MCR2023
Universidad de Burgos SPAIN

# 8TH INTERNATIONAL CONFERENCE ON MULTICOMPONENT REACTIONS AND RELATED CHEMISTRY

# BOOK OF ABSTRACTS

September 6 – 8, Burgos, Spain

UNIVERSIDAD DE BURGOS

Dear All,

On behalf of the Local Organizing Committee of the 8th International Conference on Multicomponent Reactions and related Chemistry, we send our warmest regards to the scientific community that will be participating at symposium which will take place in Burgos, between September 6th an 8th, 2023.

The Organizing Committee, in close collaboration with the Scientific Committee, has prepared an attractive program, addressing cutting edge topics with especial emphasis in young scientists. In this respect, we want to publicly thank the generosity of senior researchers for facilitating this transition, which we believe will have a very positive impact in the future of the field.

The conference will take place in a unique environment, the Hospital del Rey of the University of Burgos, a historic building and former pilgrim`s hospital on the Camino de Santiago.

We would like you to share your excellent research in Burgos, and to enjoy the welcoming spirit of our city.

We are looking forward to seeing you in Burgos

Prof. María García Valverde

Chair of the Local Organizing Committee

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## PLENARY LECTURES



## INVITED LECTURES

## ORAL COMMUNICATIONS

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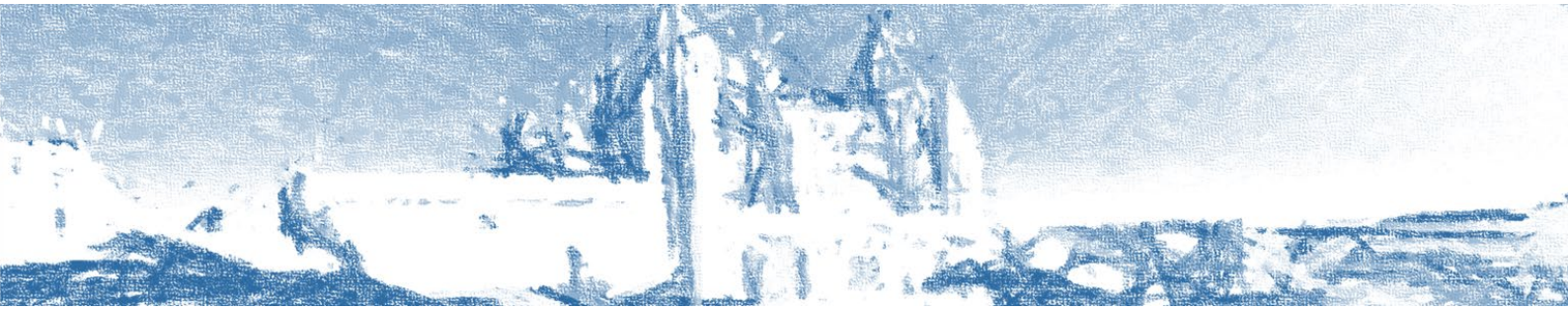

# PLENARY LECTURES

# FUNCTIONAL CHROMOPHORES BY MULTICOMPONENT REACTIONS

Prof. Dr. Thomas J. J. Müller [a]

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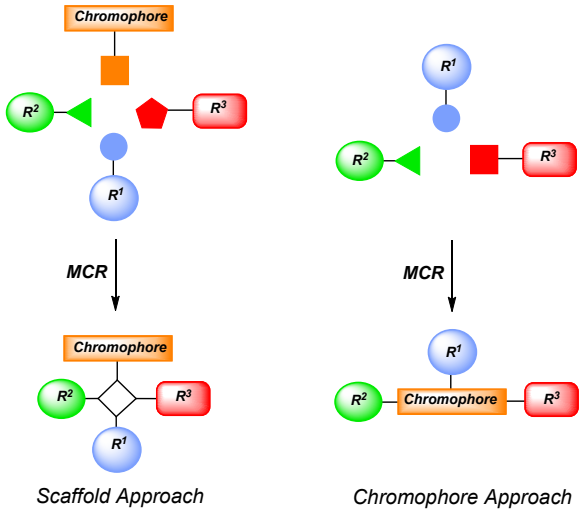
**Keywords:** *Aggregation-induced Emission, Fluorophores, Multicomponent Reactions, One-pot Reactions*

One-pot processes have considerably enhanced diversity-oriented syntheses in the past decades and have become an enabling tool for providing myriads of substance libraries, in particular, in pharmaceutical high-throughput screening and lead finding. Over the past two decades, we have paved the way of multicomponent reactions (MCR) as a synthetic concept to access functional π-electron systems, such as chromophores, fluorophores, and electrophores, by scaffold and chromophore approaches.[1] Transition metal catalyzed couplings are excellent entries to alkynones,[2] which can be transformed by multi-component and domino processes to various classes of functional fluorescent chromophores in a one-pot fashion (chromophore concept).[1c,3]




In the lecture the general concept is introduced and illustrated by the development of aroyl-S,N-ketene acetals, a novel class of polar solid-state and aggregation-induced emissive dyes.[4]

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# Catalytic Multicomponent Vicinal Difunctionalization of Alkenes

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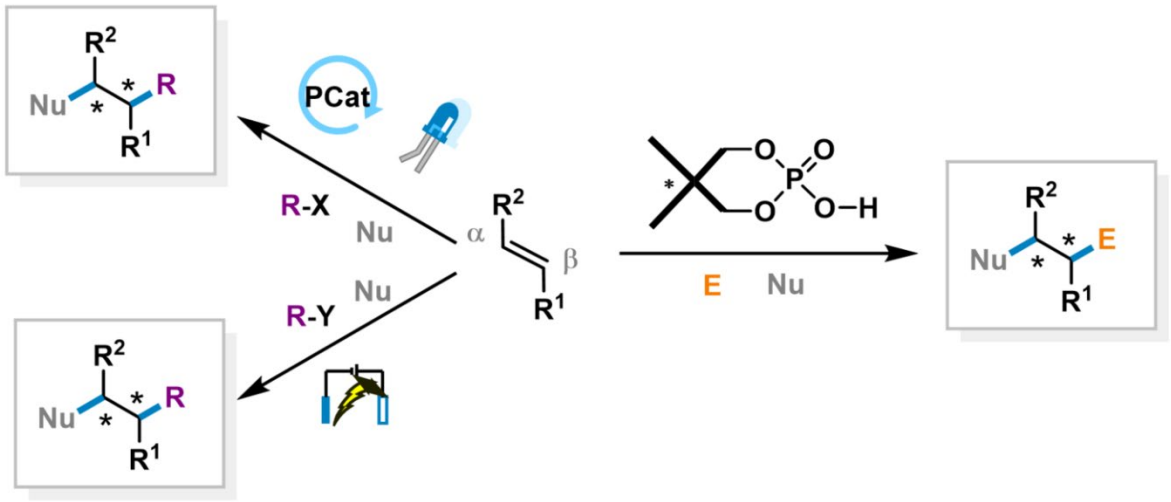
The vicinal difunctionalizations of alkenes *via* multicomponent reactions are formidable strategies to construct highly functionalized building blocks.

In this conference, we will present our recent contributions in the development of difunctionalization reactions using asymmetric organocatalysis,[1] photoredox catalysis[1,2] and electrochemistry.[3]

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# LEVERAGING ISOCYANIDE CHEMISTRY FOR DRUG DISCOVERY AND PRODUCTION

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The unique reactivity of isocyanides has earned them a central role in classical multicomponent reactions such as the Passerini and Ugi reaction. Still, some issues have prevented the wider chemical community from adopting isocyanides as standard reagants in organic synthesis. These issues include the limited accessible scaffold diversity, poor commercial availability of isocyanides, and poor stereocontrol of classical isocyanide-based multicomponent reactions.

I will present an overview of our efforts to expand the toolbox of isocyanide-based transformations, both by rational expansion of their traditional α-addition reactivity and by use of transition metal catalysis. In addition, our contributions to the development of polyfunctional isocyanides will be discussed. I will demonstrate these new reactions and reagents are not only amenable to library construction, but also to the efficient synthesis of valuable APIs and natural products. Finally, I will discuss the combination of highly functionalized isocyanides with chiral imines in the efficient and highly stereoselective multicomponent synthesis of valuable viral protease inhibitors, including nirmatrelvir, the active ingredient in the Covid-19 drug Paxlovid.

# Photochemistry & Organocatalysis: New Radical Opportunities

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**Keywords:** *photochemistry, organocatalysis*

The chemical reactivity of electronically excited molecules differs fundamentally from that in the ground state. This is the underlying reactivity concept of photochemistry, which has traditionally allowed the development of unique chemical transformations not achievable via conventional ground-state pathways. In this context, our laboratory has been exploring the potential of some organocatalytic intermediates to directly reach an electronically excited state upon visible-light absorption to then switch on novel catalytic functions that are unavailable to ground-state organocatalysis. Studying the mechanism of these photochemical approaches allowed us to expand the synthetic possibilities offered by the excited-state reactivity of organocatalytic intermediates and to develop enantioselective radical processes.

# TRANSLATIONAL CHEMICAL BIOLOGY

Gonçalo J. L. Bernardes

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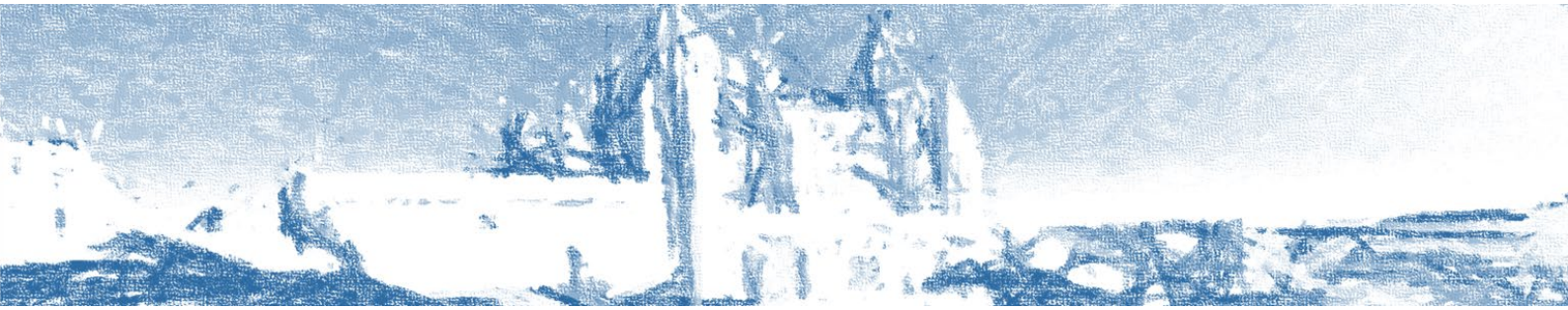
Our research uses chemistry principles to address questions of importance in life sciences and molecular medicine. This lecture will cover recent examples of emerging areas in our group in:

i. methods for site-selective chemical modification of peptides and proteins a multicomponent approach based on the combination of the isonitrile-tetrazine [4 + 1] cycloaddition and the Ugi four-component reaction to generate pyrazole amide derivatives;

ii. accelerating reaction rates of biomolecules by using shear stress in artificial capillary systems;

iii. a proximity-driven chemical approach for the site-specific cyclization of phage-displayed peptides.



# INVITED LECTURES

# KETENES AS VERSATILE BUILDING BLOCKS IN MULTICOMPONENT REACTIONS

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**Keywords:** *ketenes, diazoketones, photochemistry*

In the search for increasingly efficient and sustainable synthetic approaches, the combination of multicomponent reactions and photoinduced transformations is a very promising strategy.[1]

Our group, during the last years, has focused its attention on the photoinduced Wolff rearrangement of diazoketones and on the employment of the resulting ketenes as electrophyles in multicomponent reactions.

In this communication we will report the almost 10-year-old story of the ketene three-component reaction, illustrating the preliminary results,[2,3] the development of a silylative version of the reaction,[4] the improvement through a continuous-flow system,[5] the use of visible light,[6] the application to the discovery of biologically relevant molecules [7] and our most recent results on new applications of ketenes in cycloaddition reactions.[8]

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# EVOLUTIONARY APPROACHES FOR THE MCR-ASSITED DISCOVERY AND OPTIMIZATION OF ADENOSINE RECEPTOR ANTAGONISTS

Ana Mallo-Abreu[1] and Eddy Sotelo[1,2]

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In the past two decades, all parts of the drug discovery process have undergone radical changes.[1] In response to the need to discover valuable, pharmacologically useful compounds and to shorten the time required for preclinical research, medicinal chemists have incorporated successful new concepts and methodologies into the laborious process of lead discovery and lead optimization.

Selectivity, atom economy, time saving, environmental friendliness, cost- effectiveness, diversity, and druglike properties, as well as the reconciliation of molecular complexity with experimental simplicity, are some of the key pieces of the puzzle that must be assembled by modern medicinal chemists to achieve the maximum efficiency during library synthesis. Most of these characteristics are met by multicomponent reactions,[2,3] which have emerged as powerful strategies in medicinal chemistry and chemical biology, allowing rapid and efficient generation of diverse and complex drug candidates by the formation of new covalent bonds in one-pot transformation.

In this presentation, we will describe the results of a project that leverages the competitive advantages of multicomponent reactions to modulate all four subtypes of adenosine receptors.[4-7] The approach utilized has enabled the discovery and optimization of novel series of potent and selective antagonists, while also advancing the development of new drugs for cancer immunotherapy.

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# Enantioselective Multicomponent Reactions via Trapping of Reactive Intermediates

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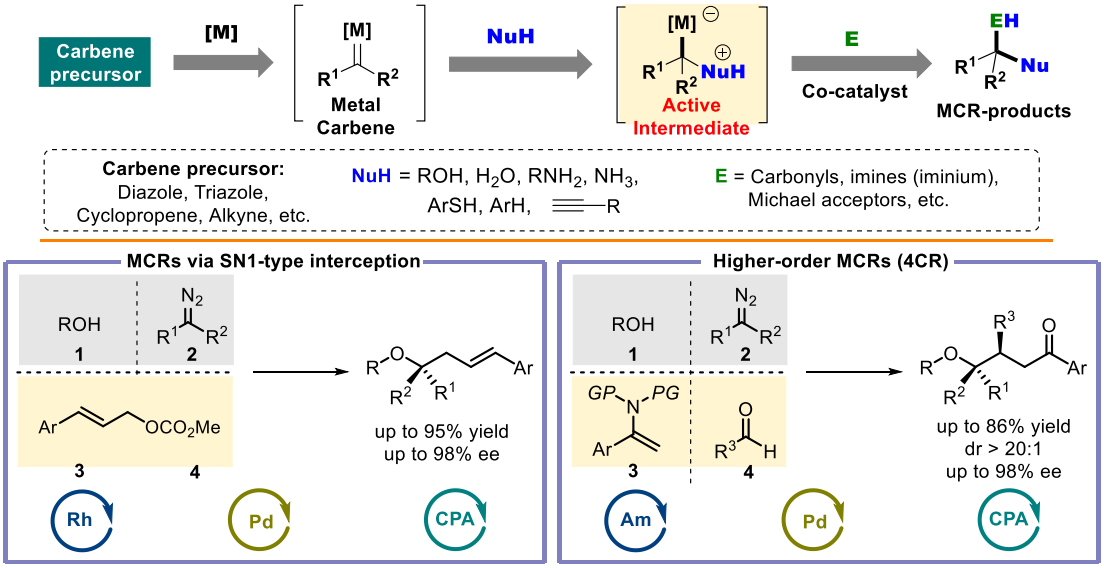
**Keywords:** Asymmetric multicomponent reactions, *Metal carbene, Active intermediates*

Multicomponent reactions (MCRs) represent one of the most efficient and practical synthetic approach towards poly-functionalized molecules with structural diversity in terms of atom- and step-economy. The interception of active intermediates that exist in traditional two-component reactions by the third component has become a practical strategy to engender versatile new MCRs. Over the past decades, our group dedicated to developing novel MCRs via trapping transient intermediates that generated in situ from metal carbene, including ammonium ylides, oxonium ylides, and zwitterionic intermediates, with various electrophiles[1]. By employing efficient synergistic catalysis strategy, the reactions were realized with excellent stereocontrol and wide substrate scope, which provides a synthetically useful method for the rapid and efficient construction of chiral structurally complex and diversified compounds. In this presentation, our recent progress of the novel MCRs via the cross-interception of two active intermediates that generated independently will be presented, including the asymmetric allylation of oxonium ylides through an SN1-type interception, higher-order MCRs (four-component) involving the coupling of two active intermediates, and their applications in synthesis of natural products and pharmaceuticals[2]. Mechanism of the reaction, especially the form of reactive intermediates and the structure of metal carbene, will also be discussed.

