquema de obtención de las oximas (b) y (c)

2-carbetoxiciclopentanona **(a)**

Tabla I **Caracterización espectroscópica**

[1]H-RMN δ [ppm a partir de las bandas del agua (b) y (c)]
[13]C-RMN (δ, ppm a partir del TMS)

b	$-CH_2-CH_2-$	2.50	Compleja	-------	8.7	4
	$-CH_2-$	1.61	Compleja	-------	4.2	2
c	$-CH_2-CH_2-$	2.30	Triplete	-------	2.40	4
	$-CH_2-$	1.10	Quíntuple te	-------	1.30	2

		Calculado		Experimental				
				Piridina		**DMSO**		
(c)	**C-1**	157.70		157.67		158.04		
	C-2	25.04		28.05		28.63		
	C-3	24.00		20.46		21.07		

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SYNTHESIS OF UNNATURAL AMINO ACIDS

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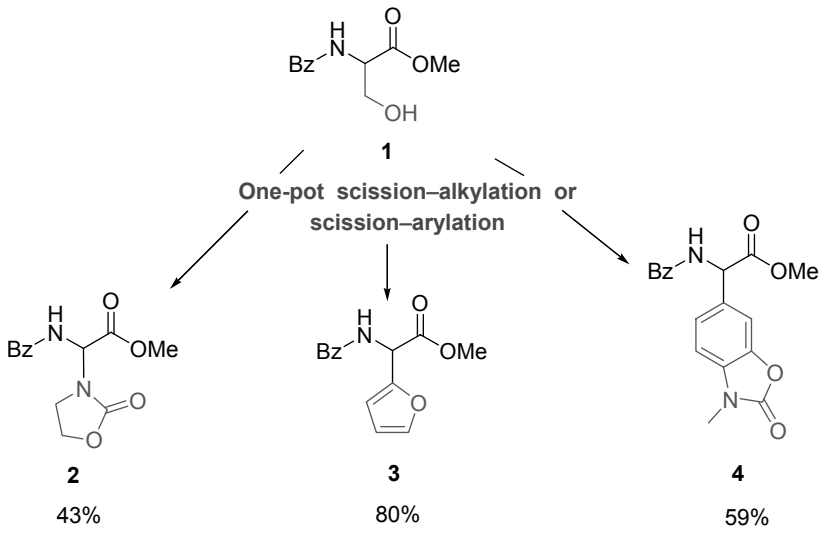
Non-proteinogenic amino acids are important building blocks in the synthesis of alkaloids, peptides, and other biologically active products.[1] Thus, they are components of glycopeptide and β-lactam antibiotics, glutamate antagonists, and other drugs. Besides, these amino acids have been incorporated into peptides to modulate their activity, and to improve their hydrolytic stability or bioavailability. As a result, the methods to prepare these amino acids have deserved much interest.

We report here an efficient route which allows the direct conversion of serine derivatives **1** into unnatural amino acids, such as **2**–**4**. The application of this reaction to the synthesis of bioactive products will be discussed.



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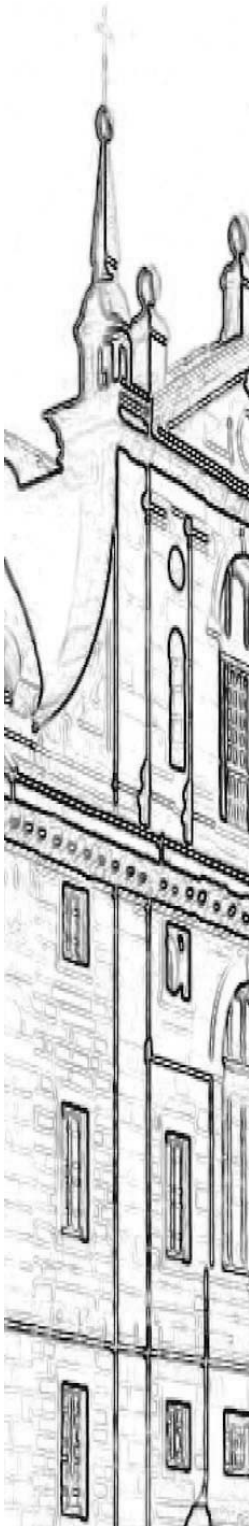

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