UNIVERSIDAD AUTONOMA DE MADRID

UNIVERSITAS COMPLUTENSIS MATRITENSIS

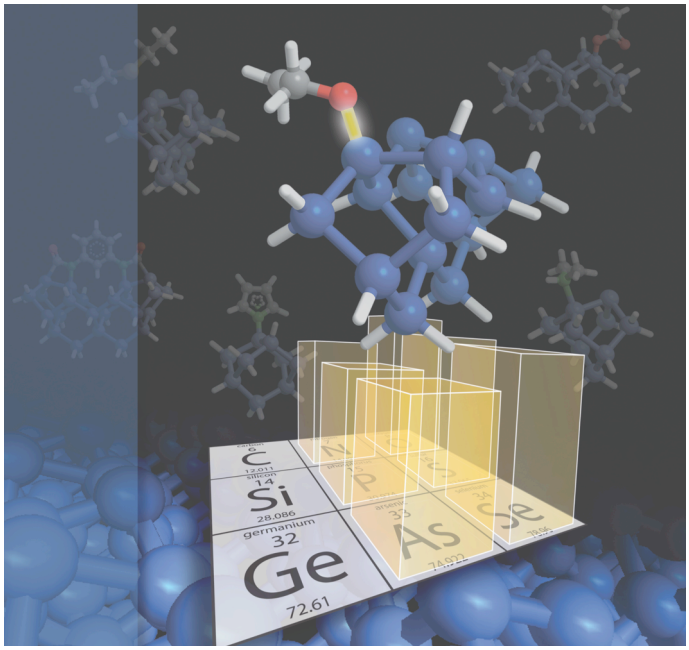
USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

MASTERQO

MÁSTER UNIVERSITARIO EN QUÍMICA ORGÁNICA

XII Simposio

Máster Interuniversitario en Química Orgánica



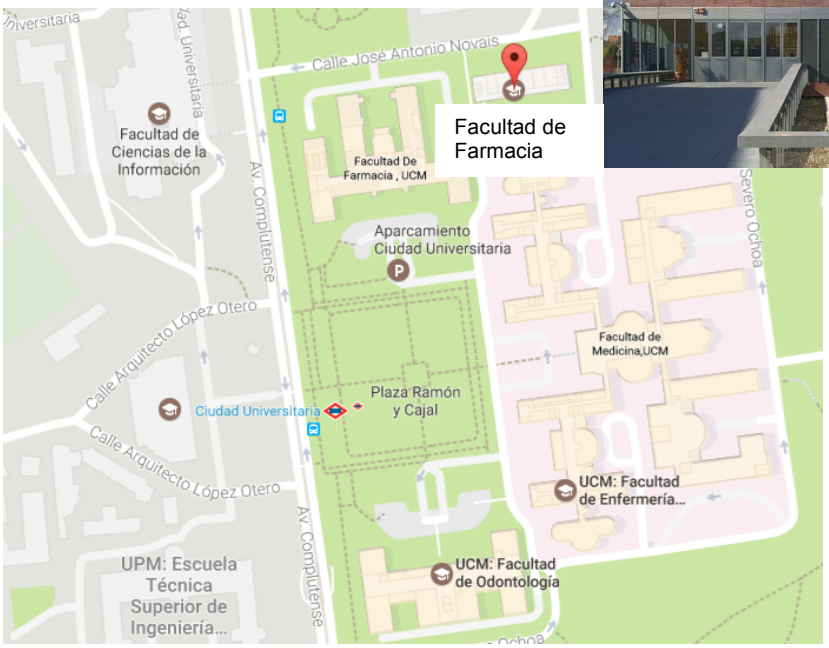
Universidad Complutense de Madrid

20 y 21 de Junio de 2019

INFORMACIÓN GENERAL

XII Simposio del Máster Interuniversitario en Química Orgánica

El Simposio tendrá lugar en el Aulario de la Facultad de Farmacia de la Universidad Complutense de Madrid. Las conferencias se impartirán en la Sala Cofares y los pósteres en la planta baja del mismo edificio.



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PROGRAMA

XII Simposio del Máster Interuniversitario en Química Orgánica

Universidad Complutense de Madrid
Aulario de la Facultad de Farmacia (Sala Cofares)

20 de Junio de 2019

12:00 Apertura
12:15 Conferencia: “Emprender desde el tubo de ensayo – El caso Gadea”.
Dr. Gerardo Gutiérrez (Fundación Gadea Ciencia)
13:30 Almuerzo
16:00 Conferencia: “Armas químicas”
Dr. Miguel Ángel Sierra (UCM)
17:30 Pausa Café
17:40 Sesión de Pósteres I (P1-P34)

21 de Junio de 2019

9:30 Sesión de Pósteres II (P35-P54)
11:30 Pausa Café
12:00 Conferencia: “La influencia en la cultura de la Tabla Periódica”
Dra. Pilar Goya (IQM, CSIC)
13:30 Almuerzo
16:00 Sesión de Pósteres III (P55-P66)
17:30 Clausura

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ABSTRACTS

SÍNTESIS DE REDES ORGÁNICAS COVALENTES

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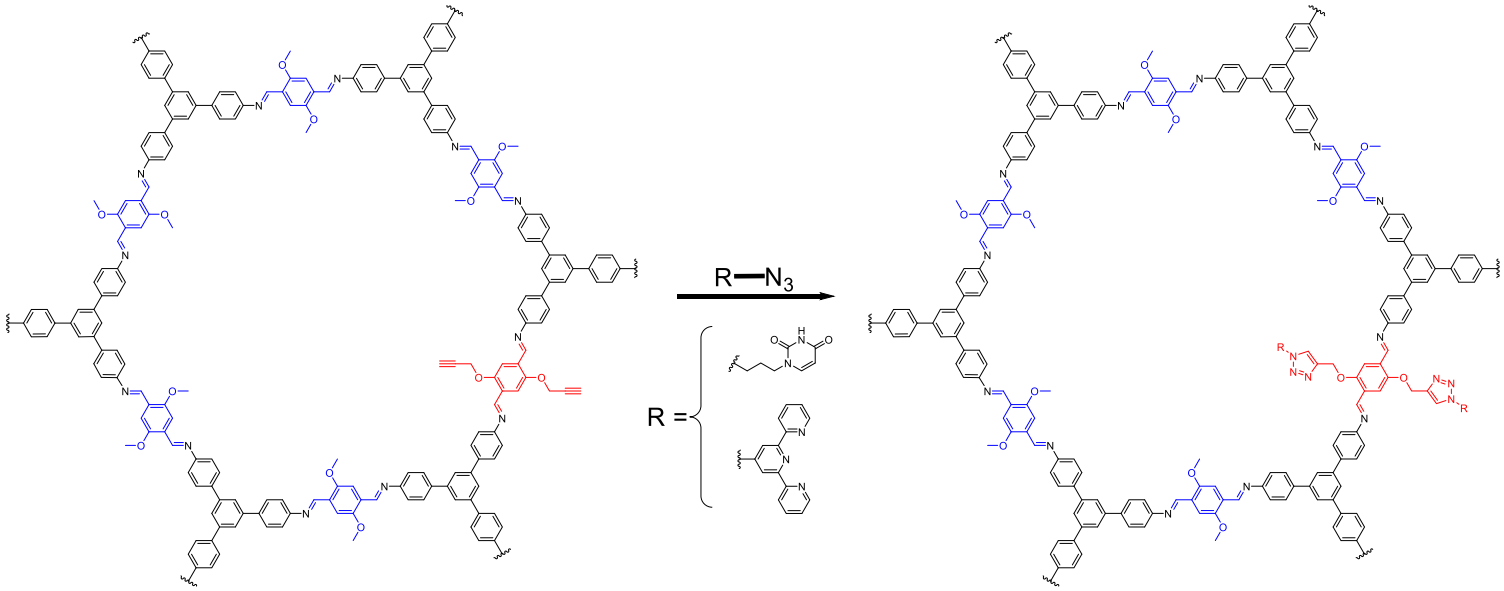
***Keywords**: Covalent organic frameworks, Post-synthetic modification, click chemistry*

Las Redes Orgánicas Covalentes, también conocidas como COFs, son polímeros con estructura cristalina formados por monómeros conectados mediante enlaces covalentes, dando lugar a poros regulares con un entorno definido.[1] El control en dos y tres dimensiones permite la síntesis de estructuras rígidas con regularidad y la posibilidad de funcionalizar el poro a través de modificaciones post-síntesis permite que el mismo esqueleto de un COF, con diferentes funcionalizaciones, pueda presentar diversas propiedades. Por dicha razón, estos materiales han sido objeto de varias investigaciones en los últimos años,[2] aumentando la colección de estrategias de modificación post-sintética. De entre ellas, una de las más utilizadas son las reacciones de tipo click, que debido a su versatilidad permiten unir una gran variedad de sustituyentes al esqueleto del COF.



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NEW SYNTHETIC METHODOLOGIES BASED IN ALLENES, ALKYNES AND BIOACTIVE HETEROCYCLES

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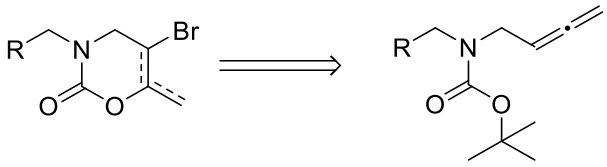
***Keywords**: allene, carbamate, oxazinone.*

The search for new synthetic routes to 1,3-oxazin-2-one derivatives[1] is of interest because of the biological activity of these molecules.[2] 1,3-Oxazin-2-ones are also used as valuable intermediates in organic synthesis.[3] Recently, allenes have attracted much attention as they have been used for the preparation of both biologically relevant drugs as well as advanced materials.[4] However, regioselectivity problems are significant (*endo-trig* versus *endo-dig* versus *exo-dig* versus *exo-trig* cyclization). The Boc protective group has been widely used in allene chemistry, being an inert and recommended partner in metal catalysis. In continuation of our interest in heterocyclic and allene chemistry,[5] We decided to examine the cyclization of *N*-Boc-allenes with the aim of establishing a convenient protocol for the synthesis of bromo-functionalized 1,3-oxazin-2-one derivatives.



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Development of new compounds for the treatment of progeria

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***Keywords**: Progeria, PROTAC, protein degradation*

Progeria is a very unusual degenerative genetic disease that provokes the premature appearance of physiological effects typically related to advanced ages, implying a strong decrease of life expectancy. The disease is caused by the accumulation of a mutated protein called progerine, primary cause of the symptoms of progeria[1]. The extreme rarity of the disease has difficulted the investigation and development of a drug able to cure it, beyond the palliative solutions, which currently are the only available alternative. In this project we will pursue the exploration of a new strategy aimed to selective degradation of progerine. We propose to develop a proteolysis targeting chimera (PROTAC), which is a bifunctional molecule aimed to tag a specific protein as a target of the proteasome, a cellular complex responsible for the proteolytic degradation of proteins[2]. Accordingly, a PROTAC molecule presents three parts: (i) the bioactive part, responsible of the selective binding to the objective protein; (ii) the E3 ubiquitin ligase recruitment for proteasome recognition; and (iii) a linker between the two moieties.

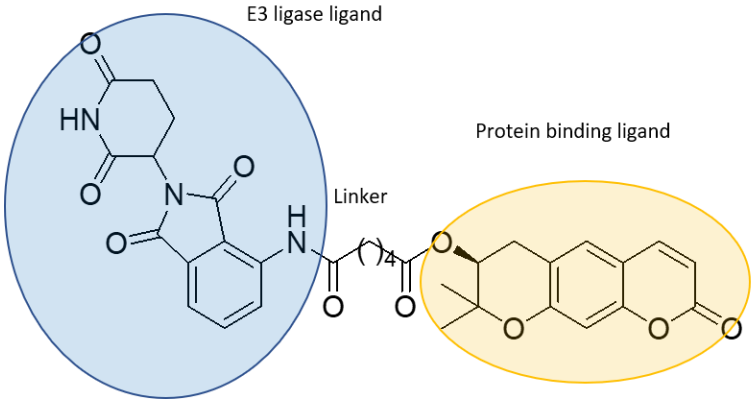

Figure 1: Proposed progerine-selective PROTAC structure.

The main objective of this work is the synthesis of the designed PROTAC and the determination of its capacity to induce the degradation of progerine.

References: [1] Santiago-Fernández O, Osorio FG, Quesada V, et al. *Nat Med*. 2019;25(3):423-426 [2] Churcher I. *J Med Chem*. 2018;61(2):444-452.

Supramolecular polymerization of *N*-annulated perylenes. Structure-property relationship.

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***Keywords**: Perylene, supramolecular polymerization, self-assembly.*

In this project, the multistep synthesis of two *N*-annulated perylene (NPC) derivatives has been carried out and their ability to self-assemble has been studied. These compounds possess four amide functional groups and a large aromatic surface that allow the formation of supramolecular polymers by H-bonding interactions, π-stacking between the aromatic cores and Van der Waals forces.[1] Different achiral or chiral aliphatic side chains have been incorporated at the peripheral positions, in order to study the impact of these structural features on the properties of these compounds.

The ability of these NPCs to build up supramolecular polymers by self-assembly has been studied by different spectroscopic techniques such as FT-IR and concentration dependent ^{1}H-NMR experiments. On the other hand, the supramolecular polymerization mechanism has been identified as cooperative by variable temperature UV-Vis spectroscopy (VT-UV-Vis).[2,3]

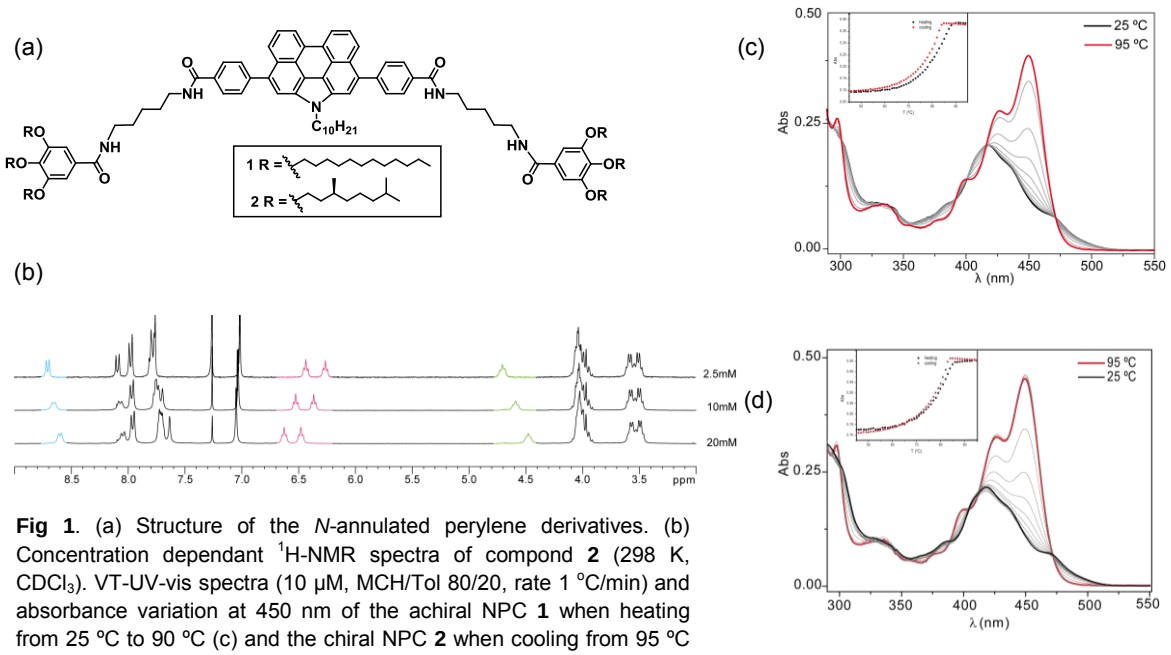

Fig 1. (a) Structure of the *N*-annulated perylene derivatives. (b) Concentration dependant ^{1}H-NMR spectra of compond **2** (298 K, $CDCl_3$). VT-UV-vis spectra (10 μM, MCH/Tol 80/20, rate 1 °C/min) and absorbance variation at 450 nm of the achiral NPC **1** when heating from 25 ºC to 90 ºC (c) and the chiral NPC **2** when cooling from 95 ºC to 25 ºC (d).

References

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Synthesis of new lactate dehydrogenase inhibitors

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***Keywords**: Stiripentol, Positron Emission Tomography, Inhibition, Lactate Dehydrogenase*

Lactate dehydrogenase (LDH) plays a central role in the development of several diseases, for example Dravet syndrome,[1] a case of epilepsy. One of the actual drugs used for this illness is Stiripentol, that metabolically inhibits this enzyme. In addition, structural analogues of Stiripentol, such as Isosafrol, also have this activity. In this work, **Stiripentol has been taken as reference compound to develop structural derivatives** that could show **enhanced activities** over LDH.

On other hand, **LDH enzyme is overexpressed** in tissues where NADH generated in glycolysis cannot be reoxidised to NAD+ due to the lack of oxygen. This is the case of **tumors in hypoxia state**, where the overgrowth of tumoral cells avoids the regular oxygen supply. This is known as the Warburg effect. [2] Detection of this enzyme by **positron emission tomography (PET)** could allow the obtention of three-dimensional **diagnostic images of cerebral tumors** or gliomas with situation of hypoxia. [3]

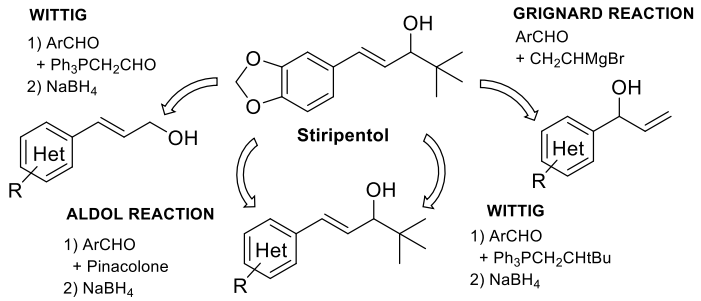

Fig. 1: Synthesis of new Stiripentol analogues

16 new structural analogues of Stiripentol have been synthesized, where both the aromatic ring and the sidechain of the reference compound have been modified (***Fig. 1***). Also fluorinated derivatives of Stiripentol have been obtained to be used as reference compounds of radiotracers of LDH (***Fig. 2***).

The objective of this work has been the **evaluation of the LDH inhibition** capacity of these new derivatives through **UV-Vis spectroscopy**, by measuring the rate of oxidation of NADH in the presence of LDH, and the selection of the best candidate to develop a **new ^{18}F-PET radiotracer** with LDH enzyme as target.