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# CATALYTIC STEREOSELECTIVE HYDROCARBON DIFUNCTIONALIZATION

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**Keywords:** *copper, boron, asymmetric catalysis, carboboration*

The development of efficient, safe, clean and operationally simple transformations is a primary challenge in modern synthetic chemistry. Traditionally, transition metal catalyzed C-C bond forming reactions have been developed using pre-made organometallic reagents. These procedures are inherently limited to the availability and reactivity profiles of the reagent itself and entail the formation of a stoichiometric amount of inorganic salt as a reaction by-product. The goal of our research program is to discover and study new metal-catalyzed reactions with the aim to develop highly selective synthetic methodologies based on the use of readily accessible materials. In this context, we have recently developed new synthetic transformations based on the use of simple unsaturated hydrocarbons as transient functionalized organometallic intermediates in multicomponent reactions.[1-5] From simple and readily available materials we can obtain complex structures with a high level of selectivity.

In this lecture, different catalytic strategies to accomplish stereoselective difunctionalization of unsaturated hydrocarbons based on selective carboboration processes will be presented.

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# REACTIVE INTERMEDIATES IN MULTICOMPONENT REACTIONS OF ISOCYANIDES: THE CASES OF THE ENOL-UGI CONDENSATION AND CYCLOADDITION PROCESSES IN TANDEM

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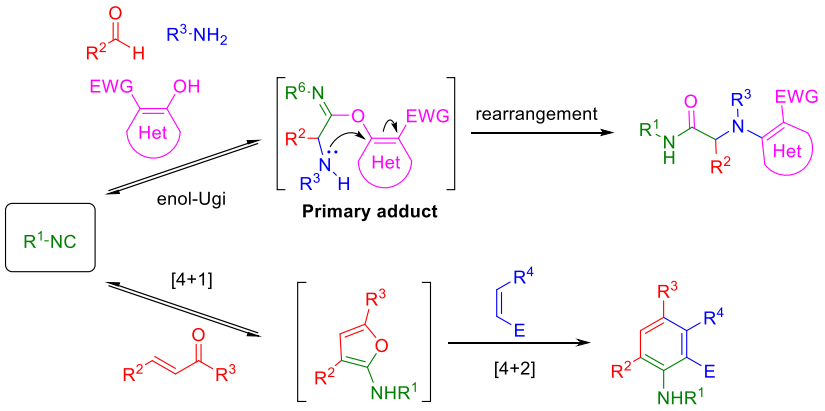
**Keywords:** *enols, amino furans, tandem reactions, cycloadditions, rearrangements, heterocycles*

Reactive intermediates play a key role in multicomponent reactions of isocyanides. The stabilisation of the primary adducts of Passerini and Ugi condensations through Mumm-type rearrangements is paradigmatic. Trapping of reactive intermediates with additional reagents or through different rearrangements has led to the discovery of new multicomponent processes, such as interrupted Ugi reactions and other variants of classical condensations. In this communication I will discuss two different processes in which a reactive intermediate is irreversibly transformed into a multicomponent final product.

The enol-Ugi reaction is a variation of the Ugi reaction that involves the use of enols as acid components.[1] As in the classical Ugi condensation, all reactants participate in a first reaction step that leads to an unstable primary adduct. This undergoes an irreversible conjugate addition-β-elimination rearrangement that is key for the success of this transformation. The starting enol must be designed to make this transformation possible, having an electron-withdrawing group on the wright position. The use of different enols and the possibility of carrying out post-condensation transformations allows obtaining a diversity of heterocyclic structures.

On the other hand, cycloaddition reactions of isocyanides can produce highly reactive molecules, such as 2-aminofurans.[2] These can be trapped with a third reagent present in the reaction medium, resulting in one-pot tandem processes useful for the preparation of complex polyheterocyclic compounds.

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# OLD DOG, NEW TRICKS. ISOCYANIDE: FROM STRATEGIC FUNCTIONAL GROUP FOR NOVEL MULTICOMPONENT REACTIONS TO INNOVATIVE PHARMACOPHORIC GROUP IN MEDICINAL CHEMISTRY

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**Keywords:** *isocyanides, medicinal chemistry*

This lecture is divided into two parts. In the first part, two relevant isocyanide-based multicomponent reactions that were recently discovered in my lab, namely chloroximes-isocyanides[1] and TosMic-aryl azides[2] will be discussed. During that period, we only considered isocyanides as reactive functional groups pivotal to the success in discovering novel multicomponent transformations. However, after synthesizing and using dozens of isocyanides, we began to ponder its potential use as innovative pharmacophoric group in medicinal chemistry. The second part of this presentation is related to this neglected aspect of isocyanides, focusing on the discovery of potent antibacterial, antifungal, and antitumoral metabolically stable compounds that were recently designed and synthesized in our lab.[3]

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# Electrooxidative Isocyanide-Based Reactions

Laurence Grimaud,[a] Maxime R. Vitale,[a] Guillaume Vincent,[b] Shanyu Tang,[b] Regis Guillot,[b] Na Pan,[a] Johanne Ling,[a] Jean-Pierre Pulicani,[a] and Alexandre Simon[a]

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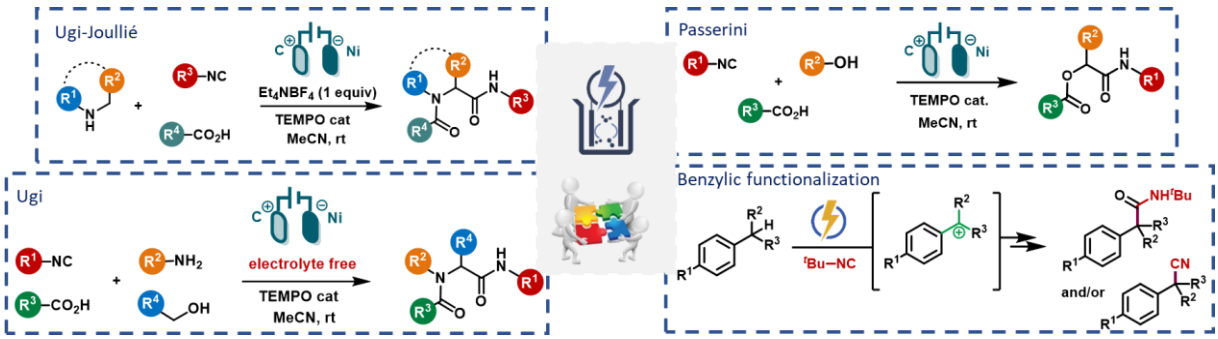
**Keywords:** *Isocyanides, Multicomponent reactions, oxidative process, electrosynthesis*

Isocyanide-based Multicomponent Reactions (IMCRs) are well-known tools for the efficient preparation of elaborated chemicals, starting from relatively simple carbonyl or imines derivatives. Since the first report of the oxidative 3-component Passerini reaction[1] by employing a stoichiometric oxidant, oxidative IMCRs have attracted much attention as they allow to generate extensive chemical diversity from stable and commercially available alcohols and amines. By merging electrosynthesis with IMCRs, we first developed a TEMPO-catalyzed C($sp^3$)-H α-carbamoylation of free cyclic secondary amines according to a Ugi-Joullié reaction in mild and sustainable conditions.[2] Capitalizing on these results, we developed the first electro-induced 3-component Passerini reaction and the more challenging 4-component Ugi reaction.[3] In collaboration with Dr G. Vincent, we recently developed a benzylic C-H functionalization based on the combination of electrosynthesis and isocyanide chemistry.[4]

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# PHOTOCATALYZED MULTICOMPONENT REACTIONS: HARNESSING LIGHT FOR EFFICIENT AND SUSTAINABLE SYNTHESIS

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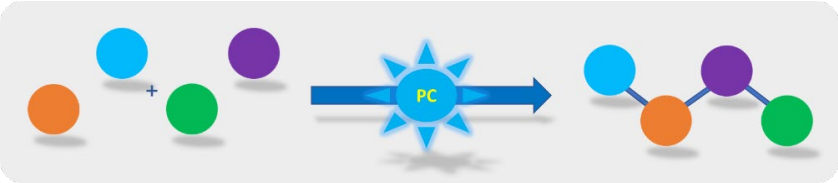
**Keywords:** *Multicomponent reactions (MCRs), Photoredox catalysis, Boronic acid derivatives, Diversity-oriented synthesis*

Photoredox-catalyzed multicomponent reactions (MCRs)[1] are one-pot transformations of at least three substrates, in which multiple new bonds are formed, furnishing complex molecules involving the visible-light assisted generation of highly active free-radicals *via* single-electron transfer (SET) processes (Scheme 1). The mild reaction conditions and operational simplicity of photocatalyzed MCRs make them attractive for large-scale industrial applications, contributing to the development of sustainable and scalable synthetic methodologies. Furthermore, the use of visible light as an energy source facilitates the development of environmentally friendly processes, reducing the reliance on traditional heating methods and minimizing the generation of waste. Photocatalysts (PC), typically based on transition metal complexes or organic dyes, absorb light and undergo photoexcitation, generating reactive species such as excited states, radicals, or radical ions. These reactive intermediates subsequently participate in a cascade of bond-forming events, involving multiple reactants, under mild reaction conditions. Nevertheless, most MCRs comprise three components, while those with four or more are uncommon, which highlights inherent compatibility challenges.

This presentation will highlight our research in these promising fields,[2-5] particularly in light of our group's long-standing interest in MCRs and the utilization of boronic acid (BAs) derivatives as alkyl radical precursors under batch and continuous flow conditions.




**Scheme 1**: Photo MCRs towards molecular complexity.

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# METAL-FREE MULTI-STEP DOMINO REACTIONS

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**Keywords:** *Domino reaction, one-pot process, organoautocatalysis, quinazolines, o-terphenyls, hexaarylbenzenes*

A domino process is a powerful tool to economically and sustainably build up complex molecular architectures, drastically reducing the number of work-up and purification steps. Recently we developed new metal-free multi-component multi-step domino reactions and one-pot processes for the waste-reducing and cost-effective preparation of versatile frameworks, which otherwise are difficult to access via traditional methods. The developed new methods engage simple and readily available compounds in a wide range of domino reactions to construct, e.g., *azabicycles, quinazolines, quinazoline-thiohydantoins, 2,6-dicyanoanilines, o-terphenyls* and *hexaarylbenzenes* of interest for medicinal chemistry and materials science.[1-4] We recently disclosed a versatile *organoautocatalytic* transamination metathesis reaction, which is a multi-step domino process.[5] This novel methodology gives rapid and atom-economical access to N-substituted 1,4-dihydropyridines, privileged structures in bioactive compounds and pharmaceuticals.

The *in vitro* tests against *multidrug-resistant P. falciparum* strains (Dd2 and K1), human cytomegalovirus (*HCMV*), and *multidrug-resistant* P glycoprotein-overexpressing CEM/ADR5000 leukemia cells revealed the selected domino products and some corresponding artemisinin-containing hybrid compounds as highly active agents, outperforming the clinical reference drugs.[6,7] These results will be discussed in the talk.

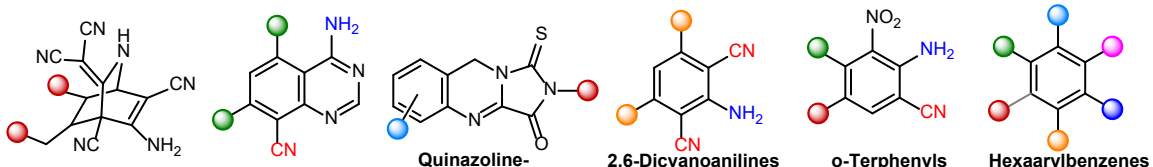


**Fig. 1** Compounds prepared via new metal-free multi-component multi-step domino reactions.

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# Phytoceramides – Scaffold Diversification and Applications as Adjuvants

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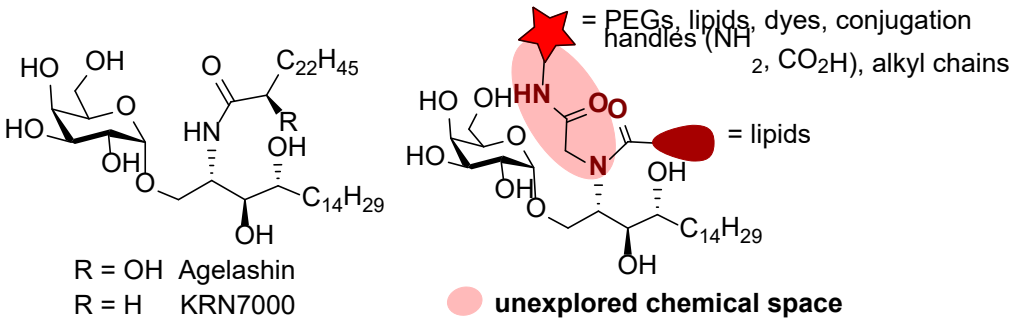
**Keywords:** *Phytoceramides, Adjuvants, Diversification*

Adjuvants are necessary requirements for improving the performance of vaccines. α-Galactosylceramides (α-GalCer, e.g. KRN7000) have attracted particular interest due to their ability to activate iNKT cells and and B cell activation. Although the structure of this glycolipid, which originates from the marine natural product Agelasphin, has been extensively studied and modified to broaden its adjuvant properties, the modifications seem to be rather limited. This restricts the potential discovery of new applications. Here, we present the use of multicomponent reactions to extend the chemical space of glycolipids beyond the classical modifications. For the first time, we show that the amide linkage is a suitable diversification point for the introduction of a variety of moieties that allow the modulation of adjuvant properties.



# INTEGRATED ONE-POT STEPWISE SYNTHESIS AND ORGANOCATALYSIS

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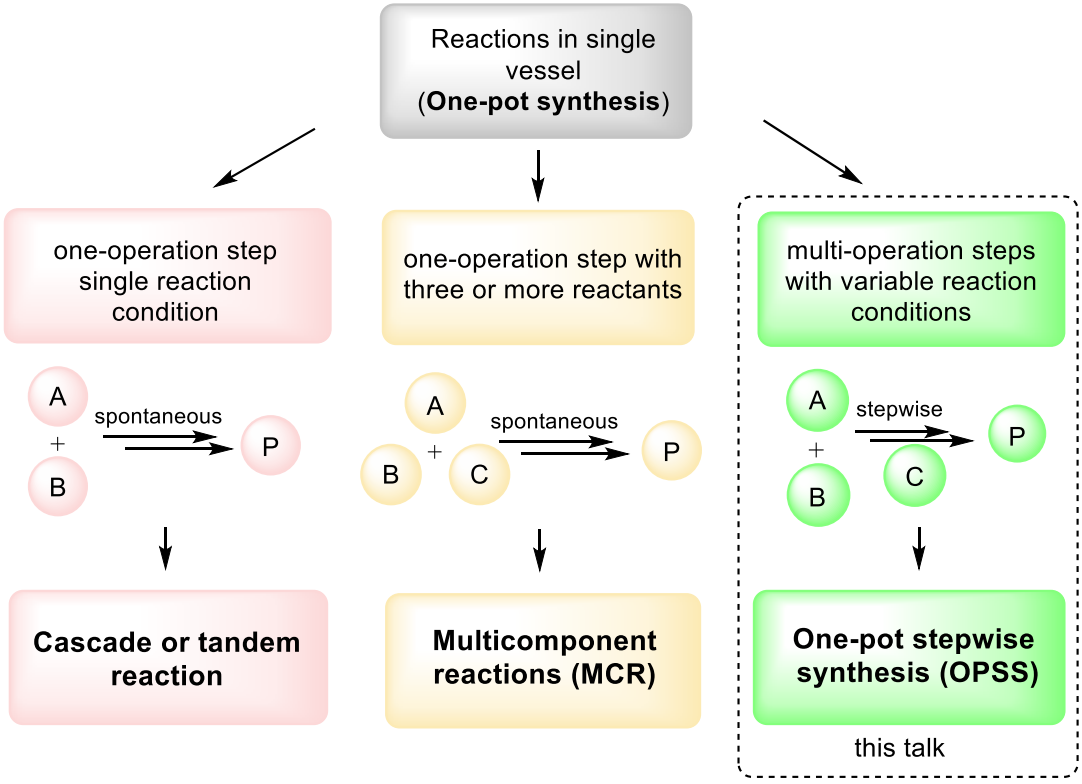
**Keywords:** *One-pot synthesis, multicomponent reaction, cascade reaction, stepwise synthesis*

One-pot synthesis is an active topic in organic chemistry due to its intrinsic advantages of simple operation, high mass efficiency, low cost, and less amount of waste. Among three kinds of one-pot syntheses 1) cascade reactions, 2) multicomponent reactions (MCRs), and 3) one-pot stepwise synthesis (OPSS), OPSS could be more flexible and practical since it is carried out stepwisely and have variable reaction conditions at different steps. This presentation highlights the recent development in our lab on the development of OPSS involving cyclization, cycloaddition, rearrangement, and organocatalysis for the synthesis of heterocyclic scaffolds, asymmetric molecules, and bioactive compounds.