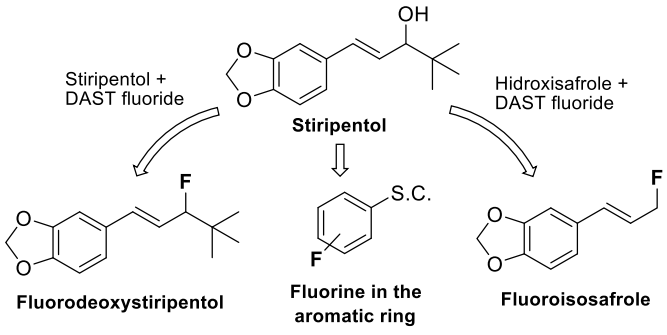

Fig. 2: Synthesis of fluorinated derivatives of Stiripentol

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ALQUENILBORONATOS TETRASUSTITUIDOS COMO FARMACOS MULTIDIANA PARA EL TRATAMIENTO DE LA ENFERMEDAD DE ALZHEIMER

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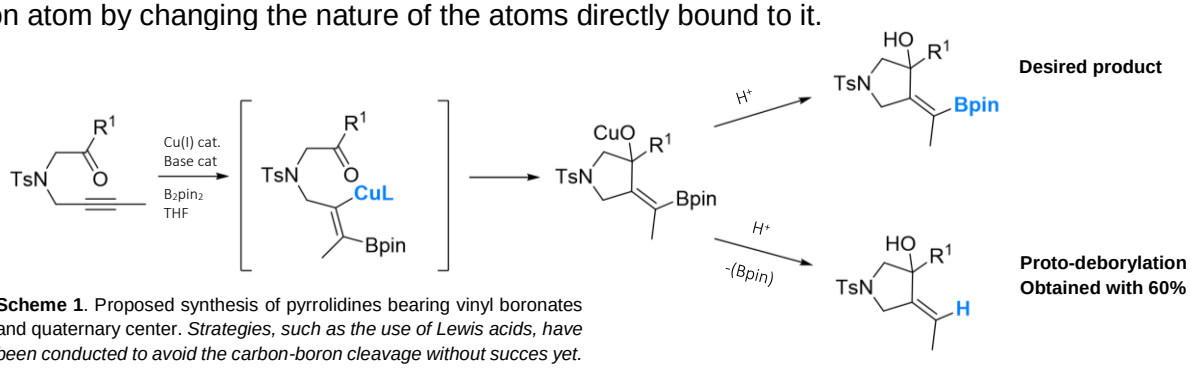
***Keywords**: Carboboration, alkyne, diboron reagent*

The production of tetrasubstituted alkenes through reactions that are stereoselective, chemioselective and regioselective remains a central challenge in organic chemistry. The carboboration of an alkyne[1] is a very efficient way to get access to this motif, since it involves formation of a C-C and a C-B bond in a single step[2,3]. The present work is centered on the development of a synthetic method for the preparation of tetrasubstituted alkenes with a boron at the olefinic position, using compounds bearing an alkyne and a ketone as model substrates. Preliminary studies in our research group have shown that this transformation is in principle feasible, although keeping the boron at the olefinic position is challenging[4]. Our current hypothesis to explain this observation involves an interaction between boron and an alcoxide that results in cleavage of the boron-carbon bond.

This work shows different trials realized in order to maintain the boron at the olefinic position by decreasing the proposed interaction between boron and oxygen. Two different approaches have been considered: firstly, we did the exploration of different reaction conditions employing Lewis acids of different nature to trap the alcoxide intermediate, along with alternative reagents to promote the formation of the initial B-Cu species. A second approach involved studies changing the nature of the diboron reagent; specifically, we considered decreasing the Lewis acidity of the boron atom by changing the nature of the atoms directly bound to it.



Scheme 1. Proposed synthesis of pyrrolidines bearing vinyl boronates and quaternary center. *Strategies, such as the use of Lewis acids, have been conducted to avoid the carbon-boron cleavage without succes yet.*

References:

[1], *for more about copper-catalyzed carboboration on alkynes see*: Alfaro, R.; Parra, A.; Alemán, J.; García Ruano, J. L.; Tortosa, M. *J. Am. Chem. Soc*. **2012**, 134, 15165−15168

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Inhibidores novedosos de hemaglutinina para el tratamiento de infecciones producidas por el virus de la gripe.

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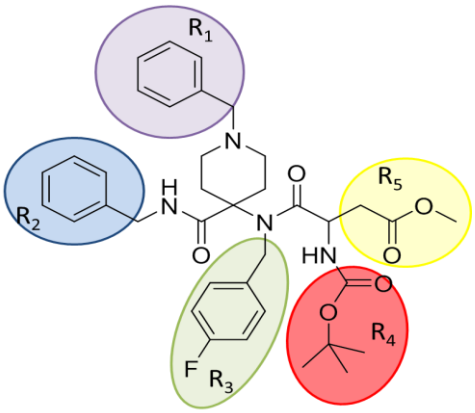
***Palabras clave**: Influenza, hemaglutinina, Ugi-4C.*

El virus Influenza representa uno de los virus más mortíferos que existen, causante de importantes pandemias a lo largo de la historia. Debido a su capacidad de mutabilidad, este virus muestra una rápida resistencia a los antivirales existentes, razón por la cual se hace necesario el estudio de nuevas dianas terapéuticas y/o mecanismos de acción para el desarrollo de fármacos más efectivos[1]. En este caso, la diana seleccionada es la hemaglutinina (HA), glicoproteína presente en la superficie del virus responsable de la entrada del virus a la célula[2]. En este trabajo se van a sintetizar compuestos análogos a un prototipo (compuesto **1**) identificado recientemente en el grupo de investigación que ha mostrado actividad inhibitoria potente frente a la cepa H1N1 del virus Influenza tipo A, el cual se comporta como un inhibidor de fusión actuando a nivel de la HA mediante un mecanismo de inhibición muy novedoso[3]. Con el fin de obtener compuestos más potentes y más estables químicamente, en este trabajo de máster se han realizado modificaciones en los sustituyentes R_1-R_5 basadas en estudios de docking previos con la HA para posteriormente, evaluar la actividad anti-influenza. Para la síntesis de las moléculas objetivo se utilizarán reacciones Ugi de cuatro componentes (Ugi-4C), utilizando diferentes aminas, piperidonas, isocianuros o aminoácidos comerciales o previamente sintetizados. Especial énfasis se realizará en la preparación de los isocianuros adecuados explorando distintas metodologías sintéticas.



Compuesto **1**

References:

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Synthesis of asymmetric bis(allyl)boronates through copper-catalyzed protoboration of borylated- dendralenes

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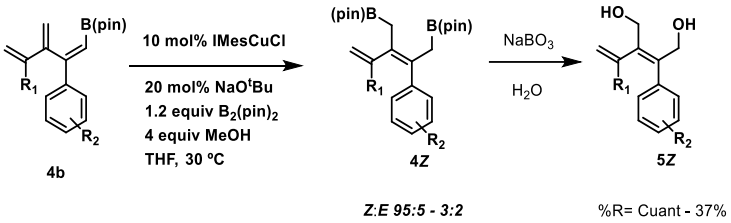
***Keywords**: protoboration, dendralenes, copper-catalysis*

Copper-catalyzed protoboration reactions generate borylated-compounds in a stereoselective and simple way. This organoboron compounds are interesting due to their synthetic versatility. This type of reactions implies the formation of a LCu^{I}-B(pin) intermediate, generated from an in-situ formed copper alkoxide and subsequent sigma bond metathesis reaction $B_2(pin)_2$. The LCu-Bpin intermediate suffers migratory insertion across the unsaturated compound to give a new organocopper intermediate, which is finally protonated in the reaction media to generate the final product.

Recently, in our research group, it has been developed an efficient and stereoselective catalytic methodology to synthesize borylated dendralenes.[2] Dendralenes are unsaturated hydrocarbons which have a structure of cross-conjugated dienes.[3] This structure presents different possibilities to react boryl-copper complex likely through a 1,2 or 1,4.

In this work, we describe a methodology that allows the regio- and stereoselective protoboration of borylated dendralenes. This reaction gives (bis)allylboronates that, after oxidation, can be isolated as 1,4-bisallyl diols with Z configuration in good yields. The study of the substitution in carbon skeleton as well as the electronic effect of different substituents have allowed to propose a reaction mechanism that involves a 1,4 stereoselective insertion of LCu-Bpin complex in the dendralene.



Scheme 1. Optimal conditions to protoboration reaction.

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Aplicaciones de nuevos organocatalizadores heterogéneos

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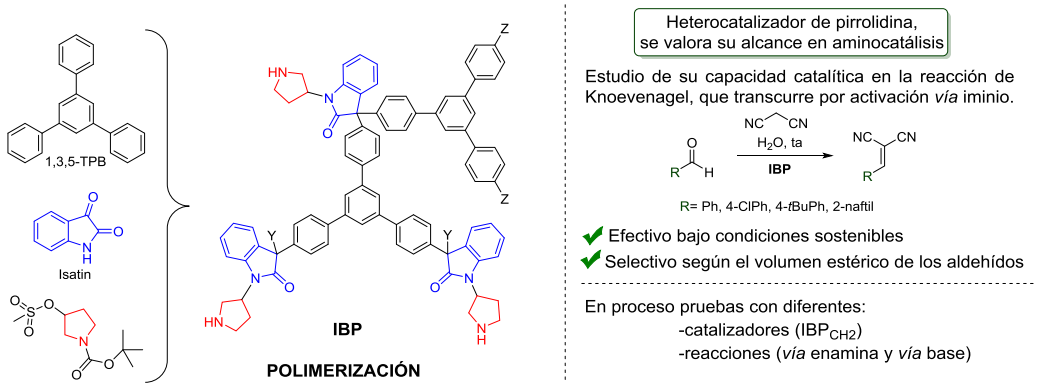
Keywords: *organocatálisis heterogénea, POPs*

La búsqueda de nuevas tecnologías ecológicas, más seguras y respetuosas con el medio ambiente promueve el uso de catalizadores reciclables para minimizar la producción de desechos[1]. Los materiales orgánicos porosos, permiten la heterogenización en soportes sólidos de procesos catalítcos homogéneos, y así poder ampliar sus aplicaciones industriales. Los *Porous Organic Polymers* (POPs), una clase de polímeros amorfos altamente entrecruzados que poseen nano-poros, han demostrado tener un gran abanico de aplicaciones, tales como el almacenamiento y separación de gases[2a] o eliminación de contaminantes.[2b] Aunque existen ejemplos de su uso en catálisis heterogénea[3] son muy pocos los ejemplos en organocatálisis.

En este proyecto se evalúan las capacidades organocatalíticas de nuevos POPs de pirrolidina. En el Esquema 1 se representa uno de los polímeros usados (IBP) que se ha sintetizado en el Cinquima y ICTP-CSIC, y caracterizado en ICMM-CSIC. Este catalizador ha demostrado su eficacia en catálisis *via* iminio usando agua como disolvente y ha resultado selectivo según el tamaño del aldehído empleado en la reacción de Knoevenagel. Adicionalmente, se están estudiando otras reacciones y otros soportes poliméricos.



Esquema 1: Estructura y aplicación catalítica del polímero IBP.

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Chirality in Graphene Quantum Dots

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Keywords*: graphene quantum dots, photoluminescent, chirality*

Among carbon nanoforms, Graphene Quantum Dots (GQDs) have been the latest members to join the carbon nanomaterials family.[1] These carbon nanoforms present a good photostability, low toxicity and are fluorescent.

In previous research work developed by our group, we combined these nanomaterials with covalently linked chiral ligands and observed the transmission of chirality from the obtained chiral GQDs to pyrene units in the supramolecular assemblies formed.[2]

In this Master work, we have explored the preparation of homogenous GQDs using a hydrothermal reactor (Figure 1),[3] with the aim to obtain GQDs with a sharper emission pattern than that of the previously obtained GQDs. Furthermore, considering the importance of chirality in the practical applications of many materials,[4] We have synthesized an enantiomerically pure 1,1′-binaphthyl-2,2'-diol (BINOL) derivative to be linked to GQDs by an esterification reaction. The obtained GQDs-BINOL nanomaterial (Figure 1) has been characterized by a combination of analytical and microscopic techniques. Finally, the initial evaluation of GQDs nanomaterials in model catalytic Friedel-Crafts reactions[5] demonstrated the activity of GQDs. Further investigations will consider the enantioselective properties of BINOL-GQDs.

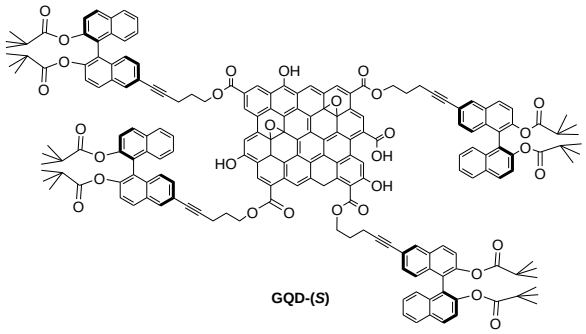

Figure 1. Left: GQDs-BINOL nanomaterials. Right: Reactor designed for the hydrotermal synthesis of GQDs.

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Sensor development for tubulin binding agents

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***Keywords**: Quantum Dots, paclitaxel, microtubules*

The increase in life expectance has turned cancer in one of the biggest health problems in developed countries. In order to target this problem, we need to learn about the mechanism of action of anticancer drugs at the most detailed level in order to design improved chemotherapeutic agents.

Paclitaxel is a microtubules-stabilizing agent able to block cells in mitosis, thus activating the spindle assembly checkpoint (SAC). It is frequently used in the treatment of solid tumours and has the ability to cause cancer's cells' death by apoptosis. However, detailed knowledge of the effect of placlitaxel on cell microtubules and its dependence on the tubulin isotypes, the post-translational modifications of tubulins or the specific function and/or localization of particular microtubules within the cell, it is not yet satisfactory.[1]

Biosensors are valuable tools to study and manipulate biological systems. An optimal biosensors should have high affinity, binding, and selectivity for the target to be studied.

Over the last years, Quantum Dots have appeared offering a wide number of useful properties. They are highly and long-lived luminescent, water-soluble and monodisperse inorganic particles. They have a broad absortion spectrum and narrow emission peaks, which wavelengths depend on the QDs size giving the possibility to work with a wide variety of colours.[2]

In this work, we aim to develop molecular biosensors using paclitaxel, making sure that affinity, binding and selectivity of the tagged placlitaxel for the target do not change. The designed biosensor using Quantum Dots will be employed to deepen the knowlege of the detailed cellular effects of paclitaxel, allowing detection of regions of the microtubule cytoskeleton in which the paclitaxel prefrentially located and stabilize.

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Helical peptides with dynamic control for cell penetration

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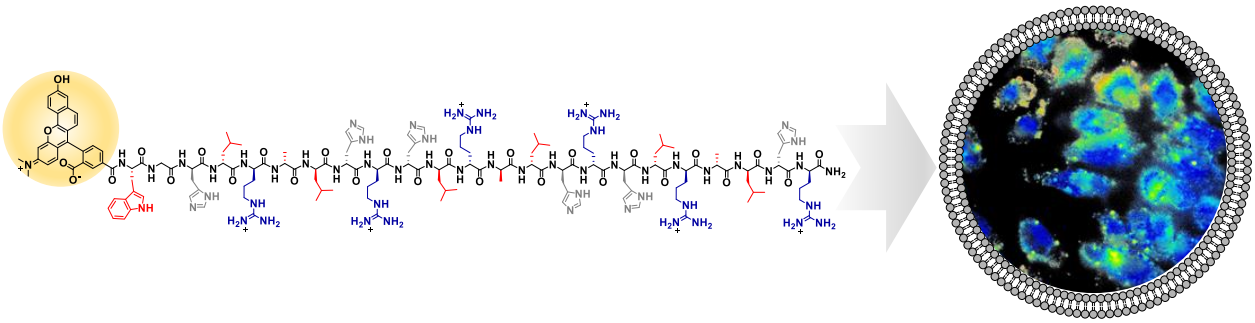
Keywords*: chemical biology, cell penetrating peptides.*

The low permeability of cell membrane represent a great control barrier for the distribution of biologically active conjugates (cargos). The discovery and development of cell penetrating peptides (CPPs)[1] it would be a possible solution to this problem, because they can translocate the membrane and transport into the cell a wide variety of cargos by a non-invasive strategy. They are usually short peptides and positively charged, in many cases having some hydrophobic residues that give it an amphipathic character[2].

The main objective of this project is design and synthesize amphiphilic alpha helical peptides. To achieve these properties, hydrophobic (leucines and alanines) and hydrophilic (arginines) residues are incorporating to the backbone peptide strategically. Additionally, we introduce histidines to get the dynamic pH control of this peptides. Its secondary structure was confirmed by circular dichroism studies and we evaluated its cellular internalization by transport in vesicles[3]. Finally, the peptide was modified with a fluorophore (SNARF-5-(and-6)-carboxylic acid) to be able to study its internalization and distribution in HeLa cells.



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New Semiconductors and their applications as photocatalyst

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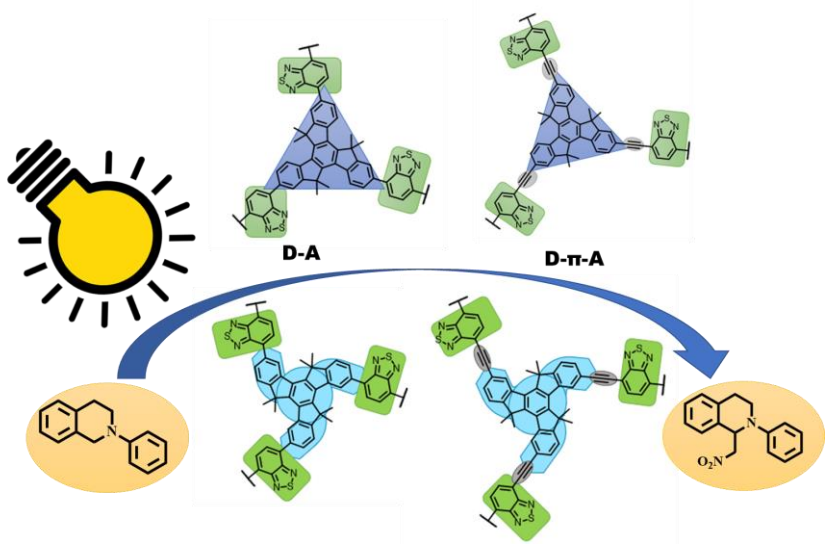
***Keywords**: photocatalisys, porous organic polymers and truxene.*

In the recent decades, porous materials have been aroused great interest due to their multiple applications in various fields of science and technology. Consequently, a new class of porous organic polymers has recently arisen whose properties can be modulated by design and selection of building blocks.

In this project, the synthesis and characterization of a new organic porous polymers type Donor-Acceptor (D-A) and Donor- π-Acceptor (D- π-A) have been done. The structure of this polymers is based on platforms of truxene[1] as donor, benzo[c][2,1,3]thiadiazole[2] (BTD) as acceptor and an acetylene group as π-linker.

These polymers have been characterized by the usual techniques of porous materials, moreover, optoelectronic properties and their possible application in photocatalysis[3] have been studied

Preliminary studies about these new metal-free polymers have demonstrated heterogeneous photocatalytic activity toward aza-Henry reaction.[4]



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Allyl-Allyl Cross-Coupling Reactions Of Secondary Electrophiles with Allylic Boronates

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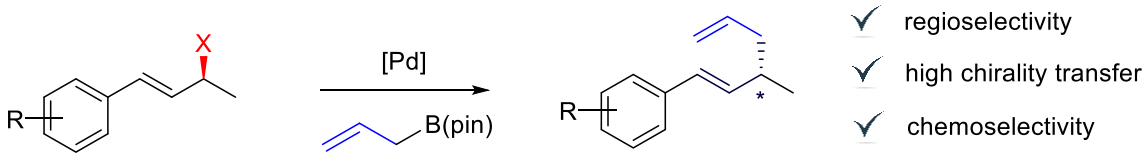
***Keywords**: (1,5-dienes, allyl-allyl cross-coupling reactions, secondary electrophiles)*

The study and development of allyl-allyl cross-coupling reactions catalyzed by transition metals to form new C-C bonds is still of great importance for the Organic Chemistry community.[1] This reaction allows for the synthesis of 1,5-dienes, which are versatile and useful intermediates in organic synthesis. In the past, synthetic chemists have studied this transformation using primary electrophiles with satisfactory results.[2] However, the use of secondary electrophiles has always led to problems in regioselectivity, stereoselectivity and β-hydride elimination.[3]

Here in we have studied the allyl-allyl cross-coupling reaction with secondary electrophiles, solving the remaining problems described above using allylic carbonates, obtaining great results in both the regioselectivity and the stereoselectivity of the reaction. Also, it is important to note that the amount of product derived from β-hydride elimination is minimized. We have also demonstrated the importance of both the leaving group and the nature of the ligand in this reaction.



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Towards the synthesis of dodecacene and beyond

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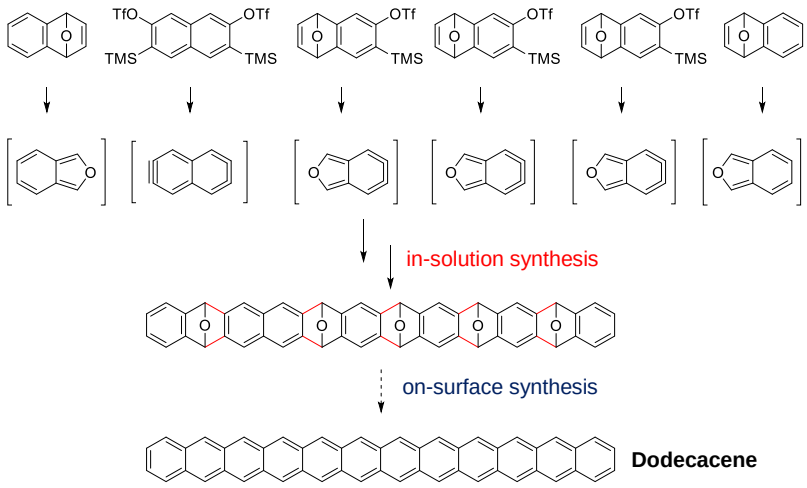
***Keywords**: Acenes, cycloadditions, arynes.*

Acenes are linear *cata*-condensed polycyclic aromatic hydrocarbons with unique electronic properties. In particular, large acenes present small HOMO-LUMO gap, diradical character and high reactivity. The difficulties in the preparation of large acenes, owing to the low stability under ambient conditions, are evident from the scarce successful synthesis of long unsubstituted acenes, in spite of the great attention they have attracted. In this project we describe our efforts towards the preparation of large acenes by the combination of solution organic chemistry and on-surface synthesis. Recently, we introduced an iterative sequence of aryne cycloadditions to synthesize stable epoxy precursors which were on-surface deoxygenated to obtain tetracene[1], hexacene[2] and more recently, decacene for the first time.[3] These large acenes were characterized with submolecular resolution by scanning tunneling microscopy (STM). Here we will discuss our recent efforts to apply this methodology to obtain a pentaepoxydodecacene that can be used to generate dodecacene by on-suface methods.



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Clickable molecular probes directed against the non-structural protein 1 (nsP1) of alphavirus

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***Keywords**: reemerging virus, clickable probes, triazolopyrimidines.*

Alphavirus, including Chikungunya virus (CHIKV) and Venezuelan equine encephalitis virus (VEEV) are reemerging arbovirus transmitted to humans by the bites of infected mosquitoes specifically *Aedes aegypti* and *Aedes albopictus*.[1] CHIKV, the causative agent of Chikungunya fever, has very much spread in the last decade reaching the Americas in 2013 with high morbidity causing serious economic and social problems. Currently, there is no effective antiviral treatment against CHIKV.

Our research group has described a series of 3-aryl-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-ones that act as potent inhibitors against CHIKV replication.[2] The studies carried out to determine the mechanism of action indicate that these compounds inhibit the mRNA capping process catalyzed by the viral enzyme nsP1.[3] Despite the importance of this enzyme as an antiviral target, very little information is available about it. For this reason, we have considered to use our compounds to prepare chemical probes that will allow to obtain more information about the enzyme nsP1 and the mode of inhibition of our compounds. Based on this, trifunctional chemical probes have been designed and synthesized, incorporating 3-aryl-[1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-ones as a recognition element into their structure, a photoreactive group and a distal alkyne able to undergo click chemistry with commercial azides that incorporate an affinity or fluorescence label. In this way, the role of the nsP1 protein in the replicative viral cycle of alphavirus and the mode of interaction of the synthesized compounds should be better established.

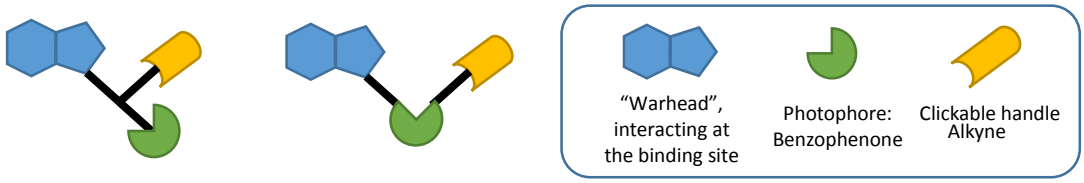

Figure 1. Trifunctional chemical probes for alphavirus nsP1

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Addition of metallated silanes to unsaturated sulfoxides

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Keywords*: Organosilylcuprates, unsatured sulfoxides, silyl compounds.*

The development of new techniques and methods of synthesis that can be applied to obtaining natural products,[1] which are biological and pharmacologically active, generates a great deal of interest currently.

In this research project, we have started the study of the reactivity of unsatured sulfoxides[2] with organosilylcuprates[3,4] as nucleophiles, involved in different reactions regarding the nature of the sulfoxides. This experimental work has been done from the synthetic point of view, through the optimization of synthetic methods, reactivity and chiral induction, as from the point of view of structural characterization.

Thus, we have studied the addition the organosilylcuprates to alkynyl, alkenyl,[5] allenyl and dienyl sulfoxides,[6] synthesizing efficiently new silyl compounds. The configuration of the new stereocenters and the selectivity of the reactions have been investigated, in the appropriate cases.

Furthermore, we have explored synthetic applications of our new silyl compounds.

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Subphthalocyanines Axially Substituted with an Extended Tetracyano-Aniline Unit: Synthesis, Structure and Physicochemical Properties

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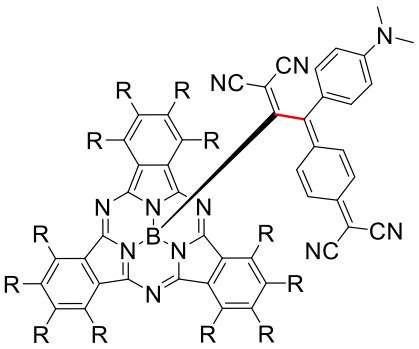
***Keywords**: Subphthalocyanine, donor-acceptor, atropisomer.*

Subphthalocyanines (SubPcs) are cone-shaped aromatic macrocycles that can be functionalized in their peripheral and/or axial positions. When properly functionalized with electroactive units, SubPcs can give rise to electron donor-acceptor (D-A) systems, in which photoinduced charge separation states can occur, which is very interesting for photoenergetic and optoelectronic applications.[1]

In this report, two new SubPc-tetracyano extended-aniline systems have been synthesized by a cycloaddition-retroelectrocyclization reaction (CA-RE)[2] between R_{12}SubPcs (R = H or F) axially substituted with an ethynyldimethylaniline subunit, with an electron-withdrawing subunit like the 7,7,8,8-tetracyanoquinodimethane (TCNQ) (Figure 1).



1 R = H
2 R = F

Molecular structure of H_{12}SubPc-TCNQ-aniline **1** and F_{12}SubPc-TCNO-aniline **2**.

Conjugates H_{12}SubPc-TCNQ-aniline **1** and F_{12}SubPc-TCNQ-aniline **2** are obtained as a racemic mixture of two atropisomers that have axial chirality. For each conjugate, both the S_a and R_a atropisomers were isolated by the use of chiral high performance liquid chromatography. The S_a and R_a atropisomers, which resulted to be configurationally stable compounds, showed mirror-image circular dichroism spectra, confirming their enantiomeric relationship. Additionally, UV-vis absorption studies on conjugates **1** and **2** and their precursors have been carried out, suggesting, in the former compounds, the occurrence of a charge transfer process between the electron acceptor TCNQ unit and the electron rich aniline. This band has a pronounced solvatochromic character, and red-shifts upon increasing the polarity of the solvent. Surprisingly, the ^{1}H nuclear magnetic resonance characterization of compounds **1** and **2** shows broad peaks. More studies are necessary to understand the reasons for this phenomenon.

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Axial functionalization of Subphthalocyanines and Subphthalocyanine fused dimers for Photodynamic Therapy

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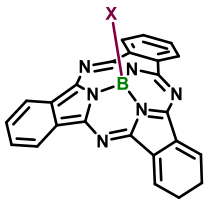
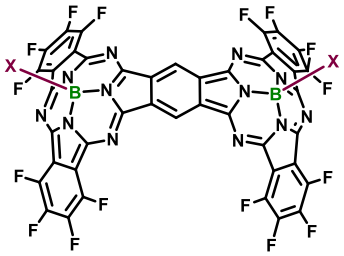
***Keywords**: Subphthalocyanine, Subphthalocyanine fused dimer, Photodynamic Therapy*

Photodynamic therapy (PDT) is a form of cancer treatment involving light, molecular oxygen and a light-sensitive compound, the photosensitizer (PS). The last one contains a π-conjugated system which, upon excitation with light of the near infrared spectral region, generates an active form of molecular oxygen, singlet state, which leads to cell death.[1]

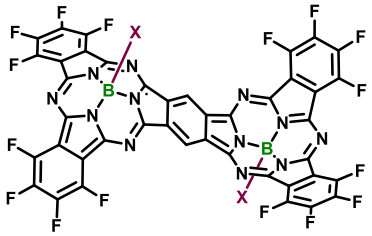
Subphthalocyanines (SubPcs) are peculiar porphyrinoid compounds, exhibiting an intense absorption in the visible region and a particular cone-shaped structure that gives rise to their characteristic reduced aggregation tendency. They have been widely studied as PSs for photovoltaic applications and more recently for PDT, among other applications.[2] On the other hand, Subphthalocyanine fused dimers ($SubPc_2$) are best known for their π-extended surface and may be even more suitable for PDT than the SubPc monomers, as they have an intense absorption at higher wavelength, in the NIR region, while keeping low aggregation tendency.[3]



SubPc



$SubPc_2$ *syn*



$SubPc_2$ *anti*

Herein, the synthesis and study of properties of several axially aryloxy substituted SubPcs and $SubPcs_2$ will be reported. The axial aryloxy groups additionally bear polar groups in order to increase the solubility of this family of intrinsically hydrophobic compounds in polar solvents.

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Formación de Enlaces C-C en Medios Acuosos Usando Fotocatálisis

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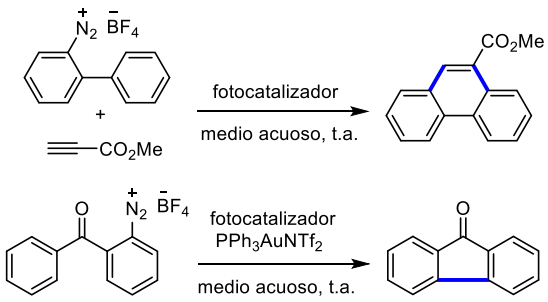
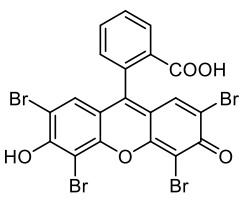
***Keywords**: fotocatálisis, luz visible, química bioortogonal*

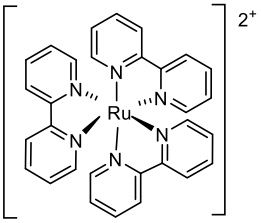
El empleo de la luz solar para inducir transformaciones químicas es una importante estrategia que hemos aprendido de la naturaleza.[1,2] De hecho, la luz se considera un catalizador ideal ya que es limpia, barata, no contaminante y no deja residuos.
La fotocatálisis con luz visible se ha empleado con éxito, por ejemplo, en la transformación de numerosos grupos funcionales o en la síntesis de productos naturales.[3] Esta nueva área emergente también está llamando la atención de investigadores en el ámbito de la Química Biológica, ciencia de materiales y diseño de fármacos. Curiosamente, y a pesar de los significativos avances en fotocatálisis, apenas hay ejemplos de reacciones fotoquímicas en Química Biológica y Química de Bioconjugación,[4] lo cual es comprensible teniendo en cuenta que muchas transformaciones fotocatalíticas requieren radicales altamente reactivos que limitan la bioortogonalidad, así como el uso de luz UV, que no es biocompatible.
Este proyecto abarca el diseño y estudio de procesos fotorédox con luz visible en medios acuosos, así como su optimización en medios biológicos empleando tanto catalizadores metálicos como fotosensibilizadores.
En concreto, en nuestro laboratorio hemos estudiado reacciones inter- e intramoleculares de formación de enlaces C-C mediante procesos fotorédox, empleando sustratos capaces de generar radicales en medios acuosos como las sales de diazonio, combinadas con fotocatalizadores de luz visible como Eosin Y o $[Ru(bpy)_3]^{2+}$, con el objetivo final de diseñar sistemas biocompatibles capaces de modificar proteínas *in vivo*.



Fotocatalizadores empleados



Eosin Y



$[Ru(bpy)_3]^{2+}$

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PREPARACIÓN DE NUEVOS POLÍMEROS POROSOS ORGÁNICOS Y PIRÓLISIS CONTROLADA PARA MEJORAR LA CAPTURA DE CO_2

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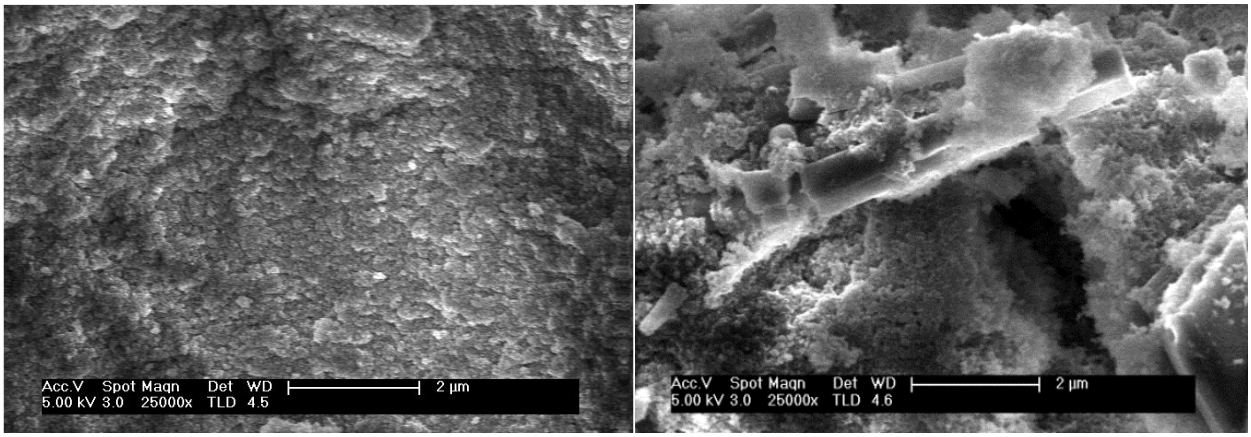
***Keywords**: Polímeros, Captura, CO_2.*

Uno de los temas que más preocupa en la actualidad es la creciente emisión de gases contaminantes a la atmósfera, entre los que destaca el CO_2 y en consecuencia un incremento en la temperatura terrestre. El desarrollo de nuevos materiales porosos capaces de capturar y/o convertir el CO_2 en productos de valor añadido, es una de las estrategias que más se están investigando para mitigar el efecto dañino del CO_2. Así, este trabajo trata de la síntesis de una serie de polímeros orgánicos porosos nuevos enriquecidos en nitrógeno y azufre y su aplicación en captura y conversión de CO_2 en carbonatos cíclicos.



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Desarrollo, optimización y síntesis de compuestos orgánicos de interés

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***Keywords**: flujo, bencino, Diels-Alder.*

La búsqueda de compuestos orgánicos con actividad biológica es una rama fundamental en la industria farmacéutica. Se desarrollan principios activos que modulen una actividad de una diana terapéutica relacionada con una o varias enfermedades, con el fin de provocar una respuesta biológica con efectos terapéuticos. De la misma manera surgen los medicamentos genéricos con el objetivo de abaratar el proceso de producción[1].

Por otro lado, la química de flujo emerge como una tecnología que ofrece unas características que abaratan el coste de la producción y además proporciona mayor control sobre la temperatura y presión del reactor, dando lugar a reacciones complicadas en reactores convencionales como las reacciones de cicloadición Diels-Alder[2].

En el presente trabajo se propone una ruta alternativa a un medicamento actual de mercado, el cual tiene lugar una reacción compleja de cicloadición, bajo un equipamiento de química de flujo con el fin de facilitar la producción y reducir el coste final.

Los compuestos obtenidos en síntesis se caracterizaron fundamentalmente por las técnicas de RMN-^{1}H, HPLC y GC, debido a que nos permiten una rápida interpretación de los resultados obtenidos.

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Síntesis de Compuestos Heterocíclicos Fluorados para Aplicaciones ^{18}F-PET

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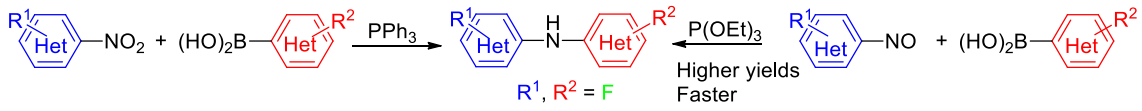
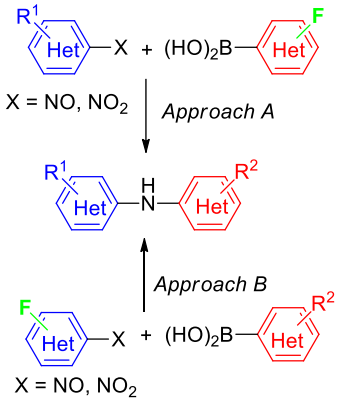
***Keywords**: diarylamines, boronic acids, PET Positron Emission Tomography*

Positron Emission Tomography (PET) is a medical radiodiagnosis technique that affords molecular images of the inside of the body. It requires the use of radioactive drug-like molecules (radiotracers) that decay by emitting positrons. Among the different options, labelling with ^{18}F is more convenient from practical standpoints. Due to the radioactive nature of these positron-emitting radiotracers, their synthesis, isolation and characterization must be carried out under conditions that warrant radioactive protection. Identification of the radiotracers is conventionally carried out under radioactive protection by High Performance Liquid Chromatography (HPLC) or Gas Chromatography (GC). This implies that of cold standards (non-radioactive compounds) should be available as reference. The objective of this work was the synthesis of fluorine-containing diarylamines to be used as cold standards in the development of ^{18}F-PET radiotracers. Their synthesis was carried out by the coupling of boronic acids with nitroso or nitro compounds under transition-metal-free conditions. The couplings was also investigated through two different paths: by placement of fluorine on the boronic acid moiety or on the nitroso- or nitroarene counterpart.



Scheme 1. Synthesis of diarylamines starting from nitroarenes or nitrosoarenes and boronic acids**.**



Scheme 2. Approaches for the synthesis of fluorine-containing di(hetero)aryl amines.