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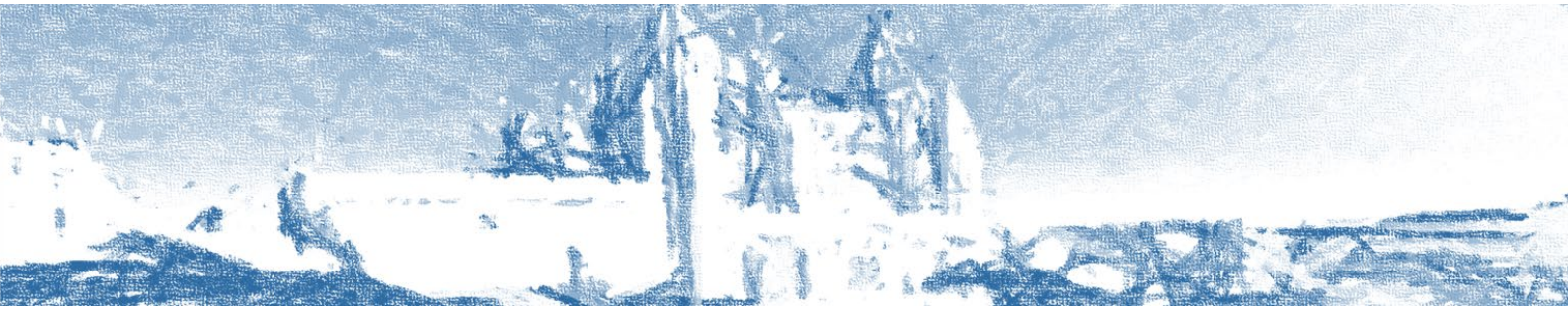

# ORAL COMMUNICATIONS

# Mechanochemical IMCR and IMCR-post transformation domino strategies: towards the sustainable DOS of dipeptide-like and heterocyclic peptidomimetics

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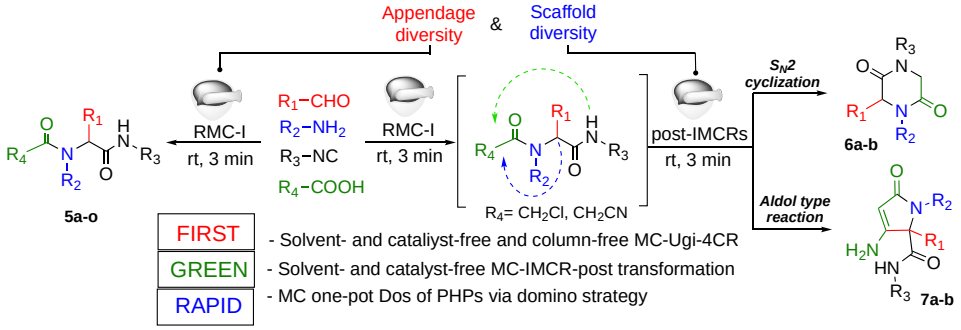
**Keywords:** *Mechanochemistry, IMCR, Diversity-Oriented Synthesis (DOS), 2,5-diketopiperazines, α,β,-unsaturated-γ-lactams*

Mechanochemistry refers to the reactions normally of solids induced by the input of mechanical energy, as a source of chemical activation to accelerate reactions under solvent-free conditions. In this context it is an efficient alternative energy source (AES) in the development of novel rapid and green synthetic methods.[1] Sonochemistry and mechanochemistry are emerging as relatively novel green technologies to improve IMCRs strategies.[1] However, sustainable IMCRs assisted by an AES under solvent, catalyst, column-free (SCCF) conditions are practically unreported.[2] On the other hand, efficient and convergent one-pot processes can be achieved using multicomponent reactions (MCRs) coupling post-transformations to minimize the waste, reagents, solvents, energy, time, and work required and mainly to increase complexity of target products. This justifies their prominence in the design and development of green synthetic methods of drug-like and bioactive molecules containing privileged heterocycles.[3] One-pot processes based on IMCR-post transformation strategies in a consecutive[4] or domino[5] fashion can deliver target molecules in a relatively short time with high yields. Here we developed a facile and rapid mechanochemical Ugi four-component reaction (MC-Ugi-4CR) for the synthesis of new dipeptide-like products in high yields under SCCF conditions at room temperature in three minutes. The scope and versatility of this efficient IMCR is demonstrated with the first one-pot DOS of privileged heterocyclic peptidomimetics (PHPs) such as 2,5-diketopiperazines (DKPs) and *α,β*-unsaturated-*γ*-lactams via a sustainable mechanochemical domino strategy that includes IMCR-post transformations in high yields with a total reaction time of six minutes.[7]

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# Materials Functionalization and Modification *via* Multicomponent Reactions and Their Applications

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**Keywords:** Multicomponent reactions, *Materials, Functionalization, Biomedical platform*

Recently, the preparation of neoteric functional materials with multicomponent reactions strategy has interestingly enhanced the union of materials chemistry. The main components (amine, carboxylic, or carbonyl groups) of MCRs are usually present in the materials structure or can be easily announced on their surfaces. Hence, materials can contribute in MCRs for the greatly talented modified/functionalized materials synthesis.[1-3] In view of our interests in design of combinatorial MCRs and functionalization of nano-materials, in this MCR conference, the design and functionalization/modification of nano-materials and natural polymers with application in the catalytically chemical transformations and materials biomedical platform will be presented.

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# DISCOVERY OF NEW MULTICOMPONENT PROCESSES THROUGH CHARTING OF THE CHEMICAL REACTION SPACE

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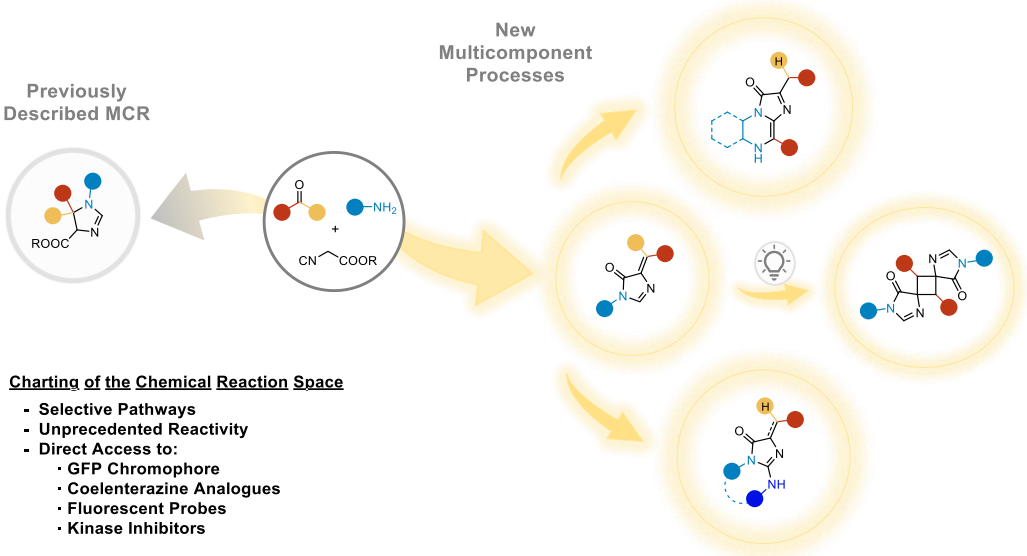
**Keywords:** chemical reaction space, charting, GFP chromophore, heterocycles

The chemical reaction space[1] (defined as the network of feasible interactions connecting all species in a given system) of a multicomponent reaction (MCR) is particularly complex by nature. Arguably, a specific reactant combination could have different possible reaction pathways. In this way, one could find divergent processes from the reported outcome in some well-established MCRs. However, the complexity of multicomponent experimental frames (substrates, solvents, catalysts, conditions, reactive intermediates, etc.) challenges this discovery of new MCRs, which is frequently associated to serendipity. For this reasons, efforts in recent years have been focused on the rational design of new MCRs.[2]

In this regard, we believe that a thorough screening of the reaction parameters of a given MCR can allow us to map the chemical reaction space and navigate through its possible reaction pathways, to selectively reach different outcomes. In this regard, a careful charting of the interaction between carbonyls, amines, and isocyanoacetates resulted in the discovery of new general multicomponent processes providing a variety of unsaturated imidazolones, analogues of the green fluorescent protein (GFP) chromophore. Moreover, we developed unprecedented chemistry upon the imidazolone core, leading to the generation of spiro and fused adducts, which include potent kinase inhibitors, natural product analogues and fluorescent probes with suitable optical and biological profiles.[3]

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# PHOTOREDOX-CATALYZED PSEUDO-4-COMPONENT ALKYLATIVE AMIDINATION OF ALKENES

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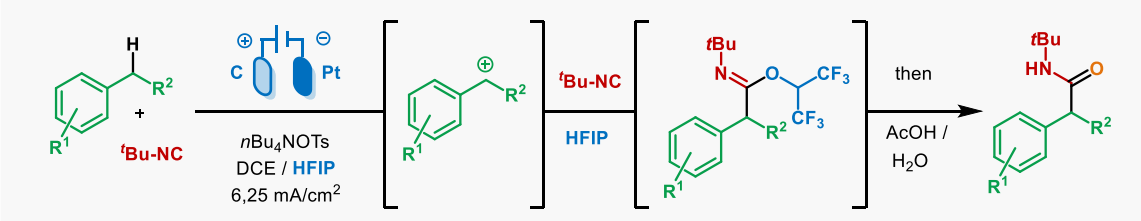
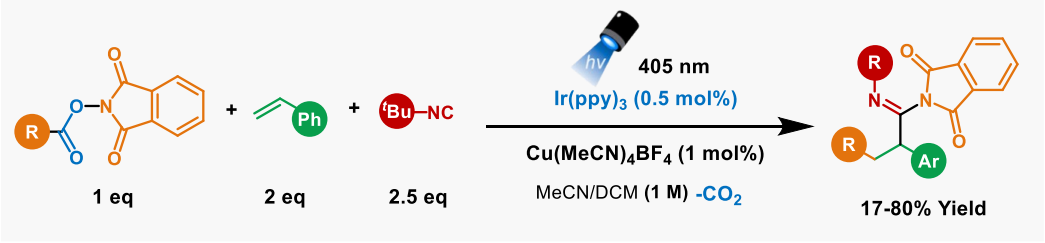
**Keywords:** *isonitriles, alkenes, photoredox-catalysis, amidination, radical-polar process…*

Isocyanide-based multicomponent reactions (IMCRs) are undoubtedly remarkable tools for generating extensive chemical diversity in in a direct and efficient manner. Ever since 1921, when Passerini reported the first IMCR, this field of research has not ceased to grow.

In this field, our group and others have implemented electrosynthesis as a means of promoting redox events in mild and sustainable reaction conditions.[1],[2] Notably, we reported the unprecedented benzylic C-H-carbamoylation of aromatic derivatives in which electrosynthesis ensures the transient generation of benzylic carbocations.[1c]




Building on our expertise, our attention turned towards the utilization of photoredox-catalysis to facilitate the formation of benzylic carbocations through a radical-polar pathway.[4] In this study, we present an innovative pseudo 4-component alkylative amidination of alkenes.[5] A crucial aspect of this multicomponent process is the incorporation of Okada's redox active esters, which not only serve as radical sources but also act as nucleophile sources to ensure the completion of the reaction.

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# ENANTIOSELECTIVE MULTICOMPONENT REACTION FOR THE SYNTHESIS OF UNSATURATED γ-LACTAM DERIVATIVES AND THEIR SYNTHETIC APPLICATIONS

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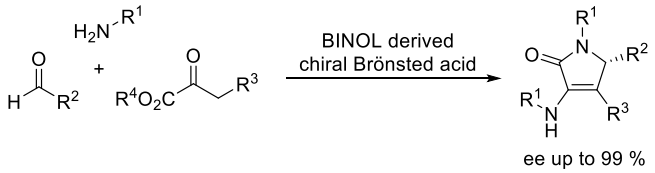
**Keywords:** *γ-lactams, asymmetric organocatalysis, multicomponent reactions, diastereoselective reaction.*

The γ-lactam ring is the fundamental part of the structure of a vast number of natural and non-natural compounds covering an extensive spectrum of biological activities. Within this family of compounds, α,β-unsaturated γ-lactams or 1,5-dihydro-2H-pyrrol-2-ones are an exceptional class of compounds, which structure can be also found in many pharmaceutically active natural and synthetic products. [1]

Nowadays, a significant focus of drug regulatory agencies and pharmaceutical industries revolves around the synthesis of chiral active compounds in their pure enantiomeric forms. In this context, strong efforts have been made during the last decades in order to develop new enantioselective protocols for the preparation of enantioenriched γ-lactam derivatives. However, the vast majority of the described protocols consist of stepwise reactions, and the reports concerning enantioselective multicomponent reactions are still scarce. [2]

Herein, we report an efficient enantioselective BINOL derived Brönsted acid-catalyzed multicomponent reaction of amines, aldehydes and pyruvate derivatives for the preparation of unsaturated γ-lactam derivatives with enantiomeric excesses up to 99%. [3]




In order to proof the synthetic utility of the γ-lactam derivatives, several synthetic transformations were performed. This includes regioselective alkylation reactions at different positions of the 5-membered ring, the diastereoselective hydrogenation of the endocyclic double bond, and diastereoselective ytterbium-catalyzed formal [3+3] cycloaddition reaction with α,β-unsaturated carbonylic compounds. [4]

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# HIGHLY CONJUGATED LUMINESCENT FURO[2,3-*c*]ISOQUINOLINES AS FLUOROPHORES BY COUPLING THE UGI REACTION WITH A Pd(0)-CATALYZED DOUBLE CYCLIZATION

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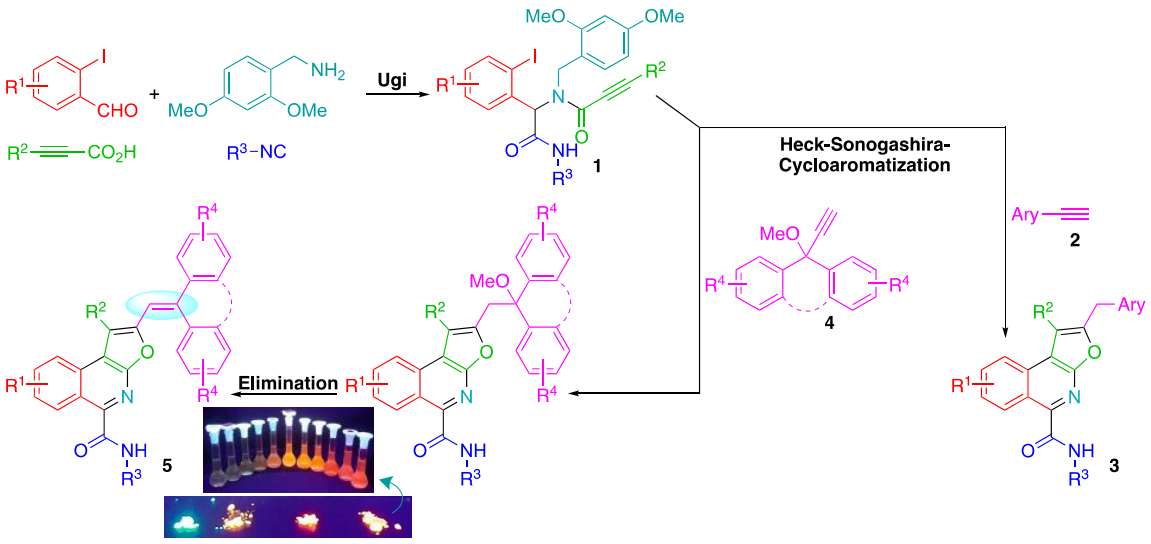
**Keywords:** *Ugi reaction, one-pot cyclization, fluorescent heterocycles, aggregation-induced emission*

Furo[2,3-*c*]isoquinolines **3** belong to a new family of almost unknown fluorophores recently developed in our group by coupling the Ugi 4-component reaction affording **1** with a complex one-pot Pd(0)-mediated double cyclization upon addition of the terminal alkyne **2**. With this efficient protocol we prepared two libraries of blue/green emitters.[1,2] Aiming to fine tune the fluorescence properties of this scaffold we planned to extend the $\pi$-electron conjugation by connecting the furoisoquinoline with the aryl moiety introduced after the MCR. This was possible installing an appropriate leaving group in the propargylic position of alkyne **4**.




The novel structure modification of **3** allowed us to realize a remarkable red-shift both in the absorption and fluorescent bands. Moreover, scaffold **5** demonstrated to be fluorescent in the solid state and displayed an interesting *Aggregation-Induced Emission effect* (AIE) in solution,[3] with a fluorescence ranging from the blue to the red region of the visible spectrum. This peculiar phenomenon holds an enormous application potential for functional materials (e.g. OLEDs, sensors, bio-imaging).[4]

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# Synthesis of Novel Tetrahydronaphthoazetidinones, 2,5-Dioxo-1,4-methanobenzoazepines and 3-Hydroxypyrrolidinones Through Copper-Assisted Post-Ugi Domino Sequences

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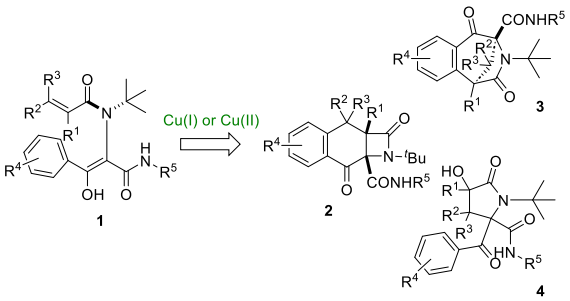
**Keywords:** *Copper catalysis, azetidinones, pyrrolidinones, benzoazepines.*

Different methodologies for the synthesis of heterocyclic systems employing the Ugi reaction followed by radical cyclizations have been described in the last few years.[1] As part of our ongoing interest in developing new strategies for the synthesis of lactams based on Ugi/post-condensation sequences,[2] we envisaged the possibility of synthesizing these compounds using the Ugi reaction followed by radical cyclizations. In this work we describe the synthesis of novel tetrahydronaphthoazetidinone, 2,5-dioxo-1,4-methanobenzoazepine and 3-hydroxypyrrolidinone (Scheme 1) derivatives through copper-assisted post-Ugi domino sequences, using simple and affordable starting materials and straightforward protocols.

The treatment of Ugi adducts **1** derived from different α,β-unsaturated carboxylic acids and arylglyoxals with copper salts afforded different lactams. The chemical results were strongly dependent on the substitution pattern of the acrylamide fragment and the reaction conditions.

On the one hand, the acrylic, 2-fluoroacrylic or 3,3-dimethylacrylic acid Ugi adducts derivatives **1** refluxed with catalytic amounts of CuCl in dry acetonitrile under a nitrogen atmosphere for 18 h afforded exclusively tetrahydronaphthoazetidinone derivatives **2**, resulting from a 4-*exo*-cyclization followed by a radical aromatic cyclization.




**Scheme 1.** Synthesis of the different structures from Ugi adducts derived from α,β-unsaturated carboxylic acids.

On the other hand, when methacrylic, crotonic, cinnamic, tiglic, 1-cyclopentenecarboxylic or 1-cyclohexenecarboxylic acid derivatives were used, the 5-*endo*-trig cyclization was preferred. However, the results were highly dependent on the reaction conditions. Thus, when the reactions were carried out in the previously described conditions, 2,5-dioxo-1,4-methanobenzoazepines **3** were obtained along with 3-hydroxypyrrolidinones **4**.[3] Interestingly, both systems could be obtained as single compounds. Thus, when the reaction was performed in an air atmosphere, 3-hydroxypyrrolidinones **4** were the only detected product in most cases. However, the 2,5-dioxo-1,4-methanobenzoazepines **3** could be obtained as single products in high yields when the reactions were carried out in the total absence of oxygen, in a nitrogen atmosphere and dry degasified acetonitrile, using a combination of copper(II) acetate with DBU in equimolar amounts.

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# Enhancing the speed of the Passerini reaction

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**Keywords:** *Passerini reaction, HFIP, rate enhancement, Multicomponent polymerizations*

Multicomponent reactions (MCRs), in which three or more reagents are incorporated in the skeleton of the product, are an effective tool to create high molecular diversity and complexity in an efficient manner. Within this field, isocyanide-based multicomponent reactions (IMCRs) have claimed a dominant position as a result of the ambiphilic character of the isocyanide functionality. In 1921, Passerini discovered the first IMCR in the reaction of isocyanides, aldehydes, and carboxylic acids giving α-acyloxy carboxamides. Even though the first discovery of the reaction dates back a century, current research continues to provide new applications and new variations of these flexible reactions.[1-2] In this studies, we demonstrated that 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as a cosolvent in organic solvents enhances the speed of the classical Passerini reaction. We are currently investigating if we can use these conditions in Passerini polymerizations to generate poly(ester amide)s with higher molecular weight.

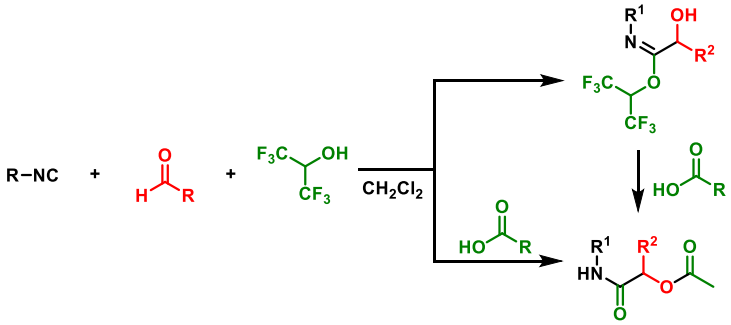


**Figure 1.** The influence of HFIP in the Passerini reaction.

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# MULTICOMPONENT DERIVATIZATION OF THE CEMADOTIN SKELETON – IN SILICO STUDY AND IN VITRO CYTOTOXIC ACTIVITY

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**Keywords:** *cemadotin analogs, docking, solid phase multicomponent reaction, cytotoxicity.*

Dolastatins are a class of naturally occurring cytotoxic peptides that inhibit microtubule assembly and tubulin polymerization. Cemadotin is a synthetic analog of dolastatin 15 (**Figure 1**) with potent antiproliferative activity in preclinical studies. [1] Dolastatin 15 analogs have been referred to be intracellularly metabolized to produce a pentapeptide derivative that shows a lower a cytotoxic activity, mainly due to the lower cell membrane diffusion compared to the parent compounds. [2] In this work, we employ solid-and solution-phase strategies based on the use of multicomponent reactions for the production of a series of cemadotin analogs. Molecular docking was carried out to predict their capacity to bind tubulin. Two approaches were used: a) the solid-phase synthesis of a pentapeptide dolastatin precursor that is subsequently derivatized by solution-phase Ugi reaction and b) the on-resin construction of the full dolastatin analog skeletons by performing all reactions – including the multicomponent ones – on solid-phase. The derivatizations include the incorporation of hydrophobic groups and reactive functionalities for suitable conjugation to targeting molecules. To the best of our knowledge, this last strategy is the only approach in which dolastatin analogs are completely synthesized on solid phase. The *in vitro* cytotoxic activity of these compounds was tested against the HCT-116, MDA-MB-468, and PC-3 cell lines. Most of the predicted active compounds showed an $IC_{50}$ < 10 μM. Furthermore, most compounds with $IC_{50}$ < 10 μM primarily acted cytostatically; in these cases, the curves reached a plateau at ~ 20 – 40% of cell viability. Such analogs have cytostatic effects that prevent further cell proliferation. However, three compounds with lipidic moieties seemed to induce cell death because their $IC_{50}$ curves reached approximately 0% cell viability.

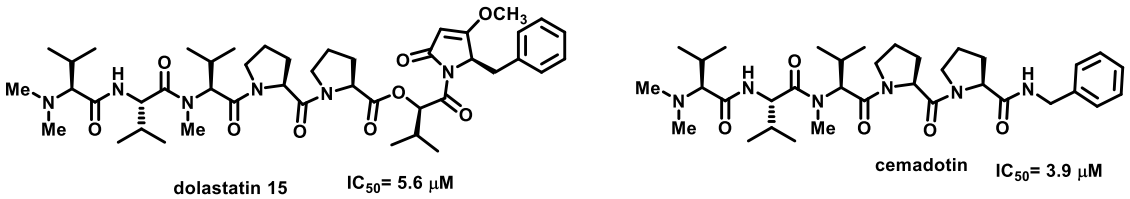


**Figure 1**. Structures of dolastatin 15 and its synthetic analog cemadotin

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# POWERFUL FLAVIN PHOTOCATALYSTS VIA THREE-COMPONENT REACTION: SYNTHESIS AND APPLICATION

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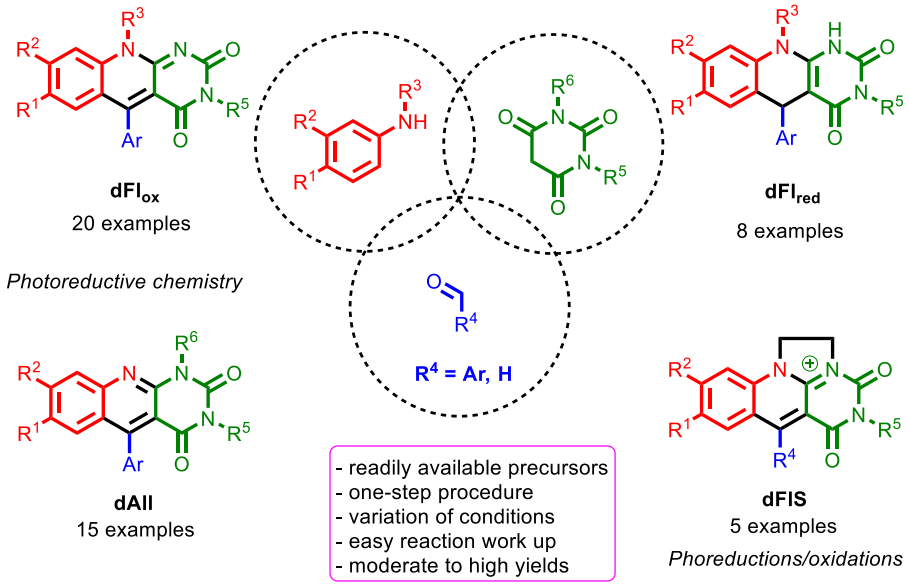
**Keywords:** *deazaflavin, deazaalloxazine, reduction, multicomponent reaction, photoredox catalysis*

Within the last decades, the visible light driven organic reactions via flavin catalysis have received increased attention in modern organic chemistry. Flavin-mediated photocatalytic oxidations are well known, yet, their use in reductive chemistry is rare [1]. Discovery of the structurally similar 5-deazaflavins (**dFl**), where the N(5) of the isoalloxazine moiety is replaced by a methine group, showed their viability for reductive chemistry due to their more negative reduction potential (ca. -1.3 V vs. SCE in ground state). Very recently, we have discovered that introduction of phenyl group into the C(5) of the **dFl** core increases the stability of deazaflavin semiquinone– extremely strong reducing agent with redox potential $E^*$ = -3.3 V vs SCE comparable with alkali metals ($E$ = -3.29 V vs SCE for Li) [2,3]. However, previously described methods for the formation of the deazaflavin core do not allow smooth inserting of aryl group to the C-5 position. Herein, we describe an elegant and efficient synthesis of 5-aryldeazaflavins (**dFl$_{ox}$**), 1,5-dihydro-5-deazaflavins (**dFl$_{red}$**), 5-aryldezaalloxazines (**dAll**) and deazaflavinium salts (**dFlS**) via the three-component reaction of barbituric acids, aromatic aldehydes and anilines, which opens the route to the combinatory libraries of synthesized heterocycles. 5-Aryldeazaflavins and 5-aryldeazaalloxazines are sufficient photocatalysts for reductive dehalogenations of electron-rich arenes and desulfonylation of amides, while deazaflavinium salts represent unique catalysts with dual nature, both suitable for photooxidation and photoreduction processes[4,5].

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# GREENER SYNTHESIS AND PHYTOTOXICITY SCREENING OF GBB-3CR ADDUCTS

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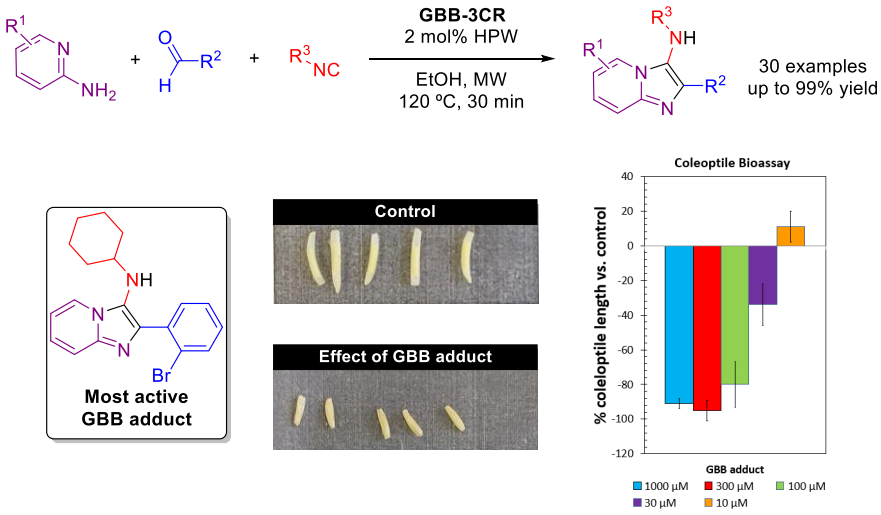
**Keywords:** *imidazo[1,2-a]pyridine, phytotoxicity, phosphotungstic acid, microwave, GBB reaction.*

Weed control is a challenge faced in agriculture due to resistance to the herbicides used, highlighting the importance to search for new and safer herbicides.[1] Imidazo[1,2-a]pyridines are important molecules with several biological activities, such as antiviral, antibacterial, antifungal, antiprotozoal, anticancer, analgesic, anticonvulsant, antitumor and anti-inflammatory.[2,3] The Groebke-Blackburn-Bienaymé three-component reaction (GBB-3CR) between amidines and a variety of aldehydes and isocyanides, under Lewis and Brønsted acid catalysis, has been successfully used as a direct access to this class of molecules.[4,5] In this work, several GBB adducts were synthesized through an economic and green attractive approach and their phytotoxic activities were evaluated in wheat estiolated coleoptile bioassays.[6] HPW (heteropolyacid of phosphotungstic acid) was used as a heterogeneous catalyst in ethanol under microwave heating. This convenient environmentally benign methodology provided the target compounds in high yields (up to 99%). Next, a structure/activity study of these adducts was carried out showing the importance of halogen groups at the *ortho* position of aromatic aldehydes and a cyclohexyl group from the isocyanide. These compounds showed remarkable inhibition (up to 95% on the two higher concentrations). Interestingly, heteroaromatic or aromatic aldehydes bearing an electron withdrawing group at the *para* position gave adducts that showed a positive effect on the coleoptile elongation. The most active compounds of this initial screening will now be submitted to further phytotoxic evaluation in seed germination and growth bioassays.

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# SUSTAINABLE ONE-POT SYNTHESES OF FUNCTIONAL DYES

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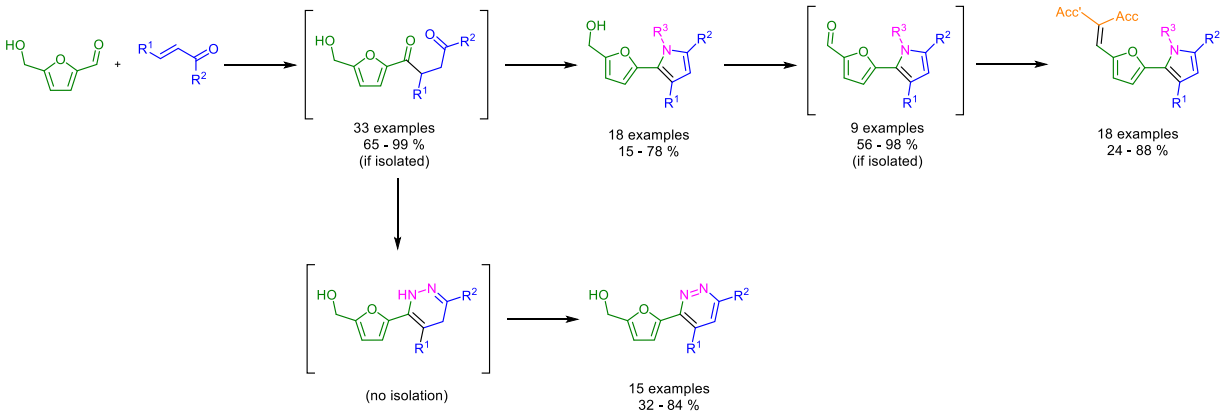
**Keywords:** *Green Chemistry, MCR, 5-(Hydroxymethyl)furfural*

In a material world, chemistry, as the science of transformation and the properties of substances, has a special significance in the pursuit of sustainable goals. The combination of three different factors, which can be summarized as the use of renewable resources, the establishment of sustainable one-pot syntheses and the preparation of functional dyes for sustainable energy conversion, proves to be a goal worth striving for. The polyfunctional, renewable molecule 5-(hydroxymethyl)furfural (HMF)[1] sets the starting point for developing sustainable catalytic one-pot syntheses of functional dyes. Diversity-oriented syntheses of functional dyes as well as systematic structure-property relationships in principle set the stage for the production of these components by sustainable one-pot processes.[2] Dyes are important functional constituents in molecular electronics and photonics, which, in addition to a steady miniaturization, can also avail and realize the efficient conversion of energy.[3]

Starting from HMF and α,β-unsaturated carbonyl compounds, a substance library of 1,4-diketones was established, which can be used as diverse pivotal building blocks for the synthesis of functional dyes, such as novel pyrroles and pyridazines.




Photophysical characterization of all pyrrole compounds by absorption and emission spectroscopy indicates a tunable fluorescence from blue to red upon photonic excitation and quantum yields up to 95 %. The fluorescence maxima range from 400 up to 650 nm with further functionalization. Structure-property relationships can be found and analyzed for the different generations of pyrroles.

Some of the synthesized pyrroles not only show fluorescence in solution, but they are also emissive in the solid state appearing with emission maxima ranging from 450 to 700 nm with further functionalization.

For the pyridazines a compound library of 15 examples has been constructed in yields ranging from 32 to 84 % including electronically diverse substituents on the pyridazine core. The newly established synthesis includes a final oxidation step, which is carried out under aerobic conditions without further additives and thus particularly represents the principles of sustainability.