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Exploring the Substrate Recognition and the Mechanism of Action of the Unexploited LpxK enzyme from *Acinetobacter baumannii*

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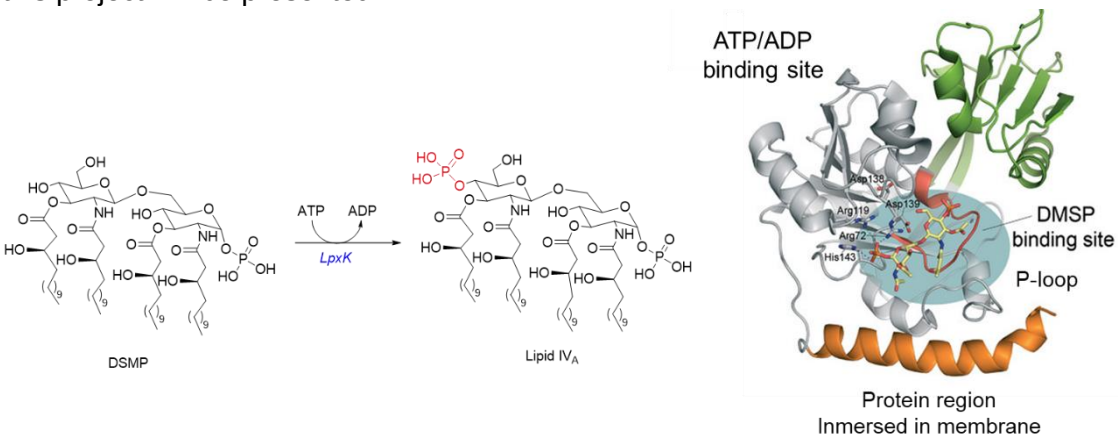
***Keywords**: (homology modelling, Acinetobacter baumannii, LpxK)*

As recently reported by the World Health Organization, *Acinetobacter baumannii* is one of the most dangerous Gram-negative pathogens since it has developed the biggest antibiotic resistance in the last decades, including to carbapenems, which are often considered as antibiotics of last resort. It is a healthcare-associated human pathogen that has been linked with a broad spectrum of infectious diseases, including pneumonia and blood-stream infections and a major concern on patients with a weak immune system undergoing surgery, cancer chemotherapy and dialysis, amongst others, for whom our ability to deal with secondary infections is crucial. It is therefore not surprising that the development of new antibiotics for the effective treatment of infections caused by this pathogen is nowadays a priority worldwide.[1]

Our research group is interested in studying the therapeutic potential of an unexplored enzyme, the tetraacyldisaccharide 4'-kinase (LpxK), which role in the viability of *A. baumannii* and its capacity to produce infection has been recently identified by us to be crucial. LpxK is involved in the biosynthesis of Lipid A, which is an essential component of the outer membrane of Gram-negative bacteria.[2] The enzyme catalyzes the stereospecific phosphorylation of the 4-hydroxyl group in the 1P-dissacharide (DSMP) to provide lipid IV_A by using ATP. As part of a project aimed at the development of inhibitors of the LpxK enzyme, in this work we propose to study at the atomic level the keys of the substrate recognition for catalysis and turnover, for the subsequent rational design of inhibitors. To this end, the Michaelis complex as well as the reaction product complex of the LpxK enzyme from *A. baumannii* (Ab-LpxK) will be studied. In order to do so, we will take the advantage of the structural information available for LpxK from *A. aeolicus* (Aa-LpxK) to create the corresponding models.[3,4] Our recent progress in this project will be presented.



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DISEÑO DE NUEVOS MATERIALES POROSOS INTELIGENTES 2D

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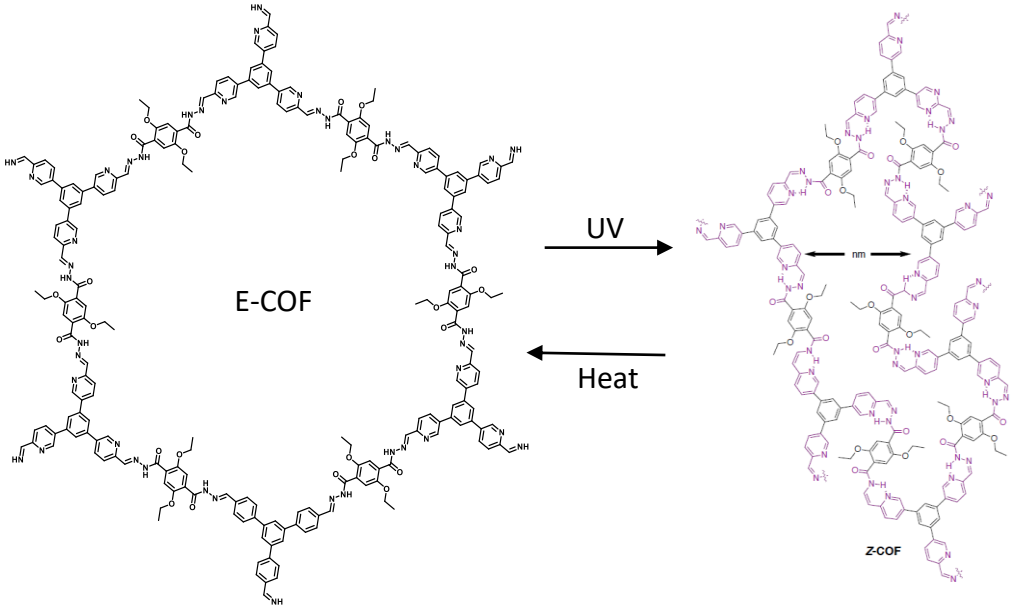
***Keywords**: COF, piridil-acil-hidrazona, inteligente.*

Los Covalent Organic Framework (COFs) son una clase emergente de estructuras orgánicas covalentes porosas cuyos esqueletos se componen de elementos ligeros (B, C, N, O, Si) y están unidos por fuertes enlaces covalentes de diferente naturaleza que permiten dotar a estos materiales de propiedades[1] tales como: porosidad inherente, cristalinidad, gran área de superficie y alta estabilidad, entre otros. A partir de las propiedades mencionadas anteriormente se han encontrado distintas aplicaciones de esta clase de materiales en diversos campos[1] como son el almacenamiento y la separación de gases, la catálisis o la administración de fármacos. Los COFs están formados por la unión de diferentes bloques de construcción, lo cual proporciona una enorme versatilidad a la hora de sintetizar materiales con diferentes estructuras y tamaño de poro.

En este proyecto, se llevará a cabo la síntesis y caracterización de COFs basados en piridil-acil-hidrazonas[2], donde se espera una respuesta "inteligente" del COF-hidrazona frente a la luz, y una respuesta reversible con la temperatura (vease figura abajo). Este material podrá ser aplicado como "drug delivery" o como "switch" on/off para distintas reacciones catalíticas.



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SÍNTESIS DE CARBAZOLES Y DE BIS(CARBAZOLES)

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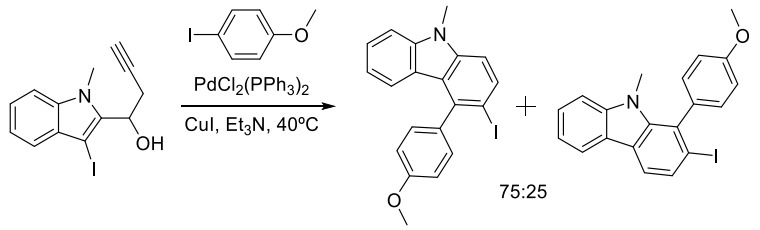
Keywords: *Carbazole, Bis-carbazole, Sonogashira.*

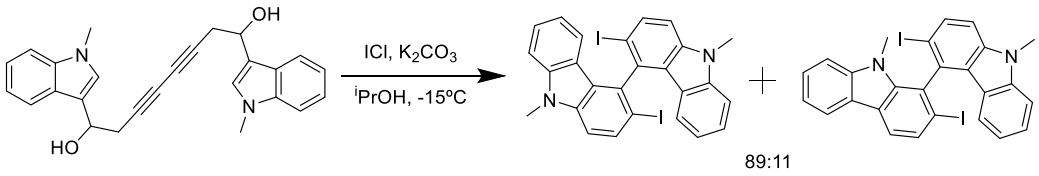
El esqueleto de carbazol y bis(carbazol) está presente en compuestos con interesante actividad terapéutica y biológica.[1] Por otro lado, cabe destacar así mismo el empleo de estas estructuras en materiales poliméricos enfocados a la electrónica.[2]

Recientemente, en nuestro grupo de trabajo se ha descrito la síntesis de 3-yodocarbazoles y de bis(yodocarbazoles) a través de una reacción que implica una carbociclación catalizada por oro, seguida por una migración 1,3 de yodo.[3,4] En el presente trabajo se estudia la preparación de yodocarbazoles y bis(yodocarbazoles) mediante dos rutas sintéticas diferentes. Por un lado, se sintetiza un carbazol mediante una reacción tándem Sonogashira/ciclación. (Esquema 1).



Esquema 1. Síntesis de yodocarbazoles

Por otro lado, se ha estudiado la reacción de adición de cloruro de yodonio a diinos, obteniendo una mezcla de bis(yodocarbazoles). Esto sucede mediante una posterior reacción de doble ciclación y un reordenamiento final de la estructura (Esquema 2).



Esquema 2. Síntesis de bis(yodocarbazoles)

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Sustainability and "Drug Discovery": Catalytic heteroannulations from alkynes to 3-benzazepines

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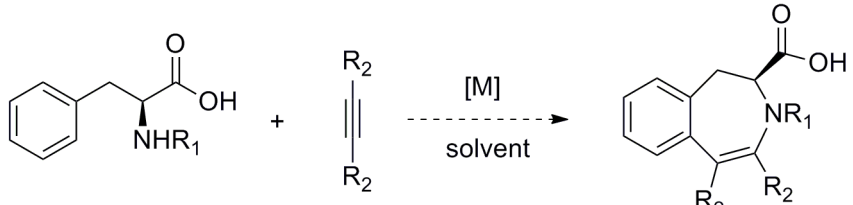
***Keywords**: benzazepines, C-H activation, phenetylamine*

Transition metal-catalyzed C-H bond functionalization of organic molecules has been recognized as a powerful atom-economy strategy for the synthesis of a great variety of benzofused azaheterocycles such as indoles, indazoles, quinolones, isoquinolines, quinazolines, etc.[1,2] However, seven-membered benzofused azaheterocycles, such as benzazepines and benzodiazepines nuclei, that show important pharmacological properties,[3] have received less attention.[4,5] Typical synthetic routes to 3-benzazepines are based on *intramolecular reactions*,[5] so it would be interesting to develop new approaches based on *intermolecular reactions* (via C-H activation) towards a more "sustainable" route.[6]

Continuing with our work on metal-catalyzed C-H functionalization, we have now initiated the exploration of metal-catalyzed oxidative cycloaddition (C-H activation processes) to 3-benzazepines from phenetylamine derivatives and alkynes. Optimization of reaction conditions and mechanistic studies are currently under investigation in our laboratory.



R_1 = Tf, Ts, Bn
R_2 = Ph, Et, CO_2Me, etc.
[M] = Pd, Ru

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Microwave-driven synthesis of cyanide polymers under hydrothermal conditions: astrobiological implications.

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***Keywords**: Astrobiology, HCN polymerization, Origin of Life.*

Icy moons in our solar system have been subject to recent discoveries. One such is the possibility of hydrothermal activity in Enceladus' hidden liquid water ocean. This moon, orbiting around Saturn[1] might present, beneath its icy surface, with interesting prebiotical conditions: the presence of liquid water and the evidence of active chemistry and energy sources. Conditions on Europa[2], another icy moon, orbiting Jupiter, are fairly similar. The chemistry that might develop in these deep ocean scenarios may have HCN as one of its main protagonists[3]. This project endeavours to explore the prebiotically relevant oligomerization/polymerization of HCN and analyse the products of such reactions carried out under plausible conditions like those in the aforementioned icy moons.

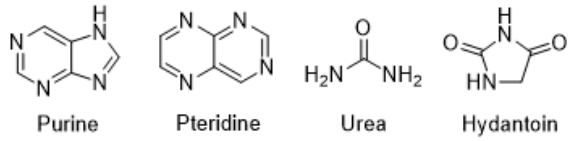

Figure 1: some molecular products resulting from the oligomerization/polymerization of HCN.

Thus, two series of experiments were completed, with NH_4Cl and KCN as reactants in concentration 1 M. The first series of experiments were implemented in the presence of air, so that comparison with the group's previous investigation was possible. The second series of experiments, on the other hand, were set under anaerobic conditions to simulate those in the icy moons. Marked kinetic dependence on reaction conditions is evident upon comparison of data from both types of reactions. Products from both reactions were analysed using various analytical techniques, such as FT-IR and UV-Vis spectroscopy, GC-MS, elemental analysis, etc.

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Metal Catalyzed β-Regioselective and Stereodivergent Hydro-oxycarbonylation of Internal Alkynes

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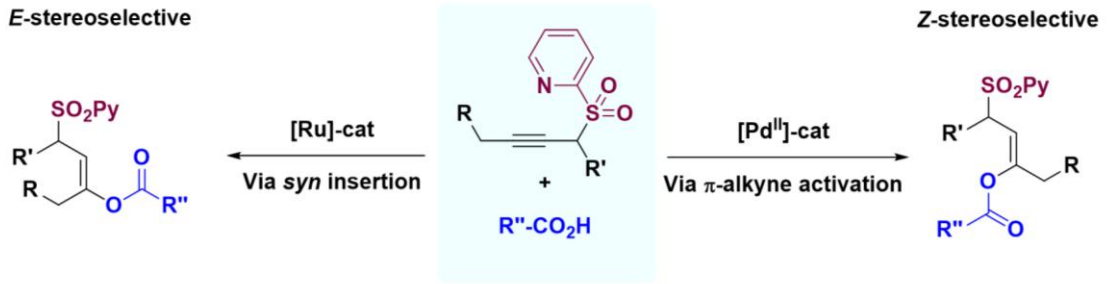
***Keywords**: Alkyne functionalization, enol ester synthesis, metal catalysis, directing group.*

The hydro-oxycarbonylation reaction of alkynes, namely the catalytic addition of RCO_2H species across C–C triple bonds, is a powerful tool for the synthesis of valuable enol esters in an atom-economical and sustainable fashion. Enol esters are valuable building blocks in organic chemistry due to their synthetic versatility, particularly in C–C bond forming reactions. The present work focusses on the development of a metal-catalyzed regioselective and stereodivergent strategy enabling the access to both *E*- and *Z*- diastereoisomers of trisubstituted alkenyl enol esters from dialkyl internal alkynes.

While achieving high regioselectivity in the functionalization of internal dialkyl alkynes is challenging, the use of an easily removable propargylic SO_2Py directing group allowed for total β-regiocontrol. The *Z*-stereocontrol is attained by using palladium catalysis, whereas the corresponding *E*-diastereomers are accessed with Ru-phosphine complexes. Despite high levels of regiocontrol and diastereodivergence achieved, the reaction yields for the *E*-hydro-oxycarbonylation are still rather low at the present, and further investigation is underway that should lead to further improvements.



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(-)-Shikimic acid based bolaamphiphilic amides and bisamides: Synthesis and study of their properties.

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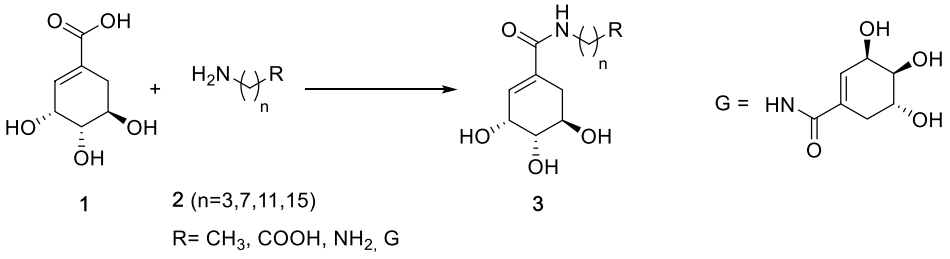
Keywords: *Gel, amphiphilic, bolaamphiphilic*

Gels are supramolecular structures formed by the aggregation of small molecules linked by non-covalent bonds.[1] These structures have the capacity of retaining large amounts of solvents (usually 98% of the gel mass or higher).

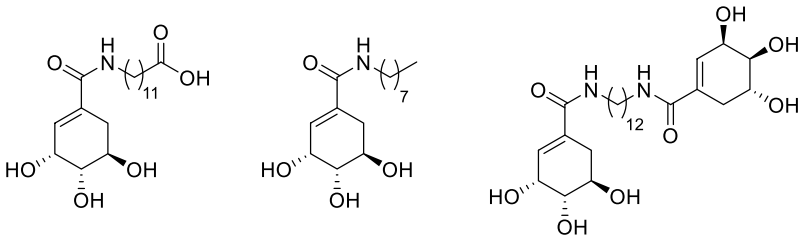
Amphihilic compounds consists of molecules having a polar water-soluble group attached to a water-insoluble hydrocarbon chain. Close related bolaamphiphilic compounds have hydrophilic groups at both ends of a sufficiently long hydrophobic hydrocarbon chain. Both kind of compounds have showns gelifying properties in a variety of solvents.

Using (-)-shikimic acid (**1**) as the polar end, a number of amphiphilic and bolaamphiphilic amides **3** were synthetized from a set of alkylamines **2** (Scheme 1).[2]



Scheme 1

Results on gelifycation studies in a set of 14 solvents were performed. Specifically, compounds 3a, 3b and 3c (Figure 1) showed promising gelifying properties in water.[3]



3a **3b** **3c**

Figure 1

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Study of the reactivity of allenols with Koshar-type zwitterions

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Keywords*: allenol, zwitterion, metal-free*

In 1976 Koshar et al. described the synthesis of a zwitterion, which contains a carbanion stabilized by bis-substitution with two triflyl groups.[1] In 2013, Yanai et al. carried out an exhaustive study of these compounds, improving their synthesis and finding an application as agents of bis(triflyl)ethynylation of activated aromatic rings.[2] These zwitterions can generate *in situ* the highly polarized molecule $Tf_2C{=}CH_2$, which can suffer cycloadditions or acts as a Michael acceptor.

The present work is part of the study of the reactivity of different α-allenols with these Koshar-type zwitterions. This metal-free protocol yielded fluoroalkylated α,β-unsaturated ketones in mild conditions and with total regiocontrol and high stereoselectivity. We have studied the effect of the electronic nature of the substituents in the starting α-allenols, along with the effect of substituents in different allenic positions.

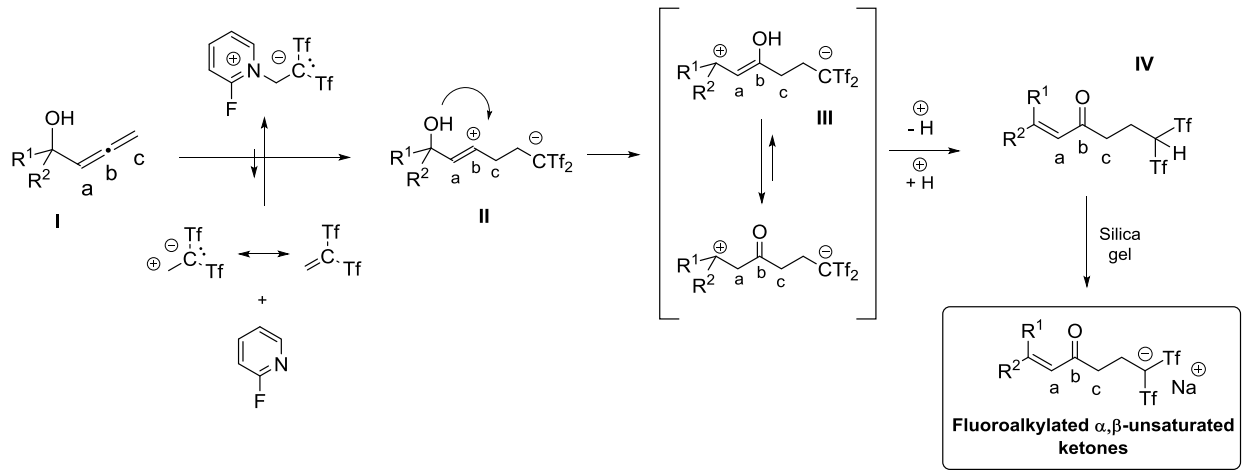

Figure 1. Proposed pathway for the formation of fluoroalkylated α,β-unsaturated ketones.

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Synthesis of Advanced Fluorescent Probes for Bioimaging.

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***Keywords**: BODIPY, fluorescent, bioimaging*

This project describes the synthesis of new fluorescent molecules for applications in biology and biomedicine. Starting from a commercially available BODIPY derivative, we selectively activated the methyl groups attached to positions C3 and C5 and subsequently performed acid-catalyzed nucleophilic substitution reactions with O- S- and C-nucleophiles to further functionalize the chromophore.[1] Thus, by adequately adjusting reaction conditions, mono- as well as homo- and heterodisubstituted derivatives have been synthesized in order to modify some of the BODIPY core's properties such as water solubility or fluorescence quantum yield. These new compounds are potentially interesting candidates for being used as probes in bioimaging, as they are expected to interact selectively with certain types of biomolecules or organelles. More specifically, pentafluorothiophenol derivatives are expected to attach to cysteine and lysine residues, allowing fluorescent marking of proteins that contain these amino acids, whereas the incorporation of ubiquinol and triphenylphosphine into the BODIPY core should lead to mitochondria-sensitive fluorescent dyes.[2]

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Supramolecular Networks based on Cooperative Interactions for their Application as Hydrogels

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***Keywords**: supramolecular chemistry, hydrogels, self-assembly*

In this project we aim to evaluate the effect of *highly cooperative supramolecular phenomena* in the properties of *gelation processes in aqueous media*. We concretely expect that the presence of multiple "*all-or-none*" cooperative interactions will allow the preparation of hydrogels with an *optimum, controlled and reversible gelating agent* and *narrow sol-gel transitions*.[1]
The hydro-gelating materials will be obtained by functionalizing a hydrosoluble polymer, *polyethylene glycol*, at both edges with two different supramolecular motifs that lead to cooperative supramolecular interactions, as previously demonstrated in the research group. The first motif is a *dinucleoside* derivative comprising a rigid central block substituted by Sonogashira coupling at each terminus by complementary nucleobases (guanine and cytosine). Watson-Crick hydrogen-bonding between these bases will induce the formation of a supramolecular network, reinforced by tubular aggregates with cyclic tetramer section driven by hydrophobic interactions.[2]
In a second system, the motif is based on the ability of guanine derivatives to form *G-quadruplex* structures in the presence of alkaline salts, which consist of cyclic tetramers stacked around the corresponding cation.[3] We expect that the formation of these supramolecular multivalent structures, which in both cases present high chelate cooperativities, results in extended networks able to gelate in aqueous environments.

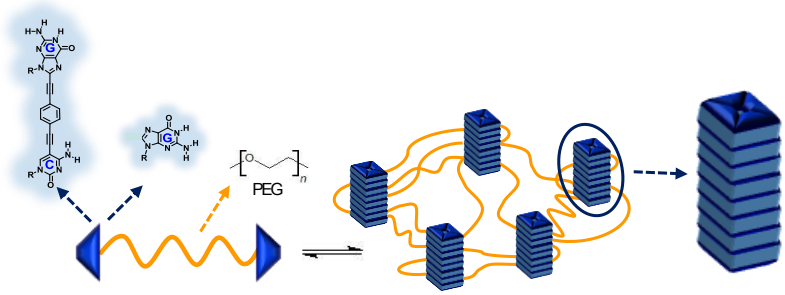

Figure 1. Supramolecular hydrogels composition.

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Large-scale synthesis of benzoxepines and coumarins and Supramolecular directed remote C-H activation

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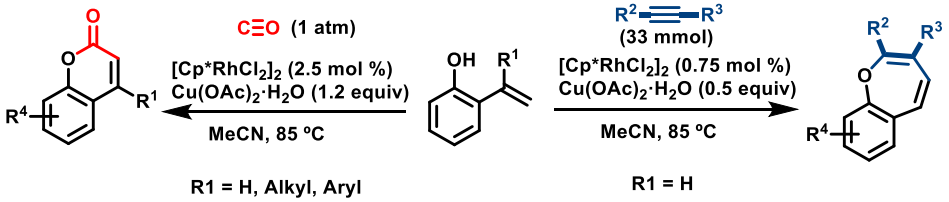
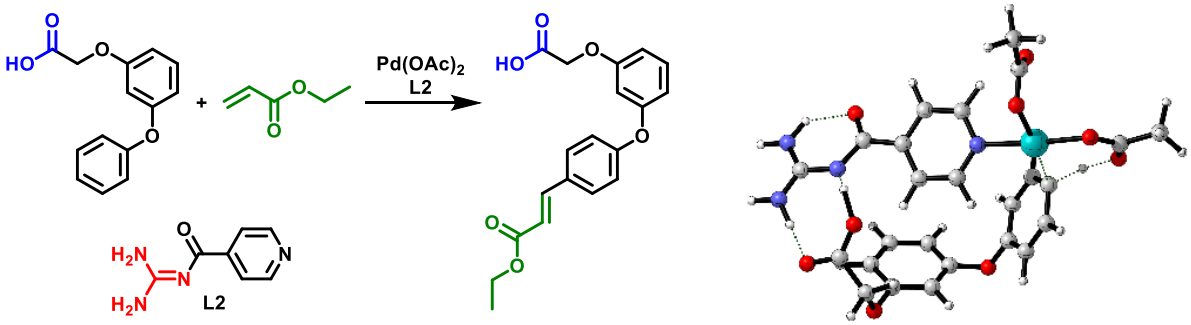
Keywords: *Multigram-scale synthesis, Rh catalysis, C–H Activation*

Transition metal-catalyzed cycloadditions can provide atom-economical approaches to heterocyclic products.[1] Inside this category we can find a number of cycloaddition methodologies based on metal-promoted C–H activation which have flourished in the last decades.[2] Recently our group has disclosed rhodium-catalyzed formal (5+2) and (5+1) cycloadditions of 2-alkenylphenols with either alkynes or carbon monoxide.[3]

In this work we describe an extension of this methodology for the assembly of benzoxepines and coumarins in up to a 33 mmol scale from 2-alkenylphenol precursors, using low loadings (<1 mol%) of $[Cp^*RhCl_2]_2$ as pre-catalyst, and alkynes or carbon monoxide as reacting partners.



We have also started a preliminary study on the development of new strategies to functionalize remote positions in polyaromatic systems using supramolecular interactions. Using DFT calculations (G. Jimenez-Oses) we have designed scaffolds that provide for low activation barriers in the C-H activation (see model). Up to now we have synthesized several ligands and substrates, and we are starting to investigate the catalytic reactions.



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Synthesis of glycomimetics derived from L-iduronic acid in the search for antivirals against dengue virus.

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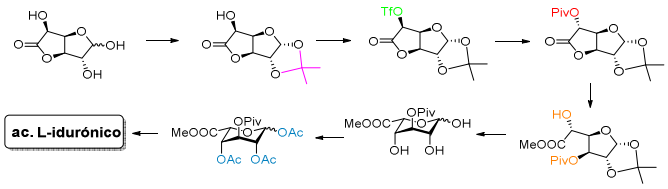
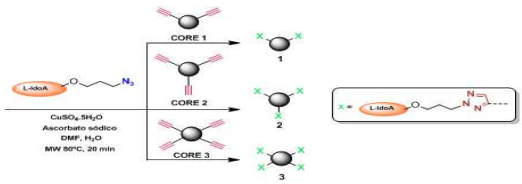
***Keywords**: glycomimetics, L-iduronic acid, antivirals.*

Dengue is an infectious disease caused by the dengue virus and currently there are no drugs and vaccines for this disease. This virus contains on its surface a lecithin (protein) that interacts with a membrane receptor of immune system cells. This receptor has recently been shown to be a glycosaminoglycan (GAG) highly sulphated, composed of N-acetylglucosamine and iduronic or glucuronic acids.[1]

In order to obtain L-iduronic acid, the following synthetic route has been proposed, supported by several research works described previously.[2]



The synthesis of three glycomimetics derived from L-iduronic acid with different degree of multivalence by click quemistry, which simulate the receptors found on the surface of the target cells, and then study the protein-carbohydrate interactions by Surface Plasmon Resonance (SPR).



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Síntesis asimétrica de 2,3-alenoles mediante reacciones de acoplamiento cruzado de Negishi catalizadas por níquel

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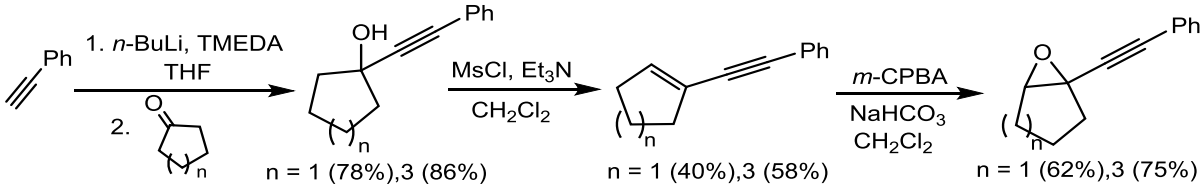
***Keywords**: (2,3-alenoles, Negishi, catálisis metálica)*

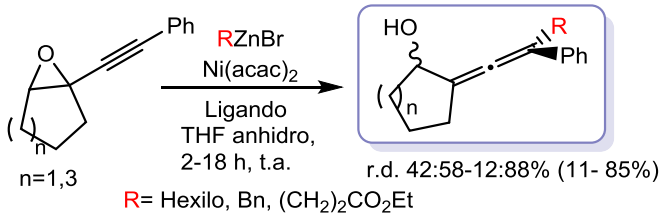
Los alenos son un grupo funcional portador de dos dobles enlaces C=C acumulados, siendo potencialmente quirales debido a la presencia de un eje estereogénico en función de los sustituyentes unidos al fragmento alénico. Dentro de la familia de los alenos destacan los **2,3-alenoles**, presentes en numerosos productos naturales con actividad biológica, que contienen un grupo hidroxilo unido al carbono en posición α al grupo alénico.[1]

En el presente Trabajo de Fin de Máster se presenta un estudio metodológico dirigido a la síntesis diastereoselectiva de 2,3-alenoles mediante reacciones de acoplamiento cruzado de Negishi catalizadas por níquel, empleando diferentes ligandos de tipo amina, de tipo fosfina y de naturaleza carbénica, que pretende tanto mejorar como comparar los resultados obtenidos por Fürstner.[2] Los sustratos empleados son epóxidos propargílicos cuya síntesis se ha abordado en tres etapas a partir de reactivos comerciales (**Esquema 1**).

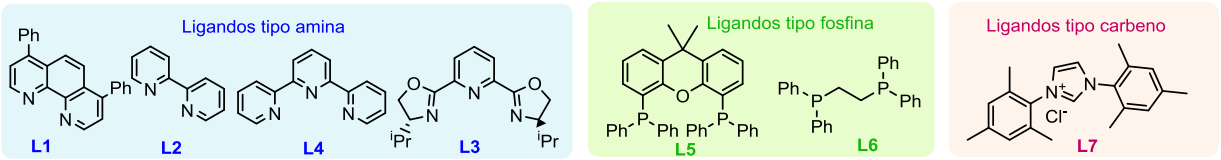


Esquema 1

Las reacciones de acoplamiento cruzado han proporcionado un mezcla diastereoisomérica de los 2,3-alenoles. El rendimiento y diastereoselectividad de las reacciones ha resultado dependiente de la naturaleza del ligando empleado (**Esquema 2**).



Esquema 2



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SIZED-CONTROLLED PREPARATION OF DENDRITIC PICSOMES

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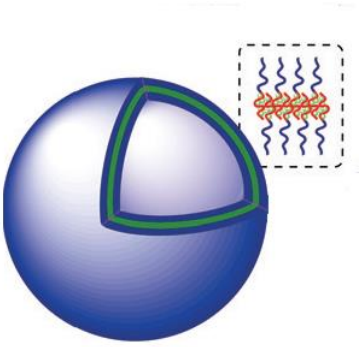
***Keywords**: PICsomes, dendrimers, size-control*

PICsomes are vesicles with a polyion complexes structure characterized by the presence of a hollow sphere surround by a semipermeable membrane. They are prepared from opposite charged block copolymers. In this work we use dendrimers to prepare this type of complexes. Recently, our group has reported the formation of PICsomes from dendrimers and the ability to control their size by selecting the generation and the family of the dendrimer[1]. In this work we hypothesize that the variation in the number of charges of a unique dendrimer will produce a change in the size of the PICsome, finding for the lower dendrimer charges the higher PICsome sizes.

We also study the effect of the ionic strength in these systems by varying the salt concentration during the formation. With this method we have achieved a regulation in the size of this PICsomes from 60 to 1000 nm with a single partially reduced dendrimer.



PICsome structure

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Formación de Vesículas Supramoleculares basadas en Nanotubos Peptídicos

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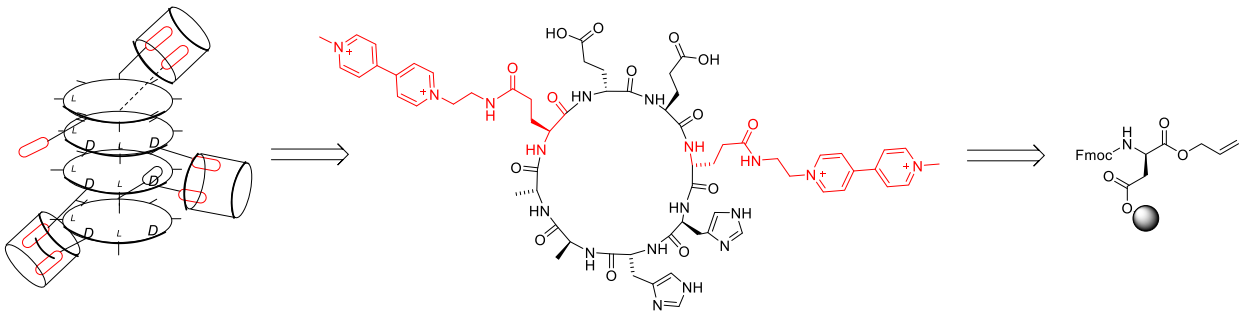
***Keywords**: Ciclopéptidos, nanotubos, cucurbit[8]urilo.*

Una de las características más importantes de los ciclopéptidos es su capacidad para formar nanotubos basados en procesos de auto-ensamblaje y reconocimiento molecular [1]. Los cucurbit[8]urilos pueden encapsular cierto tipo de moléculas en su interior, lo que les permite formar arquitecturas supramoleculares [2], en base a estas propiedades, se pretenden construir vesículas basadas en nanotubos peptídicos. Estos nanotubos tienen diversas características, como la capacidad de insertarse en membranas lipídicas y actuar como antimicrobianos[3].

En este trabajo se han diseñado distintos α-ciclopéptidos, que tras la correspodiente funcionalización adquieren la capacidad de formar nanotubos mediante un proceso de auto-ensamblaje.

El ciclopéptido sintetizado dispone de una estructura hidrofílica que le permite formar enlaces de hidrógeno entre sí, además, algunos residuos fueron funcionalizados con diferentes compuestos derivados del metil-bipiridinio, que en un medio de cucurbit[8]urilo son capaces de estabilizarse mediante la formación sucesiva de dímeros, permitiendo así la formación del nanotubo.



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Design and synthesis of antivirals against the Ebola virus

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***Keywords**: Ebola, antivirals, drugs*

The Ebola virus causes hemorrhagic fevers in humans, is extremely contagious and it has a high mortality rate. Following outbreaks in West Africa in recent years, there was a huge international concern to find vaccines or effective drugs to treat the disease and thus be prepared for future outbreaks. Currently there are neither vaccines nor treatments for this catastrophic disease, therefore, it is necessary to continue research to find drugs to fight against the virus.[1]

The entry of the Ebola virus inside the cell is mediated by the NPC1 receptor (cholesterol transporter Niemann-Pick C1), which binds to a glycoprotein (Gp) that surrounds the viral envelope. The NPC1-Gp binding site is a challenging therapeutic target to design inhibitors for the entry of the virus.[2]

In this work, it is presented the design and synthesis of new diphenylsulfides previously identified by the research group after a virtual screening at the interaction site NPC1-Gp employing the chemical library of the group.[3] The final compounds obtained will be evaluated using pseudotyped viruses that present the glycoprotein of the Ebola virus in its envelope.

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ALENOS Y HETEROCICLOS BIOACTIVOS: APLICACIONES SINTÉTICAS

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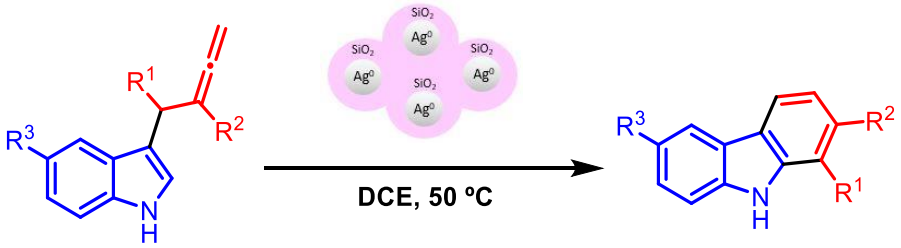
***Keywords**: allenes, catalysis, silver nanoparticles*

Allenes are a class of compounds with two cumulated carbon-carbon double bonds, which are versatile synthetic intermediates in Organic Synthesis.[1] They have shown an interesting reactivity and selectivity affording complex structures in a limited number of steps using a wide variety of transition metals.[2] On the other hand, the indole nucleus is the key component of many natural and synthetic molecules with significant biological activity.[3] Metallic nanoparticles has caught attention during the lasts years because of its efficient reactivity as catalysts. We report herein a controlled carbocyclization reaction of different allenes for the direct preparation of the chemically and biologically relevant carbazole nucleus using silver nanoparticles supported in silica.



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COMPLEJOS DE PLATINO(II) COMO FOTOCATALIZADORES EN LA SÍNTESIS DE FENOLES

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***Keywords**: platino, fotocatálisis, fenoles*

En la última década, la fotocatálisis ha ocupado un lugar privilegiado en la síntesis de compuestos orgánicos. Esto se debe, principalmente, al hecho de que satisface los doce principios de la Química Verde, siendo capaz de usar luz del espectro visible y ultravioleta para acelerar diferentes reacciones a través de la activación selectiva de enlaces bajo condiciones suaves[1a]. Los fotocatalizadores más comunes son complejos metálicos de Ru(II) o Ir(III) y moléculas orgánicas como la eosina Y[1a]. Sin embargo, el desarrollo de catalizadores basados en otros metales ha sido mucho menos estudiado[1b]. Recientemente, nuestro grupo de investigación ha sintetizado complejos de coordinación basados en platino(II) y ligandos 8-hidroxiquinolina diferentemente sustituidos, los cuales han sido fotocatalizadores excelentes en la oxidación de sulfuros usando oxígeno atmosférico[2].

En este trabajo se presenta el estudio de estos nuevos catalizadores en la fotooxidación de ácidos arilborónicos a sus respectivos fenoles en presencia de aire[3]. El mejor catalizador resultó ser el complejo de Pt(II) que contiene una 8-tioquinolina como ligando (figura 1), el cual es capaz de oxidar un gran número de ácidos arilborónicos portadores de diferentes grupos electrón-dadores y electrón-atractores, halógenos o heterociclos, con completa quimioselectividad. Además, se realizaron diferentes estudios mecanísticos, siendo capaces de sugerir un proceso de transferencia electrónica vía oxígeno anión radical como un mecanismo plausible.