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# Mixed aliphatic organozinc reagents as non-stabilized Csp3-nucleophiles in multicomponent reactions

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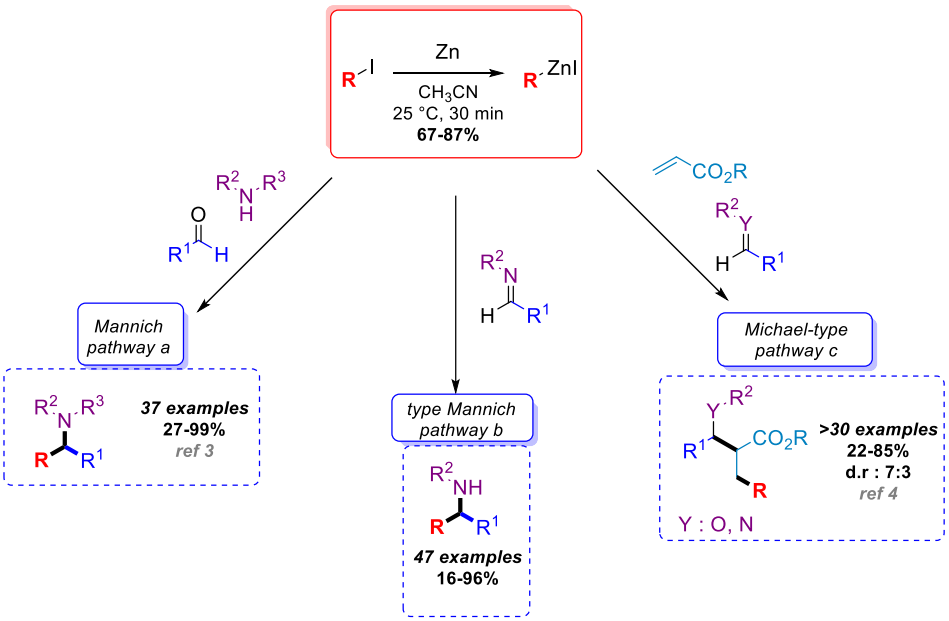
**Keywords:** *organozinc reagents, multicomponent reaction, Mannich reaction, Michael reaction, Barbier conditions, transition metal free*

Multicomponent reactions (MCRs) represent one of the most powerful tools to obtain complex scaffolds in a single step thus contributing to the development of more atom economic processes. In the past years, our activities were mainly focused on the design of new MCRs involving aromatic organozinc reagents as nucleophiles, as they are easy to prepare and present a great functional group compatibility compared to Grignard or organolithium reagents.[1] The present work aims at exploring the reactivity of aliphatic organozinc reagents in multicomponent processes. Indeed, such reagents have been only scarcely described and mainly resonance stabilized species were reported to undergo MCRs.[2]
We began our studies with organometallic multicomponent Mannich reactions between an alkylzinc reagent, an aldehyde and a secondary amine. We noticed a strong influence of the solvent used in the zincation step on the MCR outcome. By performing both reactions in acetonitrile, the reaction successfully involved different organozinc reagents (primary, secondary and tertiary), aldehydes (aromatic or aliphatic) and secondary amines (cyclic and acyclic), allowing the formation of tertiary amines under mild conditions and in good yields (pathway a).[3]
Moreover, the preparation of secondary amines was also possible under similar conditions using different imines (pathway b). Finally, by adding a Michael acceptor to the reaction mixture, catalyst-free Michael-aldol and Michael-Mannich reactions could be developed, affording β-hydroxy- and β-aminocarbonyl compounds (pathway c).[4]

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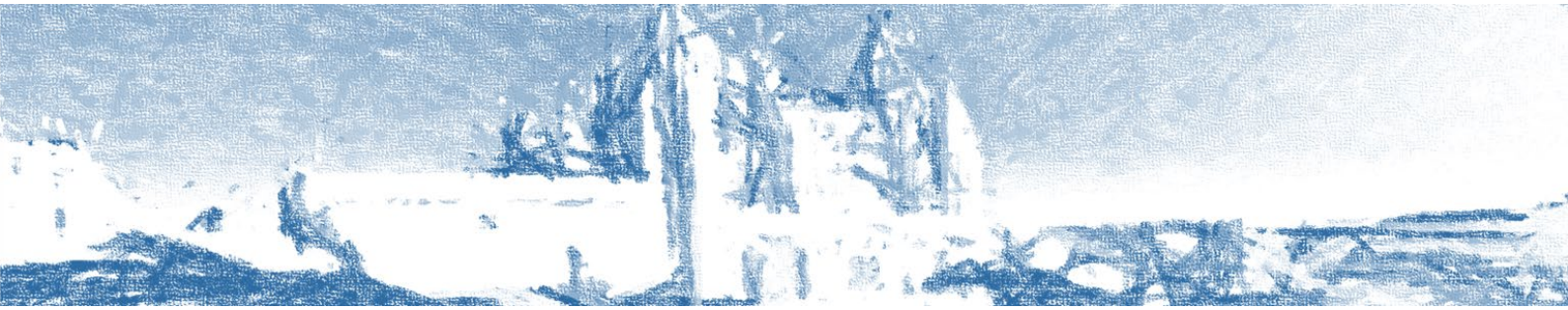

# POSTER COMMUNICATIONS

# A BIGINELLI-BASED APPROACH FOR THE OPTIMIZATION OF POTENT AND SELECTIVE $A_1$AR ANTAGONISTS

Carlos Rodríguez-Garcia,[1] Cristina Val,[1] Rubén Prieto-Díaz,[1] Jhonny Azuaje,[1] Maria Mahellaro,[1] Alejandro Díaz,[3] José Brea,[2] M. I Loza,[2] Marialessandra Contino,[4] Angela Stefanachi,[4] Xerardo García-Mera,[1] Hugo Gutiérrez-de-Terán,[3] and Eddy Sotelo[1]

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**Keywords:** *$A_1$AR antagonists, Biginelli, methyl group.*

We herein present a large collection of 2-amino-4,6-disubstituted-pyrimidines as potent, structurally simple, and highly selective $A_1$AR ligands. The library, built through a reliable and efficient three-component reaction,[1] comprehensively explored the targeted chemical space, allowing the identification of the most prominent features of the SAR and SSR around this scaffold. The intrinsic promiscuous ($A_1$/$A_{2A}$/$A_3$) adenosinergic profile of the scaffold was dissociated, by modification of the aromatic residues at positions $R_4$ and $R_6$ of the pyrimidine core, but most importantly exploiting the prominent role exerted by the substitution pattern at the exocyclic amino group on the selectivity. A magic methyl group enabled to identify highly potent $A_1$AR ligands with unprecedent selectivity profile. (Figure 1). The pharmacological characterization of the most attractive $A_1$AR ligands identified confirmed its antagonistic behavior (through cAMP assays) and its ability to overcome BBB hitting $A_1$AR at the CNS.

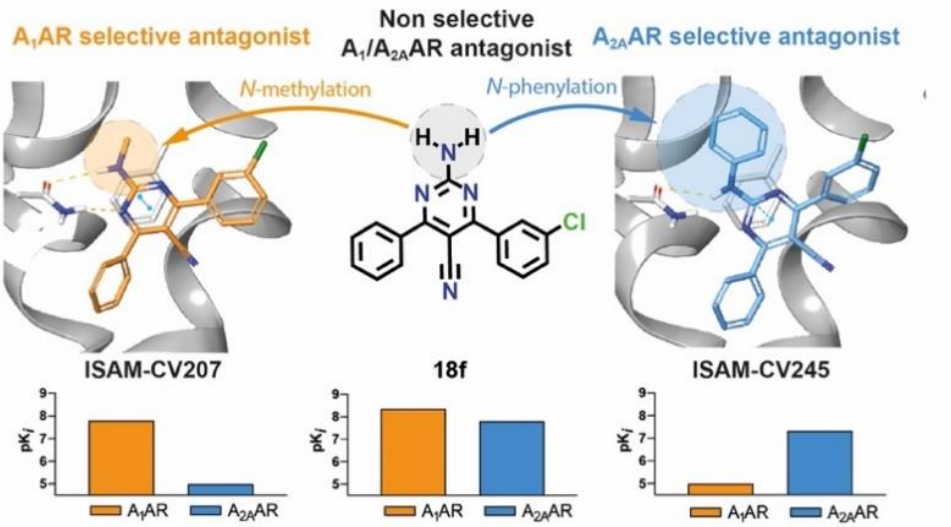


*Figure 1. Change of selectivity profile through methylation (left) and phenylation (right) of 2-aminopirimidines.[2]*

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# Synthesis, Modification and Biological Evaluation of γ-Oxocrotonic Acid Derivatives

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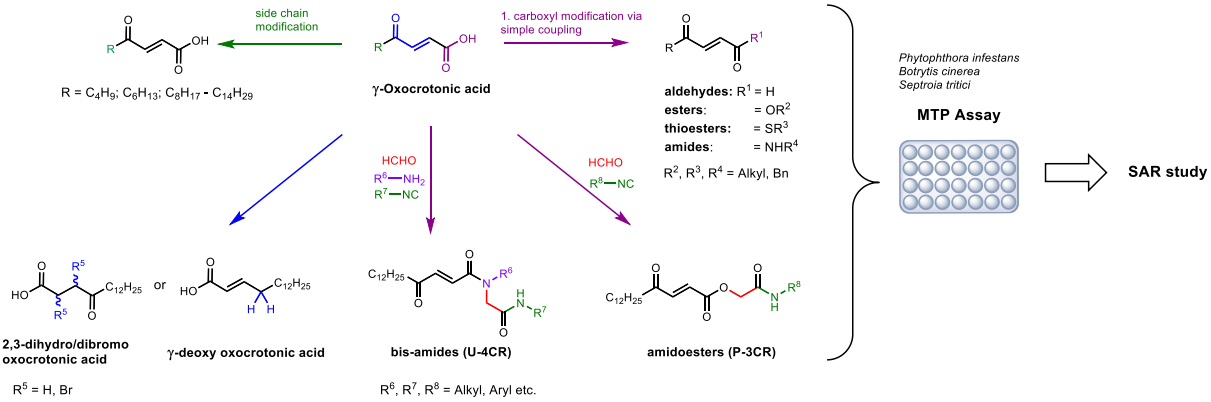
**Keywords:** *γ-oxocrotonic acid,antifungal activity, multicomponent reaction, structure activity relatioship*




γ-Oxocrotonic fatty acids, which contain α,β-unsaturated fatty acid with an additional keto group at γ-position, isolated from *Hygrophorous eberneus* are known to display antifungal and anti-oomycotic activity against certain phytopathogens.[1] Based on these results, γ-oxocrotonate functionality was applied as a lead structure for the optimization for its potential use as a fungicide in a plant protection. To this purpose, unmodified γ-oxo-crotonic acids with various chain lengths (C4, C6, C8–C14) were synthesized. In addition, based on the initial bioassay results of the synthesized γ-oxocrotonic acids with various chain lengths, further modifications of the most active (*E*)-4-oxohexadec-2-enoic acid were carried out. The modifications include ester and amide formation at the carboxylic acid functionality, modification of the double bond (hydrogenation or dibromination) of the acryl moiety as well as the γ-deoxygenation. In addition, in order to introduce a rapid functionalization, the carboxylic acid moiety was modified into bis-amides and α-acyloxy amides in U-4CR and P-3CR, respectively. The obtained derivatives were tested for their antifungal activities against *Phytophtora infestans* (Oomycete), *Botrytis cinerea* and *Septoria triticii*, three commonly found disease agents in agriculture, causing a huge crop loss and high economic damage. The structure-activity relationships were then established linking the influence and necessity of the individual structural units to their antifungal activity.

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# UGI-BASED ASSEMBLY OF OSELTAMIVIR DERIVATIVES

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**Keywords:** *Oseltamivir, UGI reaction, neuraminidase*

Oseltamivir (**1**) is a well-known antiviral drug used for treating influenza in both children and adults. Recent papers by Hou and Ju [1], [2] have reported that the derivatization of oseltamivir, by introducing diverse benzyl, aryl, and heteroaryl groups at the amino group of the C5 position, has shown improved activity compared to the reference drug (oseltamivir carboxylate). In particular, compound **3** has exhibited very high activity, being 50 times more potent than oseltamivir and 11 times better than Zanamivir (**2**) (Figure 1).

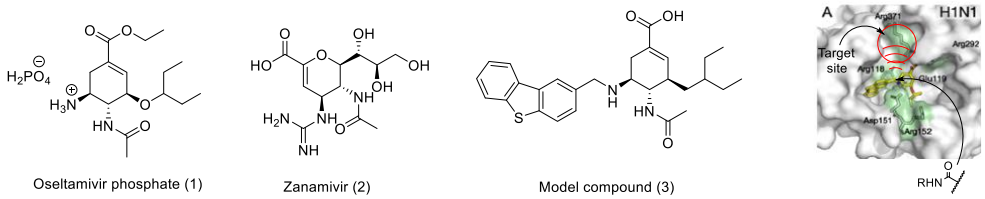
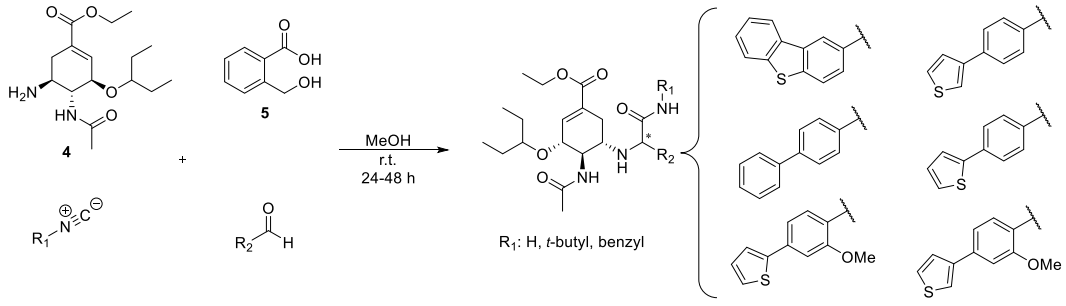



*Figure 1: Oseltamivir, zanamivir and model compound.*

The exploration of the proposed binding modes for these derivatives has revealed a previously unexplored hydrophobic pocket that efficiently accommodates the new substituents, resulting in improved potency while maintaining satisfactory pharmacokinetic profiles. Within the context of a project dedicated to developing enhanced anti-influenza drugs, it was decided to design and synthesize new neuraminidase inhibitors by introducing carboxamide groups onto the methylene group that connects the cyclohexene core with the new group. The assembly of targeted derivatives (Scheme 1) was conceived by employing a Ugi-based approach, enabling the rapid and efficient construction of a highly diverse library of Oseltamivir derivatives. The key components utilized in the Ugi Multicomponent Reaction (UMCR) were Oseltamivir amine (**4**) and 2-(hydroxymethyl)-benzoic acid (serving as a suicide acid moiety), in combination with carefully selected carboxaldehydes and three representative isocyanides (Scheme 2). The multicomponent reaction resulted in the formation of diastereoisomeric targeted derivatives, which were easily separated using chromatographic methods and subsequently evaluated as neuraminidase inhibitors.




*Scheme 1: UMCR assembly of target compounds*

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# A MULTICOMPONENT APPROACH ENABLED THE DISCOVERY OF SUBTYPE SELECTIVE AND BIASED $D_2$ BITOPIC LIGANDS

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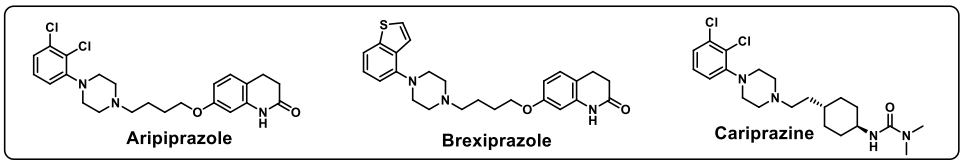
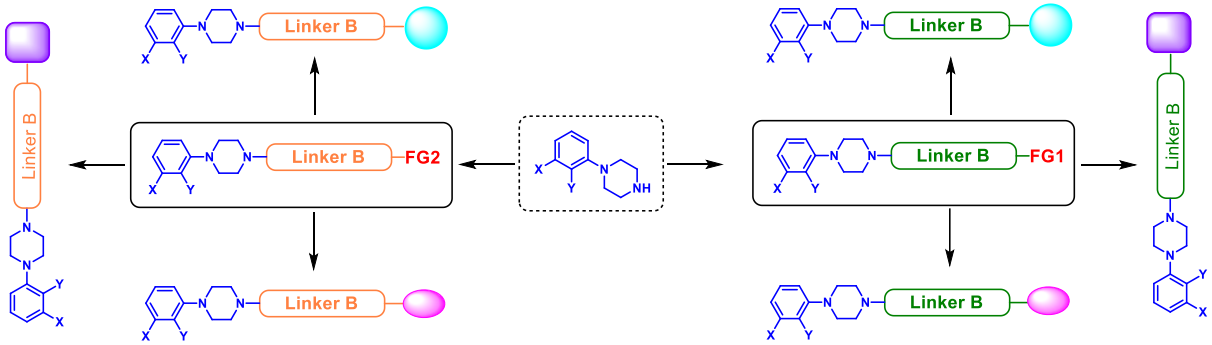
**Keywords:** *Dopamine, biased ligands, diversity-oriented synthesis, heterocycles.*

The $D_2$ receptor ($D_2R$) is one of the most validated targets in neurology and psychiatry. However, most drugs targeting the $D_2R$ are problematic, either being less efficacious than desired or possessing adverse side effects due to the activation or blockade of multiple parallel signaling pathways.[1] Despite recent advances, it remains unclear which signaling arms of the $D_2R$ are involved in the therapeutic effects of various agents used to treat neuropsychiatric disease states associated with the $D_2R$.[1] A promising approach to dissecting the importance of signaling pathways, and resolving these associated controversies, is to study them using ligands that exhibit functionally selective or biased signaling properties.[2] Inspired by the structure of Aripiprazole and Brexpiprazole, the reference $D_2R$ biased ligands,[3] we herein document the discovery of novel $D_2$ ligands exhibiting biased selectivity and exquisite receptor subtype selectivity using a multicomponent-assisted approach that follow the build/couple/pair strategy.