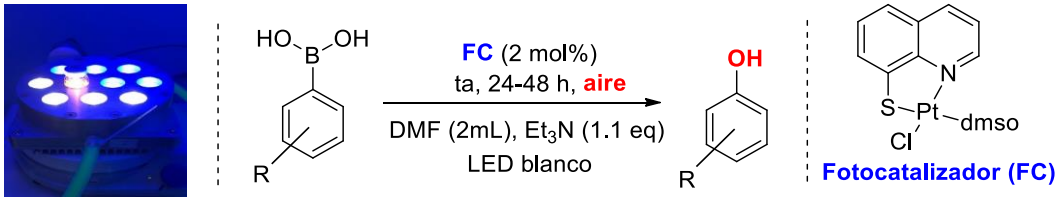

Figura 1. Sistema de irradiación, reacción estudiada y fotocatalizador de Pt(II)

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Rh(III)-catalyzed Double C-H Bond Activation and Annulation of 1-Arylpyrroles with Alkynes: A new entry to Ullazines

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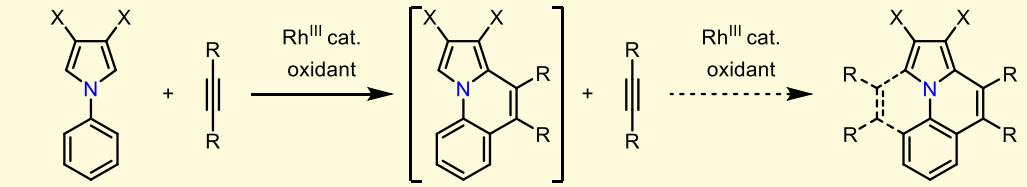
***Keywords**: C-H activation, rhodium catalyst, ullazines*

Transition-metal catalyzed C-H bond activation has proven to be a powerful synthethic methodology to access to different polycyclic aromatic hydrocarbons (PAHs) from readily available starting materials.[1] In this context, in our research group has been recently described the synthesis of a novel class of *N*-doped cationic PAHs bearing the benzo[c,d]fluoranthene scaffold by the Rh(III)-catalyzed double oxidative annulation of 2-arylbenzimidazoles with alkynes.[2] Ullazines are aza-cyclopenta[c,d]phenalenes, conjugated aromatic 16 electron π-systems isoelectronic to pyrene. These units are important building blocks found in organic materials with important aplications as in dye-sensitized solar cells.[3]

In this project we initiate the exploration of a new synthetic route to ullazines by a Rh(III)-catalyzed double C-H activation and annulation of 1-arylpyrroles and pyrroloquinoline with alkynes.



X = H, Br, CO_2Me

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DESARROLLO DE SECUENCIAS DE CICLACIÓN/ACOPLAMIENTO RADICÁLICO CATALIZADAS POR NÍQUEL

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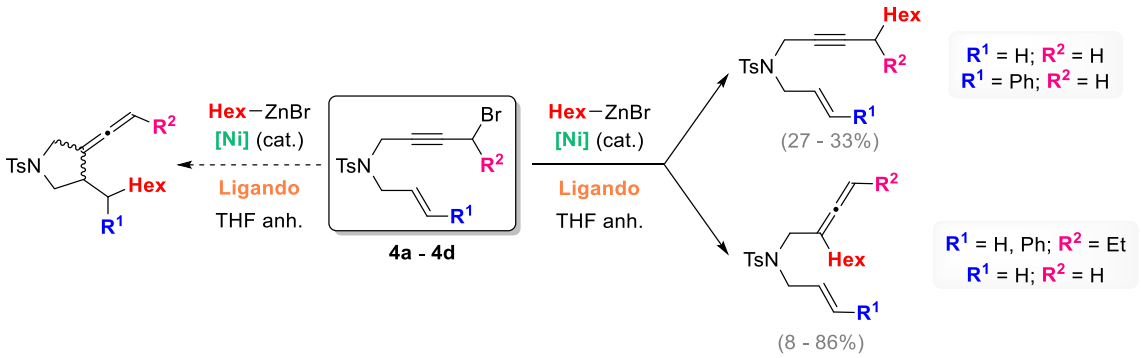
***Keywords**: (alquenilidenheterociclos, níquel, organozinc)*

La síntesis de moléculas complejas con una estructura definida a partir de moléculas precursoras simples es uno de los principales retos en Química Orgánica. En ese sentido, las moléculas que presentan dos o más dobles enlaces C=C acumulados en su estructura están adquiriendo gran importancia. Dentro de este grupo se encuentran los alenos, grupo funcional dotado de una gran versatilidad sintética, que se encuentra en la estructura de algunas moléculas con propiedades biológicas.[1]

En este trabajo se describe una aproximación a la síntesis de alquenilidenheterociclos mediante una secuencia de ciclación/acoplamiento radicálico catalizado por níquel a partir de 8-bromo-1,6-eninos diferentemente sustituidos y bromuro de hexilzinc. Para abordar el estudio de su comportamiento se han empleado como catalizadores $Ni(acac)_2$ y $[Ni(py)_4]Cl_2$ y diferentes ligandos, de tipo amina o fosfina.

Los productos obtenidos hasta el momento son alenos de cadena abierta y/o productos de acoplamiento propargílico, habiéndose obtenido los mejores resultados en presencia de ligandos nitrogenados (***Esquema 1***). Los resultados en presencia del inhibidor radicálico TEMPO sugieren además que el mecanismo por el cual se forman estos productos es radicálico, tal y como se preveía a partir de resultados previos del grupo de investigación.[2]



Esquema 1

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Diborilación de Ciclobutenos Catalizada por Base

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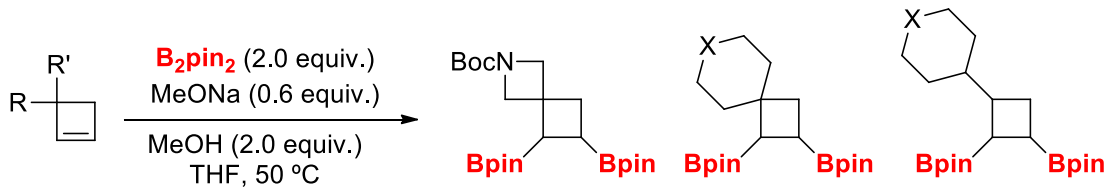
***Palabras Clave**: espirociclo, ciclobutilboronatos, diborilación.*

Los ciclobutanos son compuestos de gran importancia en química orgánica, ya que además de ser intermedios sintéticos muy útiles, se encuentran presentes en numerosos productos naturales y farmacéuticos. La importancia de estos ciclos se debe a que aportan rigidez a la molécula al mismo tiempo que tridimensionalidad. Además, la presencia de un espirociclo[1] en la estructura permite explorar nuevas regiones del espacio químico, lo cual está ligado con una mejora de las propiedades fisicoquímicas y metabólicas.

Una clase importante de ciclobutanos son los ciclobutilboronatos, que al poseer un éster borónico en su estructura, son de gran utilidad debido a que el enlace C-B puede ser transformado en numerosos grupos funcionales lo que permite acceder a una gran variedad de compuestos a partir de un mismo intermedio sintético común. [2]

En este Trabajo Fin de Máster se ha estudiado por primera vez la diborilación de ciclobutenos en condiciones que no requieren el uso de metales de transición.[3] La reacción transcurre de forma diastereoselectiva tanto para ciclobutenos monosustituidos como para espirocompuestos. Mediante esta metodología se han preparado ciclobutanos doblemente borilados, estructuras muy interesantes para una posterior funcionalización.



R' = R, H **X: NBoc, O**

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Synthesis of crosswise phthalocyanines as precursors of novel photosensitizers

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***Keywords**: Photodynamic Therapy (PDT), Phthalocyanine, Phtosensitizer (PS)*

Nuevos casos de cáncer se diagnostican diariamente siendo la causa de millones de muertes todos los años. La necesidad de desarrollar nuevas medicinas y terapias es evidente, donde la Química juego un papel fundamental. Dentro de estos nuevos tratamientos, la terapia fotodinámica (PDT) juega un papel importante. La PDT se trata de un tratamiento no invasivo basado en una combinación de tres componentes: un fotosensibilizador (PS) no tóxico, luz y oxígeno molecular. Esta combinación es capaz de producir especies reactivas y citotóxicas de oxígeno (ROS) que llevan a la muerte celular. Esta terapia puede ser usada en el tratamiento de patologías oncológicas y otras enfermedades no neoplásticas. Entre los diferentes PSs destacan las ftalocianinas (Pcs), ya que presentan una gran versatilidad química y propiedades físicas adecuadas. Sin embargo, la gran mayoría de las Pcs estudiadas son apenas solubles en medios acuosos y presentan una gran tendencia a formar agregados, causando la inactivación fotodinámica y restringiendo su uso para aplicaciones in vivo.

Este trabajo se centra en la síntesis de nuevas ZnPcs como potenciales PSs de tercera generación para la terapia fotodinámica. Concretamente, se pretende preparar ZnPcs con una geometría ABAB (donde A y B se refieren a diferentes unidades isoindólicas), funcionalizadas por una parte con un grupo sustituyente voluminoso que previene la agregación de los macrociclos, y por otra parte, con unidades de ácido fólico, que pueden actuar como agentes específicos para la acumulación selectiva sobre el tejido objetivo. Con este fin, se han preparado dos tipos de ftalonitrilos precursores de ZnPcs: i) uno de ellos funcionalizado con grupos voluminosos para dirigir la condensación con otro ftalonitrilo hacia la formación de ZnPcs ABAB; y ii) ftalonitrilos que contienen grupos funcionales capaces de reaccionar con el ácido fólico en una segunda etapa. De esta manera, se han preparado una serie de ZnPcs ABAB que, en la actualidad, están siendo probadas en diferentes condiciones para conseguir unir dos restos de ácido fólico en su estructura.

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Síntesis de nanopuntos de carbono para aplicaciones fotoquímicas avanzadas

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***Keywords**: nanopuntos cuánticos de carbono, síntesis por láser pulsado.*

Los puntos cuánticos de carbono (*carbon quantum dots, CQDs*) son nanoestructuras novedosas con carácter de punto cuántico, debido a su morfología y propiedades.[1] El creciente interés por los CQDs se debe al confinamiento cuántico de sus electrones, que afecta a su carácter semiconductor y a sus propiedades optoelectrónicas o magnéticas. Por otro lado, por estar compuestos fundamentalmente por carbono, presentan nula o baja toxicidad, a diferencia de otras nanopartículas o nanomateriales inorgánicos. Además, poseen absorción y emisión de luz en la región UV-Vis, así como bandas de emisión dependientes de la longitud de onda de excitación. Debido a estas propiedades, los CQDs se pueden aplicar en distintos campos como bioimagen, teranóstica, (bio)sensores y nuevos materiales optoelectrónicos útiles para la conversión y almacenamiento de energía o en procesos de *up-conversion* o multifotónicos.
La síntesis de CQDs se ha realizado mediante síntesis por láser pulsado siguiendo una aproximación *bottom-up* a partir de precursores orgánicos sencillos. Para ello se usó un láser Nd:YAG a 532 nm (100 mJ/pulso, 10 Hz, 6 ns/pulso) dirigido dentro de un reactor fotoquímico, como se representa en la Figura 1.[2]

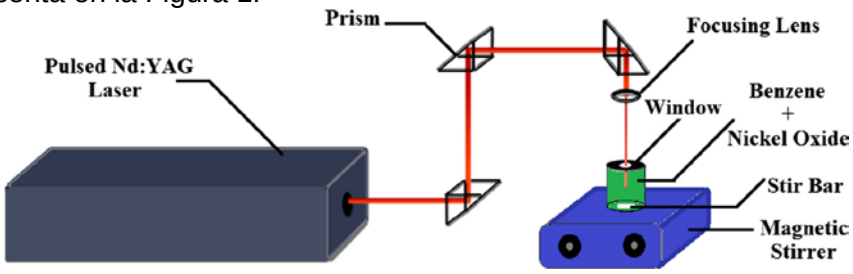

Figura 1. Síntesis de CQDs mediante láser pulsado.

La caracterización de los CQDs sintetizados se llevó a cabo mediante microscopía electrónica AFM y STEM combinada con EELS y EDS, espectroscopias XPS y FTIR, así como espectrofotometrías de absorción y emisión.

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EXTENSIÓN DE LA REACCIÓN DE DE MAYO MEDIADA POR LUZ VISIBLE A COMPUESTOS HETEROAROMÁTICOS

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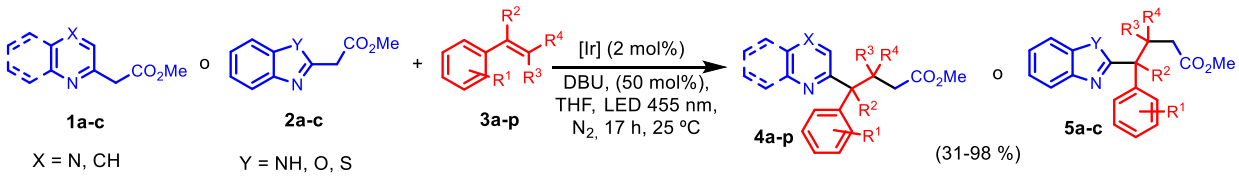
***Keywords**: Fotocatálisis, De Mayo, heteroaromáticos*

Los compuestos heteroaromáticos han demostrado ser productos con un elevado interés para la industria farmacológica y agroquímica, lo que ha incentivado el estudio de nuevos métodos de síntesis que permitan llevar a cabo su funcionalización de forma sencilla, sostenible, económica y eficaz.[1]

Por otro lado, la fotocatálisis ha emergido en la última década como una herramienta sintética muy poderosa que permite llevar acabo transformaciones no accesibles anteriormente mediante metodologías clásicas. La reacción de De Mayo[2] abrió la puerta a la obtención de compuestos 1,5-dicarbonílicos a partir de 1,3-dicarbonilos. En este trabajo se presenta la primera reacción de De Mayo fotosensibillizada entre compuestos heteroaromáticos portadores de un grupo electrón-atractor en posición β y derivados de estireno.

El estudio del alcance de la reacción se centró en modificar, por una parte el anillo heteroaromático y por otra la sustitución del doble enlace. De esta forma, se obtuvieron los compuestos **4a-p** y **5a-c**, obteniéndose mejores resultados cuando el derivado de estireno poseía grupos dadores de electrones o halogenados.



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Palladium Catalyzed [3+2] Cycloaddition Reactions of Alkylidenecyclopropanes with Imine Partners: Straightforward Access to Small Heterocycles

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***Keywords**: alkylidenecyclopropane, hetero-cycloaddition, palladium*

Transition metal catalyzed cycloaddition reactions are powerful synthetic tools that allow the assembly of highly complex hetero- and carbo-cyclic systems from simple and non-activated precursors. In this context, our group has widely explored the use of alkylidenecyclopropanes (ACPs) as 3C components in intramolecular cycloaddition reactions with a high variety of C-C unsaturated partners such as alkynes, alkenes, dienes and allenes[1] and even developing the first examples of highly enantioselective [3C + 2C] and [3C + 4C] intramolecular cycloadditions of ACPs with palladium catalysts.[2] Albeit palladium has demonstrated a high efficiency in cycloadditions that involve the formation of C-C bonds, examples of hetero-[3 + 2] cycloadditions with ACPs are almost unknown.[3]

Herein, we present our efforts on the development of novel palladium catalyzed hetero-[3 + 2] cycloadditions with ACPs. In particular, a catalytic system based on a Pd (0) complex and a precisely selected ligand shows remarkable efficiency in the intramolecular [3 + 2] cycloaddition of ACPs with oxime ethers (**Figure 1**). The reactions provide an efficient access to highly functionalized hetero-bicyclic systems.

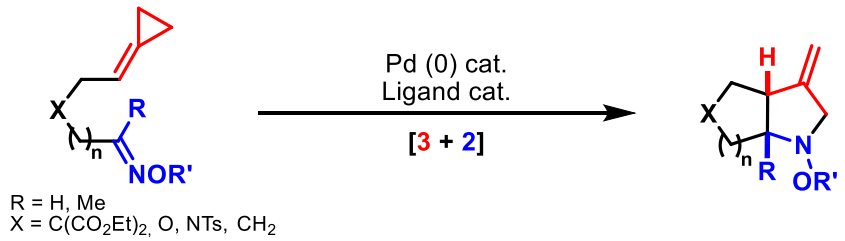

***Figure 1.** New palladium catalyzed [3 + 2] hetero-cycloadditions.*

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Study of the reactivity of organometallic indium reagents with arynes

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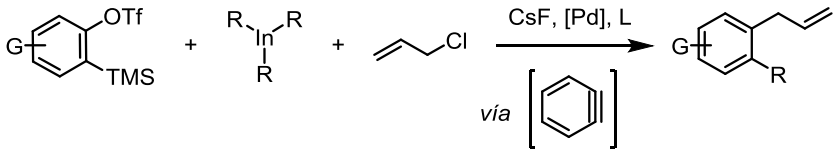
***Keywords**: indium organometallics, arynes, multicomponent reactions*

Arynes are short-lived reaction intermediates with a great interest in organic synthesis.[1] The discovery of the new reactivity of this unstable species, an area which our research group has wide experience,[2] constitutes a current challenge in organic chemistry. In this context, the project is focused on the study of the reactivity of arynes with indium (III) organometallic species.[3] This project is carried out in collaboration with the group of professors Sestelo and Sarandeses at UDC (Universidade da Coruña) who are specialist in indium chemistry.



Here we report the development of a new three component reaction for the selective and efficient synthesis of 2-allyl-1,1'-biphenyl derivatives, involving benzyne, allyl chloride and organometallic indium reagents by palladium catalysis. In addition, we focus our attention in the reaction mechanism. On the one hand, we targeted to demonstrate that the reaction takes place through aryne intermediates, rather than other plausible mechanism. On the other hand, we tried to find some experimental evidences of the insertion of benzyne into the C-In bond.

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Design of nanosensors based on azocompounds

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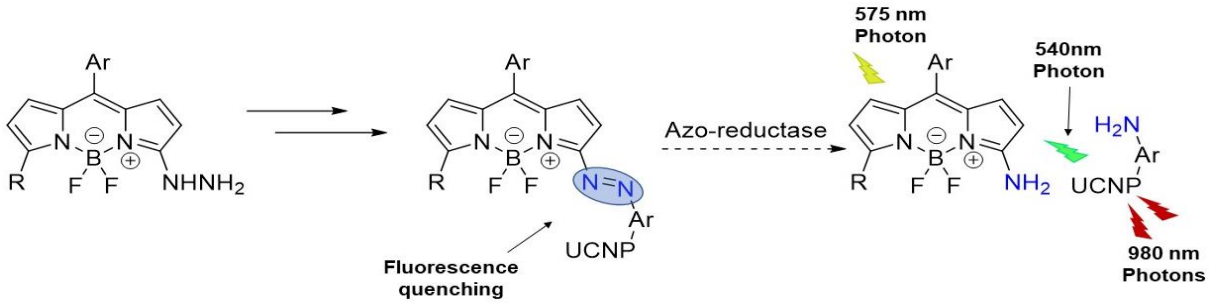
***Keywords**: BODIPY, Azobenzenes, Hypoxia detection.*

This End of Master poster enclose the design of smart nanosensors based on Upconverting nanoparticles (UCNP) functionalize with BODIPY (Boron DIpYrromethenes) conjugated to an azo bond for the in vivo bioimaging detection of hypoxia. Hypoxia is an oxygen-deprived condition in which the tissues have an increase expression of reductases enzymes associated with inflammatory processes and ischemia tissues. This sensors are based on the ability of an azo compound to inhibit the fluorescence of a fluorophore, through nonradiative emission processes associated with the isomerization of N=N bond, a characteristic that combines with the capacity to recover the fluorescence in reducing media, which favours the reductive cleavage of the N=N bond, generating the corresponding amines.