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# GOLD(I)-CATALYZED INTRAMOLECULAR BICYCLIZATION: DIVERGENT CONSTRUCTION OF QUINAZOLINONE AND AMPAKINE ANALOGUES

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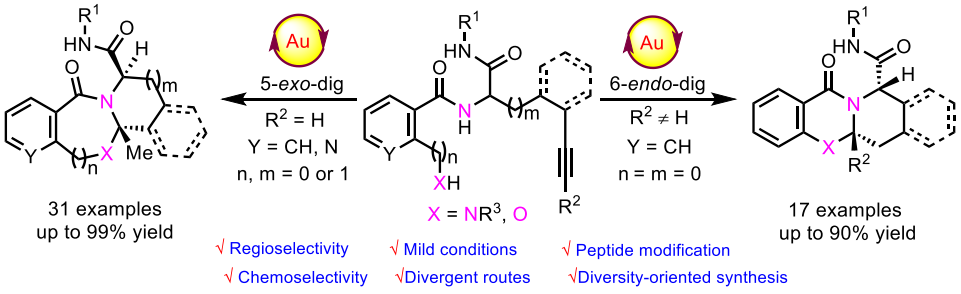
A gold(I)-catalyzed cascade intramolecular cyclization of Ugi adducts for the divergent construction of quinazolinone and ampakine analogues has been developed. Diverse fused *N*-heterocyclic scaffolds could be assembled from commercially available starting materials in a rapid, highly efficient and step-economical manner, *via* Ugi reaction and a cascade nucleophilic bicyclization process in two operational steps. This protocol shows high yields, excellent functional-group tolerance, broad substrate scope and excellent chemo- and regioselectivity. The practicality of this strategy is further demonstrated by a scale up reaction. Diverse oligopeptides are also found to be well tolerated, affording polycyclic products decorated with a peptide chain.

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# A RADICAL MULTICOMPONENT APPROACH FOR THE SITE-SELECTIVE MODIFICATION OF PEPTIDES

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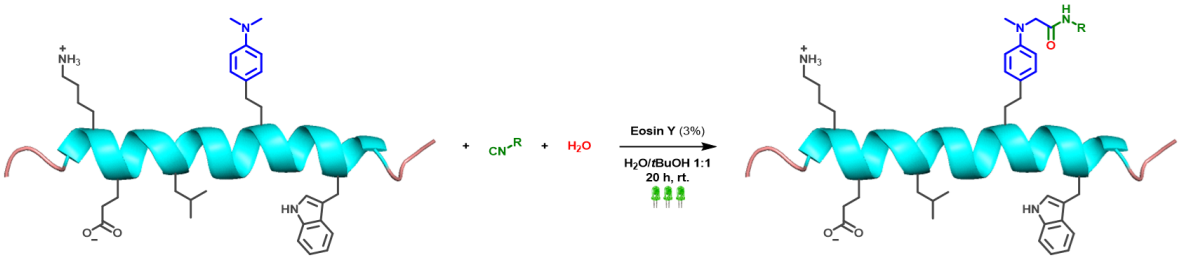
**Keywords:** *radical reactions, multicomponent reactions, peptides, labeling, octreotide*




**Main features:**
- ✓ Aqueous solvent
- ✓ Visible light
- ✓ Compatible with hydrophilic and hydrophobic side chains, Trp, His, and –$S_2$– bridge

**Applications:**
- ✓ Side chain lipidation and fluorescent labeling
- ✓ Peptide *C*-terminus derivatization
- ✓ Macrocyclization
- ✓ Octreotide derivatization

A bioorthogonal method based on a radical multicomponent condensation between dimethylaniline-containing amino acids, isocyanides and water has been employed for the modification of linear and cyclic peptides. Optimization of the reaction conditions was done either with dimethylaniline or the amino acid or short peptides containing this moiety, resulting in the selection of Eosin Y as the best catalyst for this transformation. The reaction was next extended to small and long linear unprotected peptides. Several modifications were afforded including lipidation, macrocyclization, and fluorescent labeling of a variety of peptides scaffolds. In addition, the proposed method was applied to introduce site-selective modifications in bioactive peptides such as bombesin and octreotide, resulting in the preparation of synthetic analogs for potential applications in the field of peptide-drug conjugates. For this, a functional reporter gene assay was conducted to investigate the impact of the resulting modifications at the octreotide skeleton on this ligand's ability to functionally activate the human somatostatin receptor *h*SSTR2, resulting in $EC_{50}$ values in the nanomolar range.

# MULTICOMPONENT-ASSISTED DISCOVERY OF MULTITARGET DRUGS: DESIGN, OPTIMIZATION AND *EX VIVO* TUMOR ASSAYS

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**Keywords:** *Biginelli Reaction, Cancer, immunotherapy*

Adenosine is a metabolite that suppresses anti-tumor immune response by T and NK cells via extracellular binding to $A_{2A}$ARs and $A_{2B}$ARs.[1] While blockade of the $A_{2A}$ARs effectively rescues lymphocyte activity, with four $A_{2A}$AR antagonists currently in anticancer clinical trials, less is known for the therapeutic potential of $A_{2B}$AR blockade within cancer immunotherapy. Based on our best $A_{2B}$ antagonists we have designed synthetically accessible through multicomponent chemistry compounds (Figure 1A), synthesized in one or two stages, to improve pharmacokinetic properties and generate new pharmacodynamic profiles.

A dual $A_{2A}$/$A_{2B}$AR antagonist herein synthesized [Figure 1A, **ISAM-M89A**, and our bests selective $A_{2B}$AR antagonists (Figure 1A, **ISAM-140** and **ISAM-R56A**) were evaluated in patient-derived tumor spheroid models (spheroid growth, immune cells proliferation, cytokine production and lymphocyte infiltration), against the $A_{2A}$AR antagonist clinical candidate **AZD4635**. Patient-derived breast cancer spheroid growth is prevented with dual antagonism treatment (Figure 1B). Also, T and NK cell proliferation is rescued, cytokine production and lymphocyte infiltration into tumor spheroid is increased (Figure 1C). These results demonstrate that the $A_2$ARs are promising targets in immunotherapy, identifying **ISAM-M89A** (dual $A_{2A}$AR/$A_{2B}$AR antagonist) and **ISAM-R56A** (selective $A_{2B}$AR antagonist) as potent candidates for cancer immunotherapy.[1]

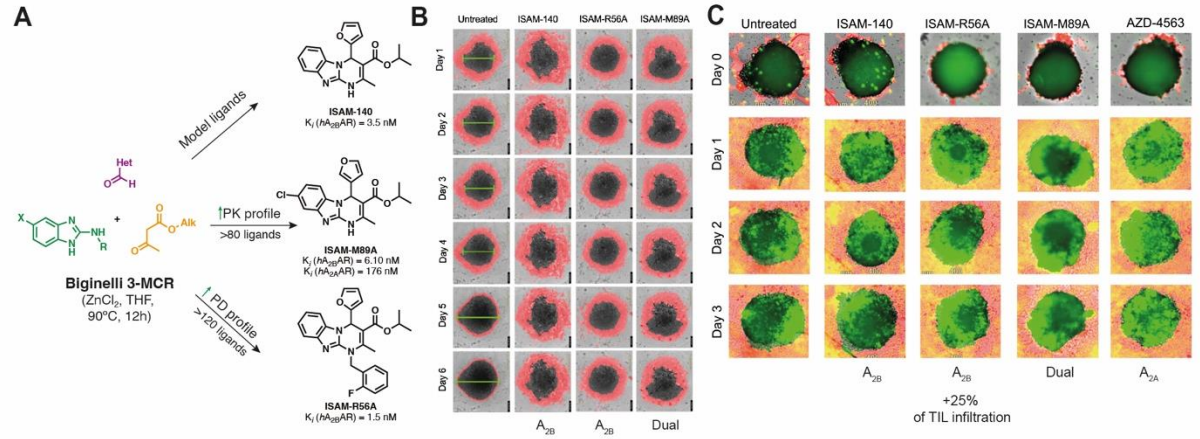


Figure 1. A) Design of halogenated antagonists. B) Patient-derived breast cancer spheroid growth *ex vivo* assay. C) Spheroid-lymphocyte infiltration *ex vivo* assay.

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# Mechanochemical IMCR and IMCR-post transformation domino strategies: towards the sustainable DOS of dipeptide-like and heterocyclic peptidomimetics

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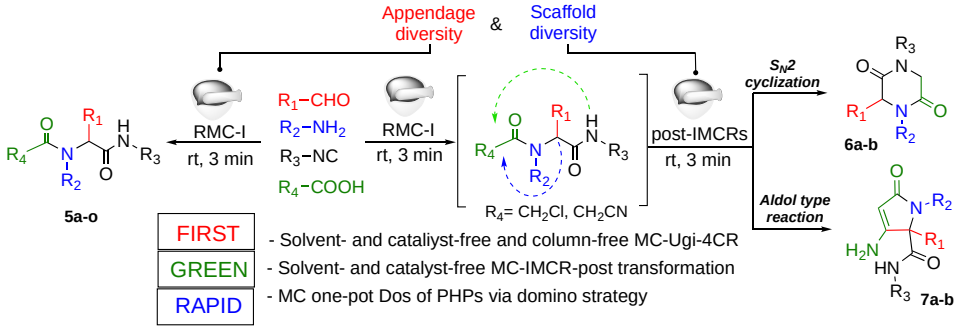
**Keywords:** *Mechanochemistry, IMCR, Diversity-Oriented Synthesis (DOS), 2,5-diketopiperazines, α,β,-unsaturated-γ-lactams*

Mechanochemistry refers to the reactions normally of solids induced by the input of mechanical energy, as a source of chemical activation to accelerate reactions under solvent-free conditions. In this context it is an efficient alternative energy source (AES) in the development of novel rapid and green synthetic methods.[1] Sonochemistry and mechanochemistry are emerging as relatively novel green technologies to improve IMCRs strategies.[1] However, sustainable IMCRs assisted by an AES under solvent, catalyst, column-free (SCCF) conditions are practically unreported.[2] On the other hand, efficient and convergent one-pot processes can be achieved using multicomponent reactions (MCRs) coupling post-transformations to minimize the waste, reagents, solvents, energy, time, and work required and mainly to increase complexity of target products. This justifies their prominence in the design and development of green synthetic methods of drug-like and bioactive molecules containing privileged heterocycles.[3] One-pot processes based on IMCR-post transformation strategies in a consecutive[4] or domino[5] fashion can deliver target molecules in a relatively short time with high yields. Here we developed a facile and rapid mechanochemical Ugi four-component reaction (MC-Ugi-4CR) for the synthesis of new dipeptide-like products in high yields under SCCF conditions at room temperature in three minutes. The scope and versatility of this efficient IMCR is demonstrated with the first one-pot DOS of privileged heterocyclic peptidomimetics (PHPs) such as 2,5-diketopiperazines (DKPs) and *α,β*-unsaturated-*γ*-lactams via a sustainable mechanochemical domino strategy that includes IMCR-post transformations in high yields with a total reaction time of six minutes.[7]

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# NITROGEN-WALK APPROACH: AN EVOLUTIONARY BIGINELLI-BASED APPROACH TO EXPLORE BIOISOSTERIC REPLACEMENTS IN $A_{2B}$ ADENOSINE RECEPTOR ANTAGONISTS

Ana Mallo-Abreu,[a,b] Rubén Prieto-Díaz,[a,b] Willem Jespers,[d] Jhonny Azuaje,[a,b] Maria Majellaro,[a,b] Carmen Velando,[a,b] Xerardo García-Mera,[a,b] Olga Caamaño,[a,b] José M. Brea,[c] María I. Loza,[c] Hugo Guitierrez-de-Terán,[d] and Eddy Sotelo.[a,b]

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**Keywords:** *$A_{2B}$ adenosine receptor antagonists, Biginelli reaction.*

The early identification of structural elements that have the potential to become structural alerts constitutes a key issue during early drug discovery. In this context, the relevance of these groups in terms of target engagement should be examined and their potential metabolic liabilities experimentally evaluated to identify alternative groups that could replace the elusive structural alerts. A systematic exploration of bioisosteric replacements for furan and thiophene cores, which can be considered toxicophores, in a series of potent $A_{2B}$AR antagonists has been carried out using the nitrogen-walk approach. A collection of 42 novel alkyl 4-substituted-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylates containing 18 different pentagonal heterocyclic frameworks at position 4 was synthesized and evaluated. This study enabled the identification of new ligands that combine remarkable affinity ($K_i$ < 30 nM) and exquisite selectivity. The structure−activity relationship (SAR) trends identified were substantiated by a molecular modeling study, based on a receptor-driven docking model and including a systematic free energy perturbation (FEP) study. Preliminary evaluation of the inhibitory activity at two cytochrome P450 (CYP) isoforms, CYP3A4 and CYP2D6, in optimized ligands evidenced weak and negligible activity, respectively. The stereospecific interaction between *h*$A_{2B}$AR and the eutomer of the most attractive novel antagonist (*S*) **ISAM-C032** ($K_i$ =3.66 nM) was validated (Figure 1).[1]

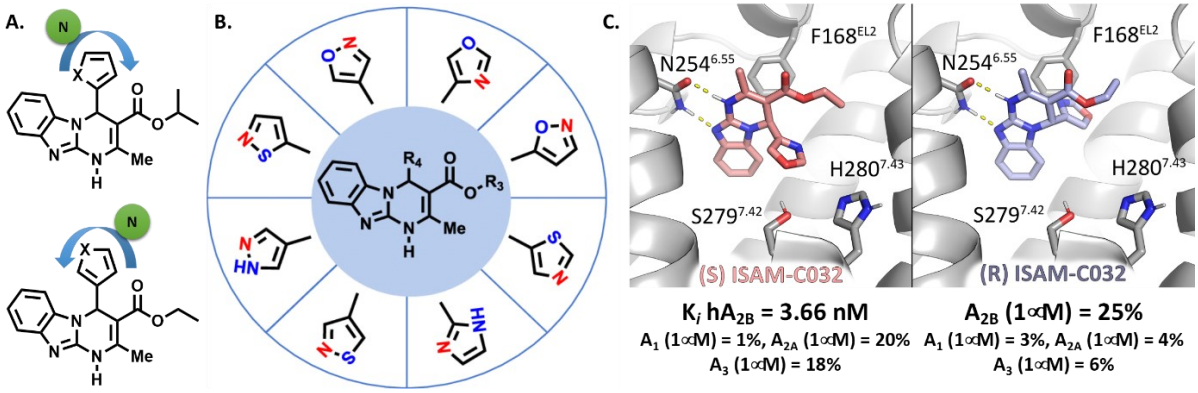


**Figure 1:** A. Nitrogen-walk concept. B. Outline of the most relevant modifications made for $R_4$. C. Theoretical model of receptor binding mode with the most active ligand enantiomers obtained.

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# Synthesis of *bis*-amides via Ugi reaction: functionalization of masticadienonic acid, a triterpenoid isolated from fruit peduncles of *Pistacia mexicana*

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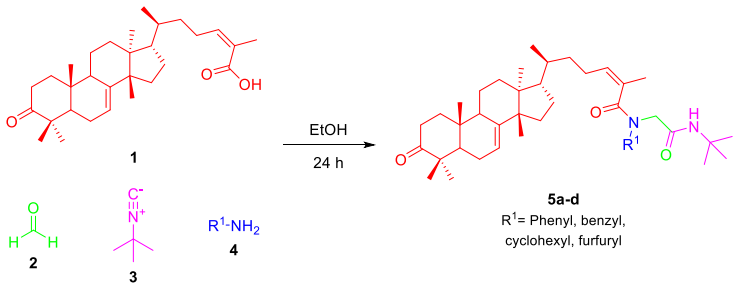
**Keywords:** *IMCR, Ugi-4CR, bis-amide, triterpenoid.*

Triterpenoids are naturally occurring compounds, which are mainly isolated from higher plants.[1] They have been studied for their potential as antibacterial, antifungal, and antiviral agents. Cytotoxicity is probably the most studied aspect of triterpenoids; compounds such as betulinic acid, oleanolic acid and cucurbitacin B have demonstrated a potent cytotoxic effect.[2] Functionalization of triterpenoids is a highlight in natural product chemistry, because their derivatives exhibit improved biological properties, for example, triterpenoids with an amide functionalization have demonstrated a better cytotoxicity and selectivity against cancer cells in *in vitro* studies.[3]

Isocyanide-based multicomponent reactions (IMCRs) such as Ugi four-component reaction (U-4CR) are highlighted strategies in modern organic chemistry. IMCRs stand out for their advantages such as convergence, bond-formation efficiency, and atom economy.[4] Furthermore they usually work under mild conditions. In recent years the U-4CR has been used for the efficient synthesis of functionalized natural products, for example steroids. However, there are only two reports on the functionalization of triterpenoids and their semi-synthetic derivatives by Ugi-4CR, leading to libraries of compounds that incorporate both the *bis*-amide and triterpenoid moieties which were evaluated *in vitro* against various cancer cell lines, exhibiting a moderate to good cytotoxicity. [3,5]

Herein we present the use of U-4CR for the efficient functionalization of masticadienonic acid (**1**), an interesting compound due to its relatively non-sterically hindered α,β-unsaturated carboxylic acid function. Triterpenoid-derived *bis*-amides **5a-d** were obtained with moderate to good overall yields (55-79%). A crucial point in the experiment optimization was the solubility of **1**. The use of ethanol as the solvent lead to higher yields compared with methanol and solvent-free experiments.

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# BIGINELLI-INSPIRED SCAFFOLD HOPPING APPROACHES FOR THE OPTIMIZATION OF $A_{2B}$ ANTAGONISTS

*Hugo Fojo-Carballo.*[a,b] *María Majellaro,*[a,b] *Rubén Prieto-Díaz,* [a,b] *Meera Chotalia,* [a,b] *Jhonny Azuaje,* [a,b] *Lucía González-Pico,* [a,b] *Xerardo García-Mera,*[b] *Adrián González-Martínez,* [a,b] *María Oliveira,* [a,b] *José M. Brea,*[c] *María I. Loza,*[c] *Hugo Gutiérrez-de-Terán*[d*] *and Eddy Sotelo* [a,b*]

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**Keywords:** b*iginelli, adenosine, $A_{2A}$ receptor, $A_{2B}$ receptor…*

Adenosine is a key immunosuppressive metabolite that regulates one of the major mechanisms supporting immune tolerance in tumors.[1] In normal cells, $A_{2A}$ and $A_{2B}$ receptors are engaged in the regulatory mechanisms that protects tissues against excessive immune reactions.[1,2] However, in the tumour microenvironment elevated adenosine concentration hijacks this protective pathway, hindering anti-tumour immunity.[2] Adenosine inhibits the biological functions of T lymphocytes, infiltrating the cancer tissue by binding to the $A_{2A}$ receptor. In addition, activation of $A_{2B}$ receptor reduce the response of dendritic cells and other parts of the innate immune system. Accordingly, $A_{2A}$ and $A_{2B}$ receptor antagonists constitute an emerging family of immunotherapeutic agents for cancer treatment. Within the frame of a project aimed at the discovery of $A_{2B}$AR antagonists for cancer immunotherapy, we herein document an evolutionary scaffold hopping approach inspired by **ISAM-140**, a highly potent and specific $A_{2B}$AR ligand developed in our laboratory,[3] to explore the structural determinants governing the optimal ligand-receptor interactions and PK properties in these series. These studies enabled the identification and optimization of novel chemotypes, with some ligands eliciting highly potent ($K_i$ 0.8-5 nM) and specific $A_{2B}$AR antagonistic profile (Figure 1).

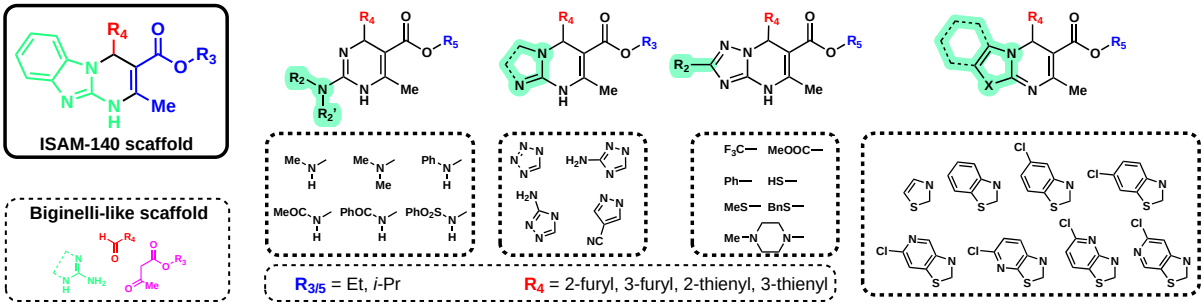


*Figure 1. Pharmacomodulation of ISAM-140 scaffold.*

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# UGI-BASED ASSEMBLY OF PERIPHERAL SELECTIVE RIMONABANT ANALOGUES

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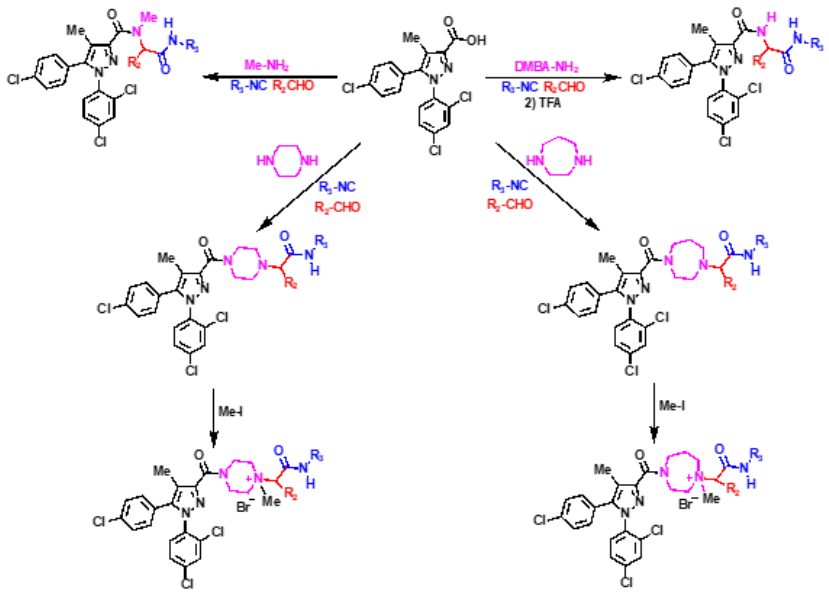
**Keywords:** *Cannabinoids, Cannabinoid receptors, Obesity, Depression, Ugi reaction.*

Rimonabant is a $CB_1$ inverse agonist approved in 2006 for the treatment of obesity that was removed from the market in 2008 due to serious psychiatric side effects.[1] Growing evidences confirmed Rimonabant´s neuropsychiatric liabilities are consequence of its binding to central $CB_1$ receptors, but also that peripheral $CB_1$ receptor blockade produces similar appetite suppression and weight loss.[2] Accordingly, the search for novel peripheral selective $CB_1$ ligands have emerged as a promising approach for obesity control.[3] In the frame of a project aimed to identify new lead compounds by using MCR-based approaches, we herein document the discovery and optimization of novel series of brain non-penetrant Rimonabant analogues. The new ligands, that were assembled by Ugi or Ugi-split reactions, exhibit high polar surface area and low Log P while retain excellent $CB_1$ affinity and selectivity profile.

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# UGI-BASED APPROACHES ENABLED THE DISCOVERY OF A NOVEL CLASS OF CANNABINOID RECEPTOR LIGANDS

David Reza,[1,2] Aitor García-Rey, Jhonny Azuaje,[1,2] Nora Piay,[1,2] Xerardo García-Mera,[1,2] José Brea,[3] M. Isabel Loza,[3] and Eddy Sotelo[1,2*]

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**Keywords:** *Cannabinoids, UGI-4CR, $CB_1R$ and $CB_2R$.*

The regulation of the endocannabinoid system, particularly through modulation of cannabinoid receptors ($CB_1R$ and $CB_2R$), embraces the emergence of novel therapeutic approaches to address serious diseases (e.g., inflammation, obesity, or diabetes).[1] $CB_1R$, expressed ubiquitously in the central and peripheral nerve terminals, mediates neurotransmitter release and control different, motor, emotional, and cognitive functions.[1] These evidences support the exploration of selective $CB_1R$ antagonists as potential drugs to treat diabetes, metabolic syndrome, dyslipidemias and liver diseases. Growing evidence suggest that blockage of $CB_1R$ activity in peripheral tissues (e.g., liver, adipocytes and pancreas) enable to suppress food intake, increase energy expenditure and reduce lipogenesis.[1] Accordingly, the discovery of novel families of $CB_1R$ antagonists enabling to restrict its action to peripheral tissues remains a highly challenging goal.[2] As part of our project to develop novel therapeutic agents by using succinct multicomponent approaches, we wherein document the discovery of a family of potent, selective and structurally simple $CB_1R$ and $CB_2R$ ligands derived of the α-*acylaminoamide* framework (Figure 1). The novel ligands, that are readily assembled by following different variants of the Ugi reaction. Although they fit perfect within the general pharmacophore of $CB_1R$ ligands, we have observed that specific modifications in their structure modify its selectivity profile rendering potent $CB_2R$ ligands. We have also explored the structural derivatization of the pharmacophore to ensure peripheral selectivity without relevant reduction in affinity or subtype-selectivity.

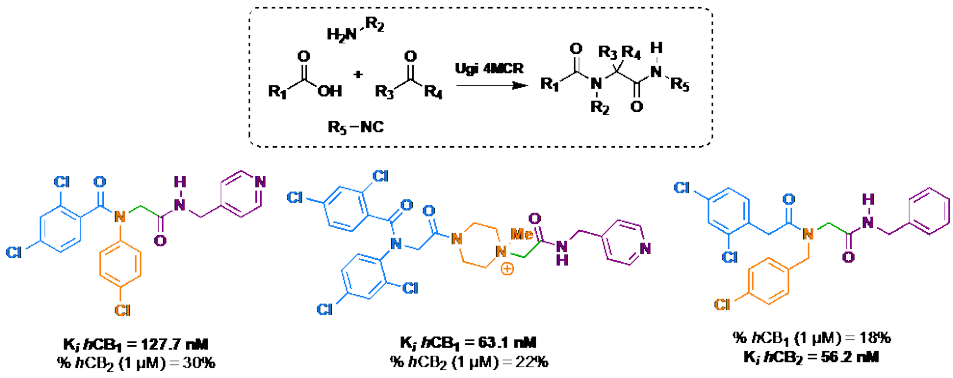


Figure 1. Ugi reaction, structure and binding data of representative cannabinoid ligands identified.

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# PREPARATION OF 3-ACYLPYRROLES AND SULFENYLATED ENAMINONES VIA FOUR-COMPONENT ONE POT SYNTHESES.

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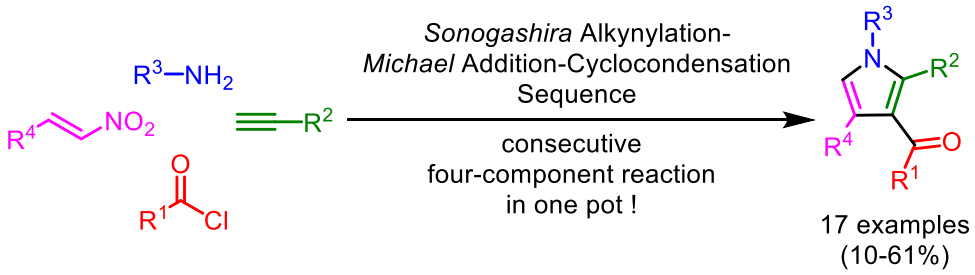
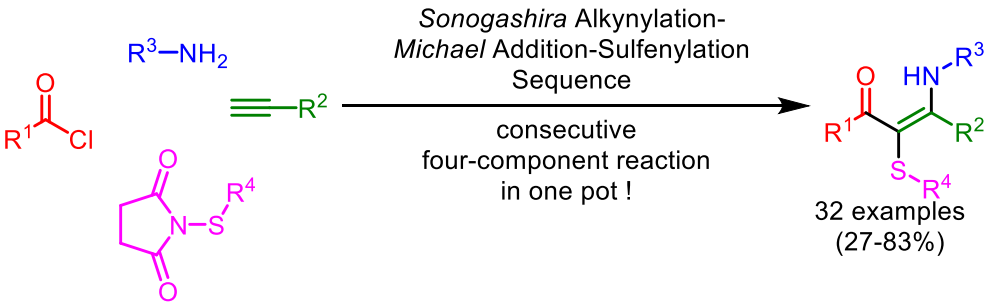
**Keywords:** *Multicomponent reaction, Enaminones, Pyrroles, Sulfenylation, Alkynylation, Catalysis, Copper, Cyclocondensation, Michael addition, Palladium*

A library of 3-acyl pyrroles has been synthesized in modest to good yields via a consecutive four-component alkynylation-amine addition-nitroalkene addition-cyclocondensation one-pot reaction of acid chlorides, alkynes, amines and nitroalkenes. The terminal addition-cyclocondensation step of the intermediary formed enaminones with nitroalkenes is supported by a synergism of Brønsted acid (acetic acid) and Lewis acid (iron(III) chloride) catalysis.[1]




A new approach to sulfenylated enaminones was found via a consecutive four-component alkynylation-amine addition-sulfenylation one-pot reaction of acid chlorides, alkynes, amines and *N*-thiosuccinimides. This multicomponent reaction furnishes a library of sulfenylated enaminones in modest to excellent yields. The generated products show strong solid-state fluorescence and can be employed as building blocks for further syntheses.[2]

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# Discovery and Optimization of New $CB_2R$ Selective Biased Agonists as Potent Anti-inflammatory Agents

Giovanni Graziano[1,2], Claudia Gioé-Gallo[1,2], Jhonny Azuaje[1,2], Maria Majellaro[1,2], Sandra Ortigueira[1,2], Josè M. Brea[3], Gemma Navarro Brugal[4], Rafael Franco[4], Marialessandra Contino[5], Angela Stefanachi[5], Giuseppe Mangiatordi[6] and Eddy Sotelo[1,2*]

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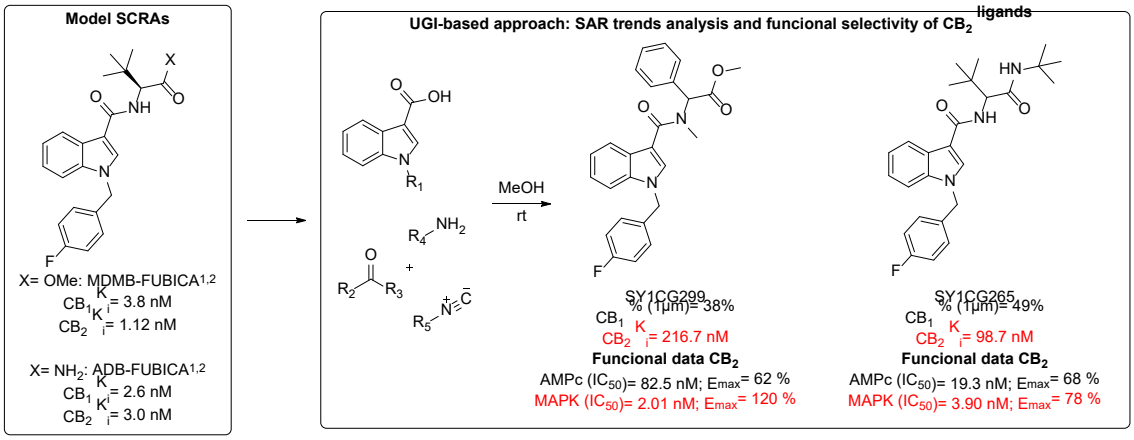
**Keywords:** *CB2 agonists, Anti-inflammatory Agents, Biased Ligands*

Although clinical evidence validated the beneficial effects of cannabis and its components in the treatment of various health conditions (such as anorexia, side-effects of chemotherapy, neuropathic pain or multiple sclerosis), its therapeutic use is limited by adverse psychotropic effect and potential abuse associated to the activation of $CB_1$ receptor in the central nervous system.[1] On the other hand, $CB_2$ G-protein coupled receptor is primarily expressed in the periphery, especially in cells of the immune system, and it is a potential target for the treatment of challenging autoimmune diseases, neuropathic pain, cancer and multiple sclerosis. The scarcity of selective modulators along with the latest discoveries on functional selectivity make the development of biased and subtype selective synthetic agonists essential to study the pathophysiological role of $CB_2R$ downstream signalling pathways.[2] Starting from the study of Synthetic Cannabinoid Receptor Agonists family (SCRAs),[1] whose excellent agonist activity and efficacy at both cannabinoid receptors has been reported, we have developed a new series of $CB_2$ selective agonists showing remarkable functional selectivity for the MAPK signalling pathway (figure 1).