Combining these two characteristics in this work, we synthetize and optimize a series of fluorescent derivatives of BODIPYs, prepared from pyrrole and different aromatic aldehydes, and perform their subsequent derivatization with an azo compound, using a synthesis methodology developed in our lab. The photophysical and electrochemical properties of the obtained compounds will be studied and their behaviour under chemical reducing conditions will be evaluated. Finally, its biological properties will be evaluated, in conditions of normoxia and hypoxia.



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REACCIONES DE CICLACIÓN-ACOPLAMIENTO DE ÉSTERES REDOX-ACTIVOS CATALIZADAS POR NI

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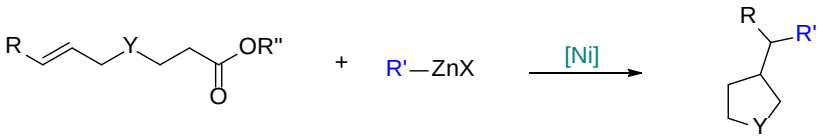
***Keywords**: Níquel, ésteres redox-activos, acoplamiento cruzado*

A lo largo de los últimos años, los estudios sobre la formación de enlaces alquilo-alquilo catalizada por metales de transición han cobrado bastante importancia.[1] Generalmente, estos procesos de acoplamiento cruzado implican el uso de especies alquil-metálicas junto con haloalcanos. Sin embargo, recientemente ha surgido una alternativa interesante que consiste en sustituir estos haloalcanos por ésteres redox-activos (RAEs), cuyo empleo presenta ventajas derivadas de su mayor estabilidad y menor toxicidad.[2]

Este proyecto describe las reacciones en cascada de ciclación-acoplamiento de tipo Negishi catalizadas por Ni de ácidos carboxílicos que contienen un alqueno, a través de sus ésteres redox-activos derivados, lo que consigue generar dos enlaces C(sp^3)-C(sp^3) en una única operación sintética. La reacción podría transcurrir mediante un mecanismo radicalario que implicaría una etapa de transferencia de un solo electrón entre el complejo metálico y el éster redox-activo.



Esquema 1: Reacción en cascada de ciclación-acoplamiento de tipo Negishi de RAEs catalizada por Ni

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Carbon Nanostructures for biological applications

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***Keywords**: DC-SIGN, nanostructures, multivalent.*

The Ebola virus outbreak in Africa in 2014 caused a great impact due to its quick global spreading, thus generating a need to face this disease. Since there is no specific treatment for Ebola virus, the development of new compounds able to inhibit viral infection is crucial.

The designed nanostructures consist on fullerene derivatives functionalized with carbohydrate moieties. These multivalent systems act as glycomimetics of the virus in its interaction with a receptor present in the plasma membrane of certain cells, known as DC-SIGN.[1] This cellular receptor is characterized by its affinity for carbohydrates, basing this recognition on multivalent carbohydrate-protein interactions. For this reason, the designed nanostructures can be considered as very promising and interesting tools to interfere in biological events where lectins such as DC-SIGN are involved.[2]

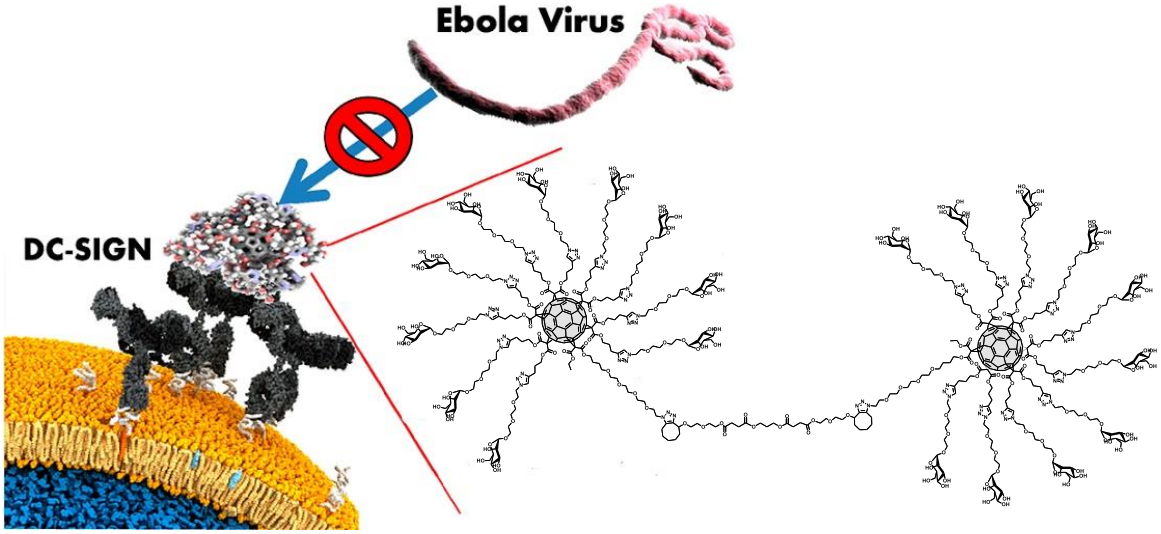

Figure: Glycofullerenes as efficient inhibitors of Ebola virus infection

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SEEING MICROBES: DEVELOPMENT OF SPECIFIC FLUORESCENT DYES FOR TARGETING BACTERIA CELL-WALL

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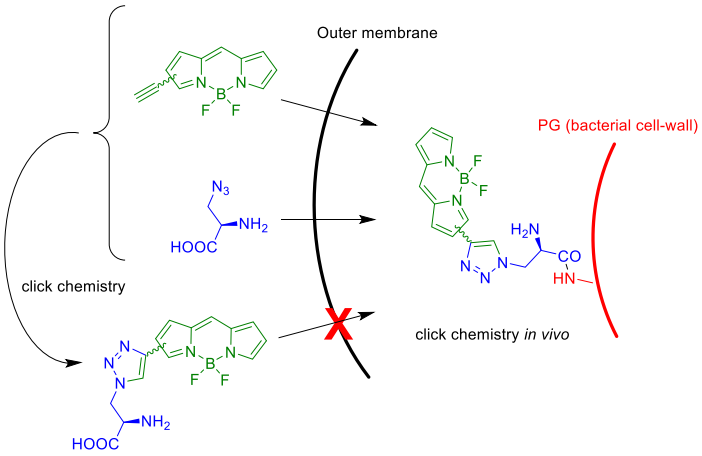
***Keywords**: Fluorescent bioprobes, Peptidoglycan, BODIPYs*

Shedding light on the complex machinery involved in the dynamics of bacterial peptidoglycan (PG) is key to advance in the rapid development of new antibiotics. These antibiotics should provide a rapid solution to the growing problem of the bacterial resistance to penicillin and related β-lactam antibiotics.[1] To this end, smarter fluorescent PG probes are demanded to conduct accurate studies on PG dynamics (forming, remodeling and repairing) by high-resolution fluorescence microscopy,[2] especially on gram(-) bacteria due the resistance exerted by their outer membrane to dye trafficking. Bioorthogonally combining a highly fluorescent BODIPY unit (small or polar enough) with a proper D-amino-acid rest (D-ala) could be an interesting strategy to efficiently probe nascent PG in living gram(-) bacteria (Figure).[3] This communication shows preliminary results in relation with this strategy, which include the synthesis of a selected battery of alkynylBODIPYs, to test differential ability to probe azide-functionalized nascent PG by *in-vivo* click chemistry; the synthesis of related triazole amino-acids, to test differential capability to directly mark PG in both gram(+) and gram(-); and the first bioimaging experiments conducted with these dyes.



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Molecular Recognition in Self-Assembled Nanotubes

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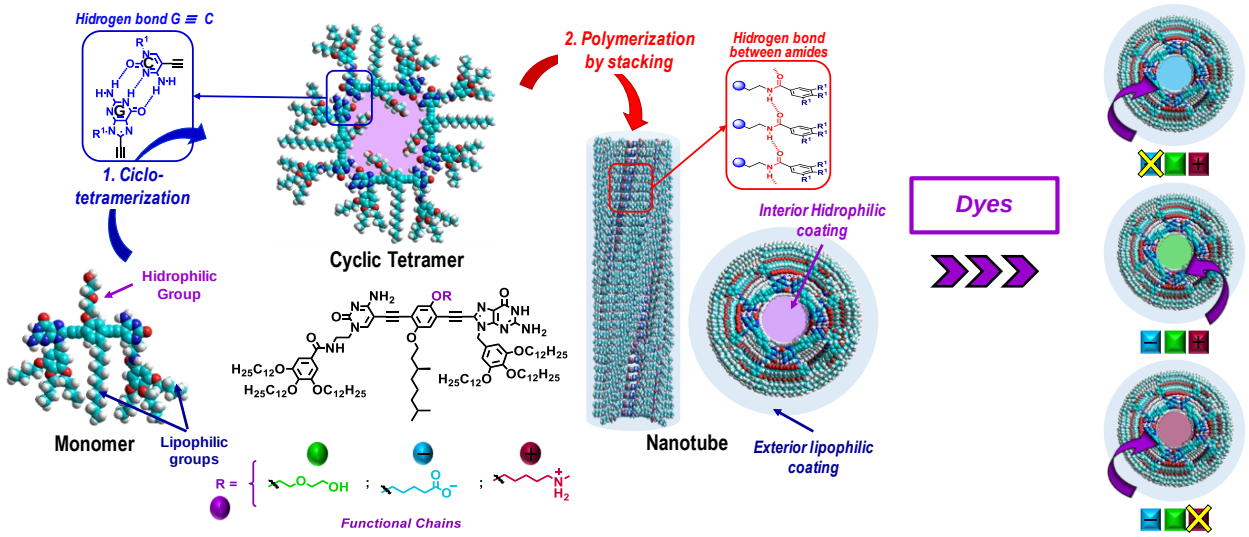
***Keywords**: nanotubes, self-assembly, functionalization*

Self-assembled nanotubes are one of the most relevant supramolecular structures due to their dimensions and the possibility of housing and transporting inside them. Introducing different functionalities to these supramolecular entities would be an elegant tool to increase their applicability. However, there are only a few examples where pore functionality is used.[1]
In our research group, self-assembly processes for the formation of cyclic tetramers through hydrogen bonding of nucleic base derivatives (guanine and cytosine) has been widely studied.[2-4] This project is focused on the preparation of *liposoluble self-assembled nanotubes having an inner pore that can be functionalized with hydrophilic groups*, either neutral or charged, *able to extract selectively polar substances in their interior*. The use of dyes will allow to observe the inner pore functionality, an open gate for future research.



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Reacciones catalíticas de formación de enlaces C—C a partir de derivados de yodo hipervalente generados en un proceso *one-pot*

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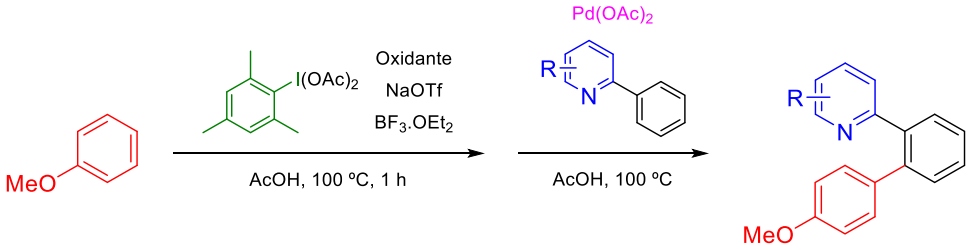
Keywords: *catálisis, funcionalización C—H, yodo hipervalente.*

Las reacciones de funcionalización C—H catalizadas por metales de transición son una herramienta muy útil en Química Orgánica que está siendo objeto de estudio en los últimos años. Esto se debe a que para formar un enlace C—C o C—heteroátomo no necesitan un sustrato previamente funcionalizado y por tanto permiten rutas sintéticas más cortas, económicas y sostenibles en comparación con los acoplamientos cruzados clásicos.[1]

Además, la funcionalización C—H permite acoplar el sustrato utilizando diversos agentes de acoplamiento. En este ámbito están cobrando importancia las especies trivalentes de yodo como el diacetoxiyodobenceno (PIDA) o las sales de diarilyodonio, que pueden actuar como agentes acetoxilantes o arilantes respectivamente. Estos compuestos, debido a su carácter oxidante, implican un ciclo catalítico de Pd(II)/Pd(IV), que, aunque es menos común, es más resistente a la humedad y el oxígeno.[2, 3]

En este trabajo se va a estudiar la reacción de funcionalización C—H dirigida utilizando sales de diarilyodonio generadas en un proceso *one-pot* a partir de diacetoxiyodomesitileno y el areno que se pretende transferir.



Los resultados obtenidos hasta el momento prueban que los derivados de 2-fenilpiridina son sustratos con un grupo director óptimo que conduce únicamente al producto monoarilado. El uso de $Pd(OAc)_2$ (10 mol%) y varios aditivos, consigue la transferencia de anisol con un rendimiento moderado.

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Synthetic studies of ionic liquids such as electrolytes for batteries

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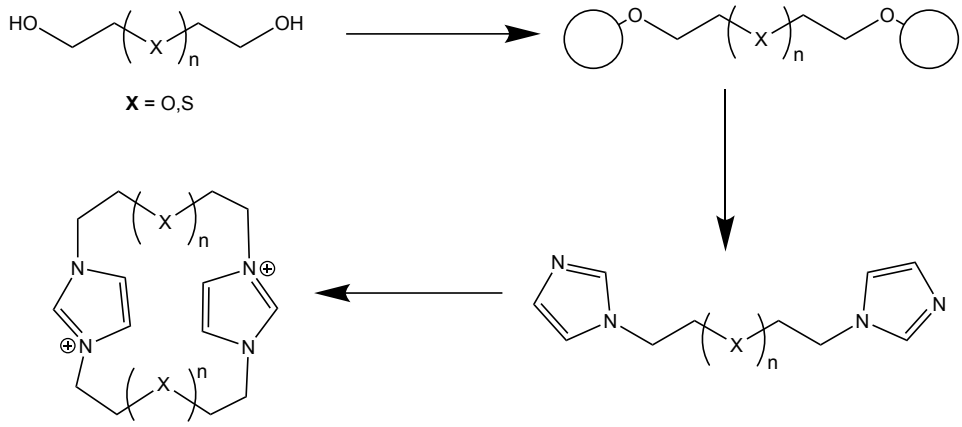
Keywords: *Sodium-Ion Batteries, Room Temperature Ionic Liquids, crown ethers.*

The replacement of lithium-ion batteries (SIBs) with sodium-ion batteries has become a highly explored alternative due to the greater abundance and low cost as energy storage technologies.[1]Being the electrolyte a crucial component in the construction of the batteries, the PEPARO group has participated actively in the synthesis, characterization and determination of the properties of these, interested in the RTILs (Room Temperature Ionic Liquids) for their low volatility, excellent thermal stability, safety and conductivity, using imidazolium and thiazolium cations.[2]

The present project is the beginning of the synthesis of a new family of crown ethers which study will be continued to finally perform the electrochemical tests.



Scheme 1. Synthetic route mould.

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Catálisis heterogénea soportada en grafeno en la oxidación de sulfonamidas.

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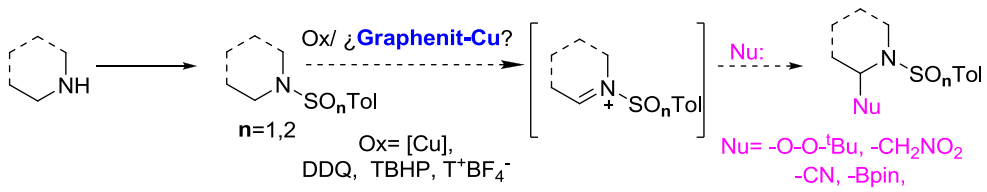
Keywords*: Catálisis heterogénea, grafeno, sulfonamidas*

La química verde ha ganado mucha relevancia en los últimos años y con ella el empleo de catalizadores heterogéneos sobre los homogéneos, tanto por su sencillez en el manejo como por la recuperación de éstos tras la reacción. Materiales como el grafeno han demostrado su utilidad en la catálisis heterogénea, siendo capaces de interactuar con metales gracias a su deslocalización electrónica y modificando las propiedades de éstos de forma muy interesante a la hora de utilizarse como catalizadores.[1]

Tenemos interés en aplicar el graphenit-Cu (I); un material robusto y versátil de Cu(I) preparado en nuestro grupo de investigación;[2] en reacciones que impliquen intermedios radicalarios o catiónicos, ya que éstos podrían ser estabilizados por la lámina de grafeno.[3]

Centramos nuestra atención en el proceso de oxidación de aminas, el cual implica tanto intermedios catiónicos como radicalarios y pueden ser catalizados por especies de cobre(I). En particular, hemos analizado el efecto del graphenit-Cu(I) comparándolo con otras especies de cobre en la transformación de sulfinamidas y sulfonamidas al correspondiente iminio usando diferentes métodos. Estas reacciones, que no han sido estudiadas previamente con sulfinamidas y muy poco estudiadas con sulfonamidas, permitirían la introducción de nucleófilos proporcionando compuestos de gran interés sintético (Esquema 1). El objetivo sintético último de este estudio preliminar es la borilación de la posición alfa al nitrógeno de forma asimétrica con ayuda de un grupo quiral unido al nitrógeno.



Esquema 1

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‘Síntesis de derivados indólicos y evaluación como potenciales semiconductores en OFETs’

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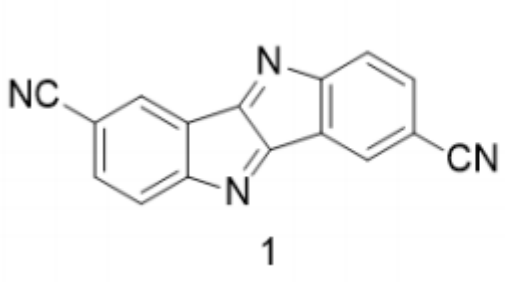
***Keywords**: materiales, electrónica, indólicos.*

Los transistores de efecto de campo basados en materiales orgánicos (Organic Field Effect Transistors, OFETs) están llamados a jugar un papel de gran importancia en el desarrollo de la electrónica molecular[1] . Los materiales orgánicos presentan grandes ventajas: su estructura y propiedades pueden ser modularas fácilmente mediante la introducción de sustituyentes, pueden ser manipulados en disolución, reduciendo costes de procesado, y pueden ser depositados en láminas flexibles. Sin embargo, hasta la fecha no se han desarrollado materiales que, reuniendo las propiedades necesarias para actuar como semiconductores en un OFET (transporte de cargas, estabilidad, etc), presenten niveles electrónicos adecuados para interaccionar eficazmente con los electrodos utilizados habitualmente (ITO, plata, calcio).

Con objeto de disponer de materiales que reúnan las condiciones requeridas, hemos diseñado una serie de derivados indólicos. El objetivo de este proyecto es llevar a cabo la síntesis de los derivados indólicos sustituidos como los nitrilos 1 y 2, para estudiar experimentalmente sus propiedades.



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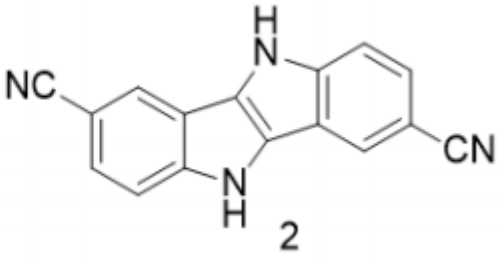

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Synthesis of Cyclic Peptide Capsules for the Development of Nanoreactors

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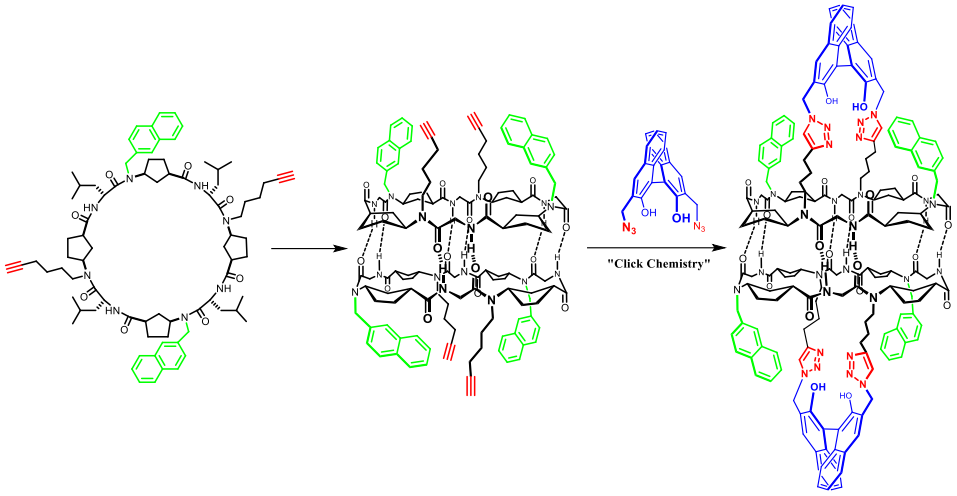
***Keywords**: catalysts, enzymes, capsules.*

In the last decades, the development of new catalytic system has experienced a huge growth with important contributions in both academia and industry. However, despite all the improvements achieved, the development of new catalysts with more selectivity control able to mimic enzyme properties is still highly necessary. Inspired by the way enzymes complex a substrate in their binding pocket several research groups have designed self-assembled nanoreactors that are able to select between a range of different molecules or intermediates to fit inside as a new tool to gain selectivity control.[1]

In our group, we have synthesized self-assembled cyclic peptides which are able to encapsulate transition metal complexes[2], anions[3] and organic molecules[4]. Herein, we present the synthesis of a novel cyclic octapeptide as precursor of new capsules. For this purpose, this peptide is endowed with two alkynyl chains. This allow the *click* reaction with diazide derivatives, such a chiral BINOL, in order to form new molecular containers with potential catalytic applications.



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ESTUDIO DE LA TRANSFERENCIA DE QUIRALIDAD AXIAL A CENTRAL POR DESAROMATIZACIÓN OXIDANTE DE BINOLES ENANTIOPUROS UTILIZANDO OXONO COMO FUENTE DE DIMETILDIOXIRANO

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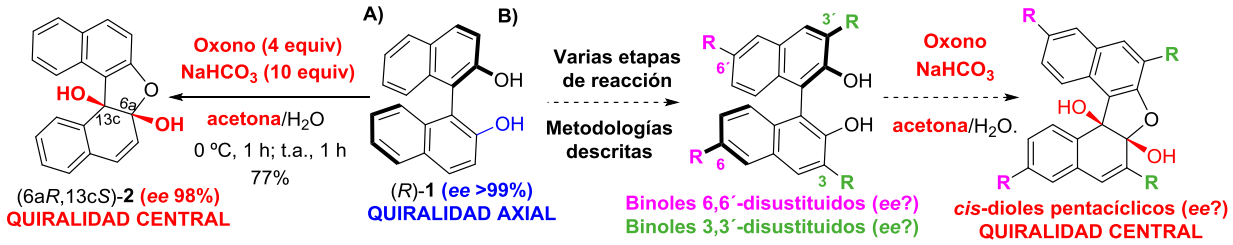
***Palabras clave**: Desaromatización oxidante, Oxono, transferencia de quiralidad.*

En los últimos años se ha estudiado en nuestro grupo de investigación la desaromatización oxidante de *p*-alquilfenoles utilizando el sistema Oxono/$NaHCO_3$/CH_3CN, como fuente de oxígeno singlete,[1] para dar *p*-peroxiquinoles o *p*-quinoles, tras la correspondiente etapa de reducción.[2] Más recientemente, se ha descubierto que si el procedimiento de desaromatización oxidante se lleva a cabo con el sistema Oxono/$NaHCO_3$/acetona, como fuente de dimetildioxirano (DMDO),[3] se obtienen de manera selectiva los *orto*-quinoles o epoxi-*orto*-quinoles dependiendo de la sustitución del fenol o naftol.[4] Además (**Esquema 1A**), si la reacción se realiza sobre el binol enantiopuro (*ee* >99%) (*R*)-**1**, que posee quiralidad axial, se obtiene el *cis*-diol pentacíclico (6a*R*,13c*S*)-**2**, que posee dos centros estereogénicos y presenta un 98% de *ee* lo que indica que durante el proceso se ha producido una eficiente transferencia de la quiralidad axial de (*R*)-**1**, hacia la quiralidad central de (6a*R*,13c*S*)-**2**.



Esquema 1

En este trabajo se pretende estudiar el alcance de la desaromatización oxidante de binaftoles enantiopuros diferentemente sustituidos, así como la evaluación de la eficiencia en la transferencia de quiralidad. Por ello (**Esquema 1B**), se ha realizado la síntesis de binaftoles 6,6´- o 3,3´-disustituidos a partir del binol comercial (*R*)-**1** utilizando metodologías descritas en la bibliografía que implican una o varias etapas de reacción y se ha evaluado su exceso enantiomérico mediante HPLC quiral. Seguidamente, se ha llevado a cabo la reacción de desaromatización oxidante sobre estos derivados y se ha evaluado su pureza enantiomérica, así como la eficiencia en la transferencia de quiralidad axial a central.

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Synthesis of difunctionalized 1,4-dienes using synergistic Cu/Pd catalysis

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***Keywords**: 1,4-dienes, copper, palladium*

1,4-Dienes, so called skipped dienes, are key structural motifs present in a wide array of biologically active natural compounds.[1] An interesting feature in the construction of these structures is to incorporate stereodefined functionalization in both termini of the diene as a handle for the construction of complex target molecules.

Our group reported a methodology to afford borylated skipped dienes with total regio-, stereo- and chemoselectivity based on synergistic Cu/Pd catalyzed reaction of alkynes, B_2pin_2 and allylic carbonates. This reaction entails the use of alkynes as transient alkenylcopper reagents in palladium catalyzed allylic substitution reactions.[2]

Based on these precedents, here we propose two different strategies to afford difunctionalized 1,4-dienes with high regio-, stereo- and chemeoselectivity. In the first approach, we applied our reported methodology using allylic carbonates and alkynes catalyzed by Cu/Pd to obtain skipped dienes with two boronic esters in both ends of the structure *(Figure 1).*

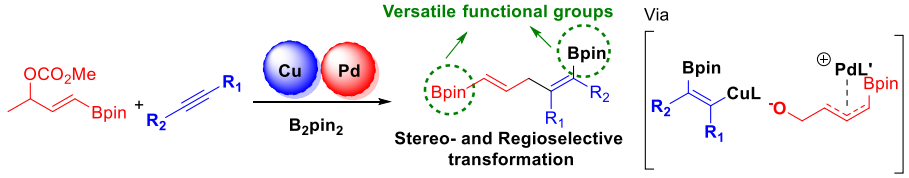

Figure 1. Synthesis of difunctionalized 1,4-dienes using synergistic catalysis from allylic carbonates.

In the second approach, we propose the synthesis of skipped dienes bearing two different functional groups, a boronic ester and allylic alcohol from vinyl-substituted cyclic carbonates[3] and alkynes using synergistic catalysis *(Figure 2).*

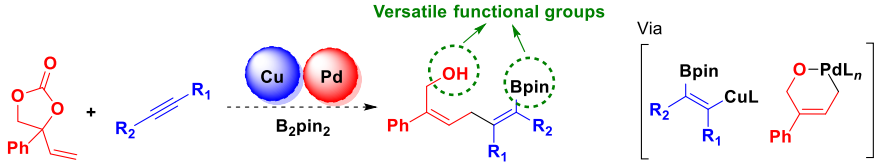

Figure 2. Synthesis of 1,4-dienes using vinyl-substituted cyclic carbonates and synergistic catalysis.

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Exploring Surfactant Peptide Replication

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***Keywords**: system chemistry · micelle · autocatalysis*

Life is a paradigmatic example of a non-equilibrium system, where cells and other living-containing structures act as sophisticated nanoscale machines. **Nature** has integrated **supramolecular self-assembling** structures that operate under **non-equilibrium** regime, and where **replication** plays a key role[1]. **Artificial replication** induced by templates has been achieved both in small molecules capable of recognition and in larger supramolecular structures[2]. An alternative and very attractive strategy uses systems where self-assembly structures of an amphiphilic product, catalyze an **interfacial reaction** to form their own components[3]. Moreover, this mechanism can form compartments which allow for enclosure of chemical components and reactions[4].

Here, we hypothesize that amphiphilic molecules derived from natural-occurring aminoacids and fatty acyl chains through amide bond formation can yield micelle-generating compounds, self-assembling in **supramolecular structures**[5], and even displaying an autocatalytic mechanism (**Figure 1**). We have obtained a library of fatty acyl amino acids, comprising eight **amphiphilic compounds** derived from apolar aminoacids (alanine, phenylalanine, valine and glycine), and six compounds derived from polar aminoacids (serine, cysteine and histidine). Their surfactant properties have been qualitatively assessed through a **foaming test**. A first attempt towards spontaneous self-assembly of these amphiphilic structures, via interfacial reaction using phase separation conditions, has been conducted. Results from kinetic studies, although preliminary, suggest that one of our compounds could display autocatalysis in phase separation conditions, demonstrating spontaneous **physical micellar catalysis**, as our proposed mechanism suggests.

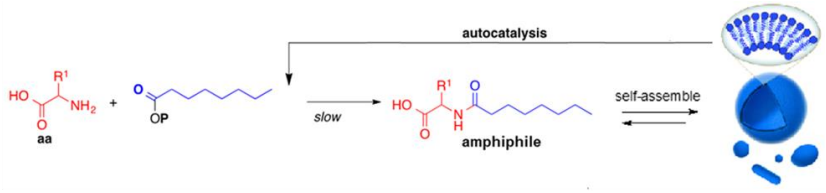

Figure 1. Proposed autocatalytic system using N-fatty acyl aminoacids.

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Self-Assembling Cyclic Peptide Dimers for *cis*-Platinum Complex encapsulation

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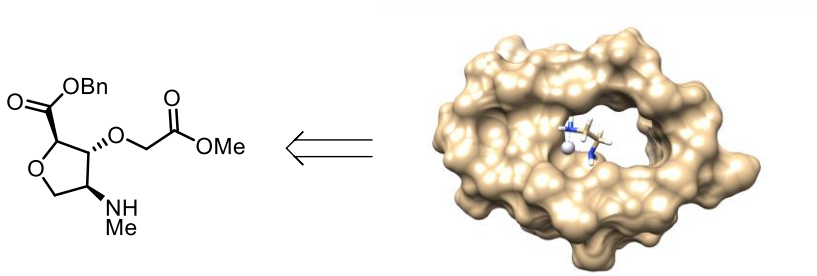
Keywords*: cyclic peptides, supramolecular chemistry, drug delivery*

Cis-platinum is still one of the most used chemotherapeutic agents against a wide range of cancers. However, its clinical application is limited due to its high toxicity and low selectivity.[1] One of the main challenges in this field is the construction of efficient drug delivery vectors that would reduce its side effects. In this context, self-assembling cyclic peptide dimers emerge as suitable tools for the coordination and selectively transport of platinum complexes to carcinogenic cells due to its structural modulability.[2]

Recently, our group have prepared an artificial γ-amino acid containing a hydroxyl group at its β-position (γ-Ahf) which allows the functionalization of the internal cavity of dimeric cyclic peptides. In fact, we have reported a cyclic peptide containing this residue which was able to encapsulate platinum complexes and showed cytotoxic activity against A2780 cancer cells.[3]

In this work, we present a new self-assembling cyclic peptide dimer bearing a carboxylic acid group oriented toward the cavity that will enable the encapsulation of platinum complexes. It also contains a hydrazide moiety that will allow to incorporate a vector to increase the selectivity. The synthesis of the basic components will be described in this communication.



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Developvement of a smart biosensor to study KRAS oncoprotein

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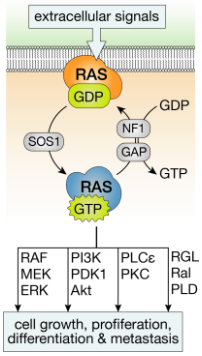
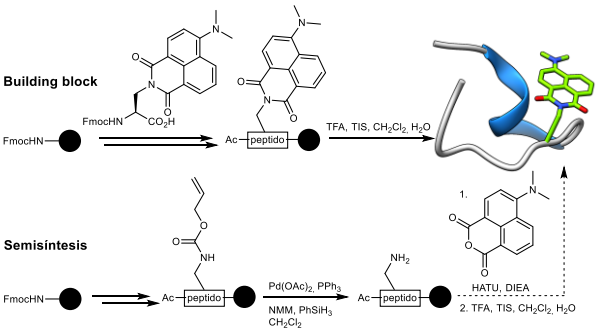
***Keywords**: KRAS, solvatochromic, fluorescence*



The RAS proteins are molecular switches linked to signaling paths that regulate the cellular growth, proliferation and differentiation. It is known that up to 30% of all cancers, including 95% of pancreatic and 45% of colorectal, are caused by RAS mutations.

This Project, at the boundaries of Chemistry and Biology, aims to developing an intelligent biosensor to study the protein $KRAS^{G12D}$ in a simple and reliable way. The proposed biosensors are called *intelligent* because they will actively respond to $KRAS^{G12D}$ with a change in their spectroscopic properties. This is achieved by insertion of a solvatochromic fluorophore, which displays low fluorescence in polar solvents and high fluorescence in apolar solvents or when inserted in hydrophobic pockets in proteins, into a peptide scaffold.

The proposed biosensor is based in a peptide sequence that recognizes KRAS with high affinity and selectivity. The biosensor will include a fluorogenic 4DMN side chain replacing one of the aromatic residues, which will be buried in a hydrophobic pocket when bound to KRAS. Once synthesized, we will characterize the binding of the peptide sensor to $KRAS^{G12D}$ by a *in vitro* fluorescence assay.



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Desarrollo de nuevos compuestos con actividad antitumoral desde el reposicionamiento farmacológico de la sertralina

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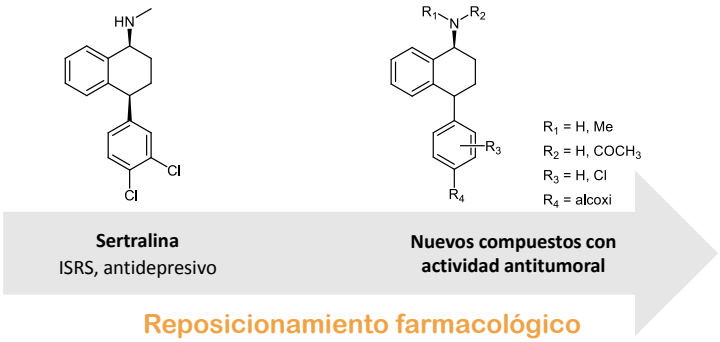
***Palabras clave**: reposicionamiento farmacológico, antitumoral, aminotetralina*

En la actualidad, a pesar de los avances en el conocimiento de las enfermedades humanas, los beneficios terapéuticos son más lentos de lo esperado. El descubrimiento de un nuevo fármaco continúa siendo un proceso largo que implica del orden de 15 años de desarrollo y una ingente inversión económica con opciones limitadas de alcanzar el éxito. En este sentido, la identificación de una nueva indicación o diana terapéutica en un fármaco aprobado o en investigación clínica, llamada reposicionamiento farmacológico, surge como una nueva vía a la hora de introducir nuevos medicamentos en el mercado.[1] Esta estrategia terapéutica de "viejos fármacos para nuevas terapias" resulta particularmente atractiva ya que permite reducir el tiempo, el coste y el riesgo en el proceso de desarrollo, pues la molécula ha superado las pruebas de seguridad en humanos.

En este contexto, en un *screening* de inhibidores selectivos de la recaptación de serotonina (ISRS) comercializados como antidepresivos, la empresa Vivia Biotech ha identificado actividad pro-apoptótica en muestras de pacientes de leucemia linfoide crónica para la sertralina. A partir de este reposicionamiento farmacológico, nuestro grupo de investigación ha iniciado un proyecto de colaboración enfocado al desarrollo de nuevos compuestos con actividad antitumoral. En este trabajo se describe la síntesis de nuevos derivados de aminotetralina capaces de potenciar la apoptosis de células tumorales a la vez que se elimina la unión al transportador de serotonina y al canal iónico hERG, responsables de los efectos centrales y la cardiotoxicidad en la sertralina, respectivamente.



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APLICACIÓN DE LA "CHIRON APPROACH" A LA SÍNTESIS DE NUEVOS β-AMINOÁCIDOS CONFORMACIONALMENTE RESTRINGIDOS

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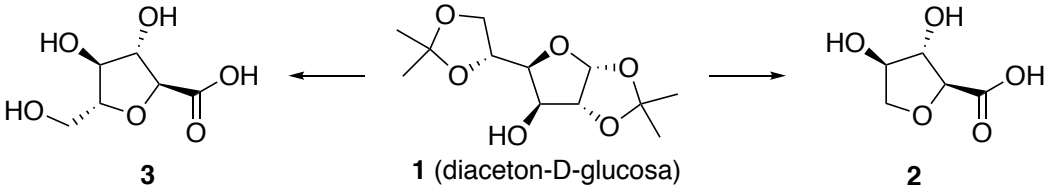
***Palabras clave**: (azúcares, chiron approach, β–aminoácidos, peptidomiméticos)*

Los péptidos juegan un papel crucial en el mundo de la Biología (desempeñan importantes funciones biológicas en los organismos vivos), así como en el de la Farmacología, por su potencialidad como agentes terapéuticos.[1]

Los β-aminoácidos han demostrado ser los candidatos ideales para reemplazar α-aminoácidos en las cadenas peptídicas, con objeto de generar peptidomiméticos que permitan obviar las limitaciones de los péptidos naturales (α-péptidos), para su empleo como fármacos (baja estabilidad metabólica, escasa diversidad estructural y elevada flexibilidad conformacional). Son particularmente importantes para ello los β-aminoácidos cíclicos, por su alta capacidad de estabilización de las conformaciones peptídicas, una propiedad que ha sido relacionada con la alta tendencia de sus homopolímeros a plegarse en estructuras secundarias rígidas, en secuencias peptídicas cortas.[2]

Como parte de un proyecto en curso destinado a la síntesis de péptidos de β-aminoácidos, se presentan aquí la síntesis de los nuevos ácidos 3,4-dihidroxifuran-1-carboxílicos **2** y **3** (Esquema 1), que han sido sintetizados a partir del derivado **1** de la D-glucosa, mediante una estrategia sintética novedosa, basada en la "Chiron Approach".



Esquema 1

Se presentarán también los estudios preliminares de transformación de **2** y **3** en los correspondientes β-aminoácidos

[1] T. E. Creighton, in *Proteins: Structures and Molecular Properties*, 2nd ed., Freeman, New York, **1993**.
[2] *Amino Acids, Peptides and Proteins in Organic Chemistry*, Andrew B. Hughes (Series editor), Wiley, **2009**, vol 1