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# CONVERGENT ONE-POT SYNTHESIS OF INDOLO[3,2-*a*]PHENAZINE DERIVATIVES – INVESTIGATING MEDICINAL AND PHOTOPHYSICAL PROPERTIES

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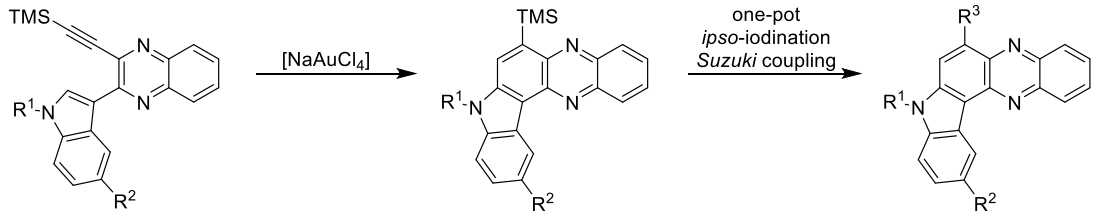
**Keywords:** *Multicomponent Reactions, One-pot Procedure, Organic Synthesis, Medicinal Chemistry*

Indolo[3,2-*a*]phenazines refer to a subclass of the widely used phenazines. With its five fused rings and its electronic properties the structure is resembling berberine, which belongs to the protoberberines (benzylisoquinoline alkaloids) and has various pharmacological applications.[1] These applications also include the treatment of the parasite *Toxoplasma gondii* that causes toxoplasmosis.[2] Previously, we introduced multicomponent reactions to synthesize 3-ethynylquinoxalines,[3] which are precursors of indolo[3,2-*a*]phenazines. Starting from 3-[((trimethylsilyl)ethynyl)]quinoxaline **1** we could perform a cycloisomerization under gold catalysis. These silylated heterocycles **2** were transformed into 6-aryl-indolo[3,2-*a*]phenazines **3** by *ipso*-iodination *Suzuki* coupling sequence.




**1** **2** 10 examples (9-75%) **3** 19 examples (16-74%)

The obtained compounds represent a novel type of tunable luminophores that can be fine-tuned by the *para*-aryl substituent and show positive solvatochromism. Moreover, it was found, that the indolo[3,2-*a*]phenazines tend to be bioactive against the medically important pathogen *Toxoplasma gondii* with an $IC_{50}$ up to 0.59 ± 0.069 µM (berberine hemisulfate as standard 0.94 ± 0.48 µM).[4]

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# BIGINELLI REACTION ENABLED THE IDENTIFICATION OF A2B AND DUAL A2B/A2A ANTAGONISTS FOR CANCER IMMUNOTHERAPY

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**Keywords:** *A2B receptor antagonists, cancer immunotherapy*

The A2B adenosine receptor (A2BAR) is a low affinity receptor which is overexpressed in chronic inflammation. The binding of adenosine (ADO) to the A2BAR only occurs under pathological conditions. It has been demonstrated that the A2BAR is involved in immunosuppression and may increase tumour growth and metastasis through different mechanisms.[1]

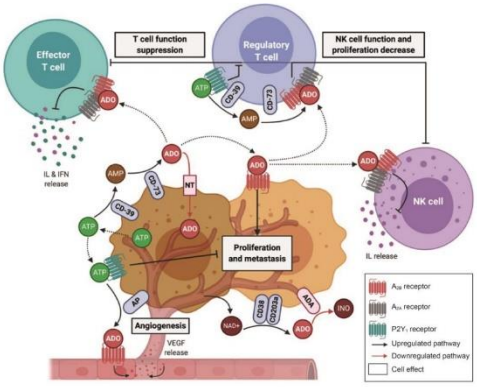


*Figure 1. Biosynthesis and effects of ADO in the tumor microenvironment*

Therefore, A2BAR is a promising target for immunotherapy. Ever since the possibility of GPCRs forming dimers was demonstrated, a new opportunity for A2BAR ligands arose. A2BAR forms a heterodimer, acting as the dominant receptor, with A2AAR, which is also present in immune system cells, as such, both are attractive cancer targets. Our group has discovered a novel A2BAR pharmacophore, derived of the pyrimidin-2-one core, and explored its structural diversification by using a scaffold hoping approach. Thus, novel bicyclic and tricyclic derivatives were discovered (e.g., ISAM-140).[2] The nitrogen at position 1 has never been modified before, as computational models suggest its role in a water-mediated hydrogen bond with specific residues. However, the presence of a hydrophobic pocket located near the binding site led us to introduce alkyl groups at position 1 in a representative subset of our A2BAR scaffolds. Herein we report novel series of 1-substituted pyrimidine derivatives as potent and selective A2BAR antagonists. We will discuss new SAR trends, highlighting important increase in A2B affinity for 2F-Bn group and the discovery of three new dual A2B/A2A ligands as promising agents for cancer immunotherapy.

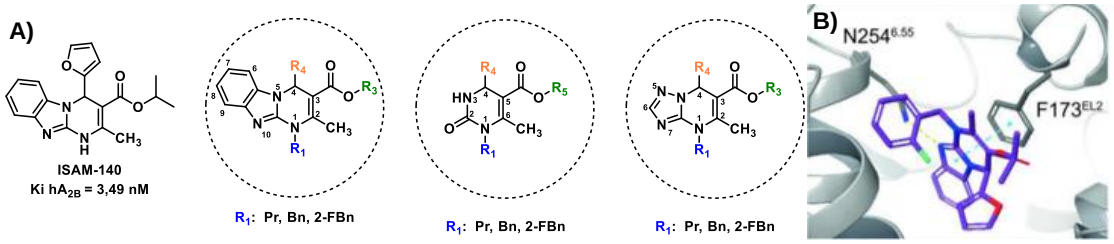


*Figure 2. A) ISAM-140 and general structure of the novel ligands. B) Predicted interaction of a novel compound with $A_{2B}AR$.*

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# PRELIMINARY STUDIES ON MCRs USING LEVOGLUCOSENONE AS BIO-BASED STARTING MATERIAL

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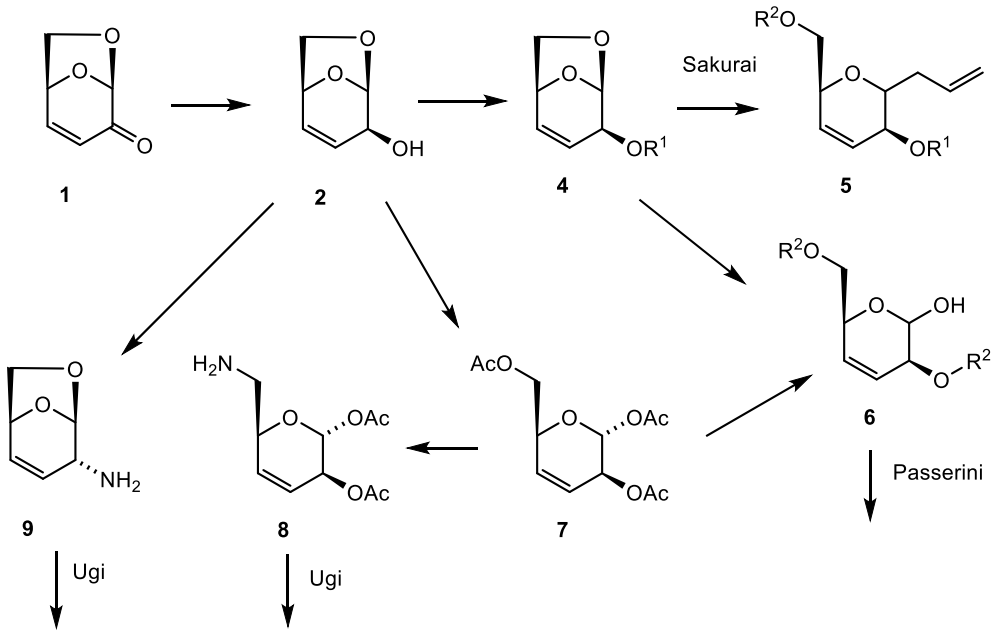
**Keywords:** *Levoglucosenone, lignocellulosic biomass, glycomimetics*

Levoglucosenone **1** (LGO) is the main volatile product obtained from pyrolysis of cellulose containing products,[1] including low value materials such as waste or lignocellulosic matters. It is considered one of the most important biomass-derived building blocks. Although some synthetic applications have already been reported,[2] there is still ample room for further applications, especially in the diversity-oriented synthesis of nitrogen containing glycomimetics or glycopeptide analogues. LGO or their derivatives have never been used, to our knowledge, in MCRs. We reasoned that MCRs may represent an ideal strategy to introduce nitrogen functionalities with simultaneous generation of molecular diversity.

LGO is small, yet highly functionalised, and therefore its manipulation requires the regio- chemo- and stereoselective differentiation of the three oxygen moieties[3] to give the necessary building blocks to be used as inputs for various MCRs.




In particular, we have carried out a thorough study on the opening of the bridge under the catalysis of protic or Lewis acids. This may lead to *C*-glycosides, like **5** or to other building blocks suitable for MCRs. We will thus describe the selective manipulation of the three masked hydroxy groups, taking advantage of biocatalysis, in order to produce hemiacetal **6** and amines **8**, **9**, to be used in isocyanide-based MCRs.

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# The use of new isocyanides in the GBB three-component reaction for the synthesis of novel organic fluorophores

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**Keywords:** *Groebke-Blackburn-Bienaymé reaction, fluorescence, one-pot, isocyanides*

Novel structural modifications of already extensively studied fluorescent compounds have been investigated. The introduction of the isocyanide group on 1,8-naphthalimide[1] and coumarin-based[2] cores allowed us to perform a Groebke-Blackburn-Bienaymé reaction (GBB)[3],[4] in order to obtain potentially fluorescent complex heterocyclic molecules **5a** and **5b**. **Fig.1**.

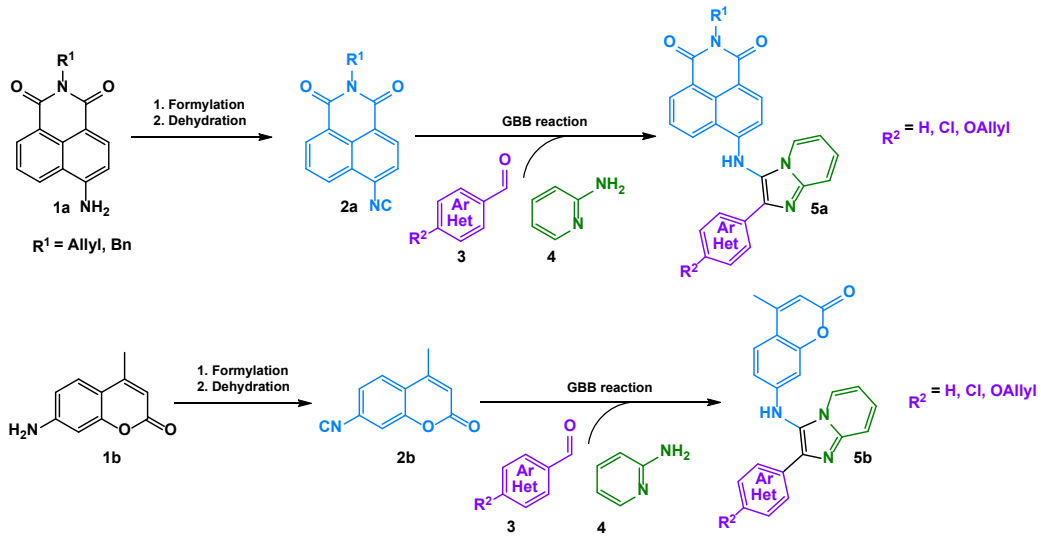


**Fig.1**: synthesis of GBBR adducts with 1,8-naphthalimide and coumarin-based isocyanides.

The synthesis of the isocyanides has been deeply studied also from the perspective of fluorescence, with the characterization of all the intermediates. This led to the understanding of the structure-photophysical properties related to the nature of the functional group (-$NH_2$, -NHCOH, -NC). Since organic fluorophores hold a huge importance for different applications, such as bio-imaging and innovative luminescent materials, we decided to pursue our set goal following the synthetic pathway above represented. The optimization of the GBB reaction for the proposed starting material, allowed us to synthesize some of our target molecules.

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# UGI-BASED EXPLORATION OF NON-ORTHOSTERIC INTERACTIONS WITH A SERIES OF POTENT $A_3$ ANTAGONISTS

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**Keywords:** *Ugi reaction,Glaucoma, $A_3$ antagonist, Non-orthosteric Interactions.*

The $A_3$ adenosine receptor ($A_3$AR) is the most recently characterized AR subtype,[1] albeit not yet at the structural level. It is actively involved in a range of cardiovascular and neurological diseases and overexpressed in several cancer cells. Because of its contradictory signaling and dual behavior in various pathological conditions, only a few of $A_3$AR ligands have reached clinical trials. Hence, the discovery of $A_3$AR modulators and specific pharmacological tools is crucial to better define its pathophysiological role and validate its therapeutical potential.

Herein, we report the exploration of non-orthosteric interactions in the $L_1$ region (figure 1) in a series of selective $A_3$AR antagonists derived of the 4-amido-2,6-diarylpyrimidine scaffold.[2] The study included the design, synthesis, pharmacological characterization and in silico evaluation of the novel series, that were readily assembled by using two efficient and experimentally simple Ugi-based multicomponent reactions. The obtained library enabled to identify highly potent and subtype-selective $A_3$AR ligands with improved aqueous solubility, while provided a complete picture of the role and underexploited potential of the $L_1$ region non-orthosteric interactions within $A_3$AR, paving the way for the development of novel covalent and bitopic $A_3$AR ligands.

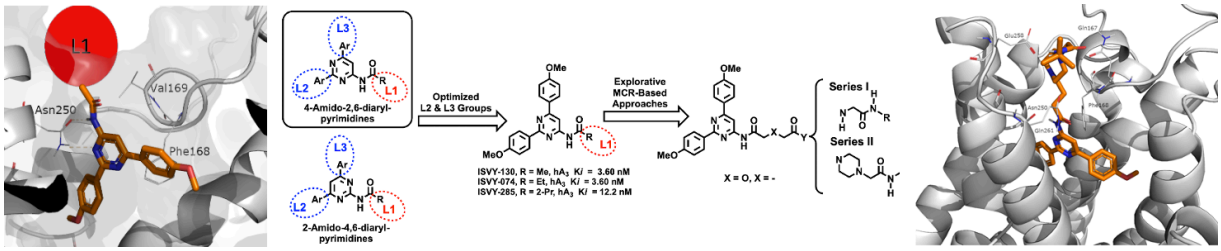


Figure 1. Design strategy, structure of herein explored ligands and simulated docking models.

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# ONE-POT SYNTHESIS OF ISOINDOLIN-1-ONES UNDER ULTRASONIC IRRADIATION

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**Keywords:** *isoindolin-1-ones, one-pot reaction, ultrasonic irradiation,* N-*acyliminum ion intermediates, multigram synthesis*

Isoindolin-1-ones are abundant moieties found in many natural products or designed pharmaceutical molecules displaying significant biological properties. In this context, the construction of these nitrogen heterocycles in effective and efficient manner has triggered considerable attention. Several synthetic approaches of isoindolin-1-ones have been reported in the literature. However, these methods suffer from drawbacks like poor selectivity, low chemical yields, long reaction time, extreme reaction conditions and substrates limitations. To this effect, this works deals with the development of a general and straightforward approach to 3-hydroxyisoindolin-1-ones under ultrasonic irradiation from readily available starting materials. By taking the potential of 3-hydroxyisoindolin-1-ones as the precursors of *N*-acyliminum ion intermediates, our strategy can be further extended to access other motifs of isoindolin-1-ones namely 3-alkylisoindolin-1-ones, 3-alkylideneisoindlin-1-ones and polycyclic isoindolin-1-ones in one-pot fashion. Performing the one-pot reaction under ultrasonic irradiation allows us to create a library of various motif of isoindoli-1-ones in more efficient way[1]. It is also interesting to note that the synthesis of isoindolin-1-ones can be carried out in multigram scale.

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# THE ISOCYANIDE AS NOVEL PHARMACOPHORIC GROUP: ONE- POT SYNTHESIS OF POTENT ANTIBACTERIAL AGENTS USING MULTICOMPONENT REACTIONS

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**Keywords:** *isocyanides, medicinal chemistry*

The role of the isocyanide group in the biological activity of natural substances is crucial, but medicinal chemists have overlooked it due to an erroneous belief that the isocyanide group is toxic, highly reactive, and metabolically unstable, and because natural isocyanides have complex molecular architecture and are obtained in very low yield. Recent efforts by our group have shown that in specific molecular contexts, the **isocyanide** group can be stable to human metabolism [1] and may serve as a promising **pharmacophoric group** in medicinal chemistry. [2] Its features, such as being a hydrogen bond acceptor with a high dipole moment, a σ and π hole acceptor, and the ability to behave as a metal coordinating agent, along with its chemical inertness at room temperature to the major nucleophiles present in the organisms, make it an aggressive pharmacophore. Therefore, our aim was to generate a library of isocyanides through more efficient and expedient synthetic methods to obtain a variety of compounds useful for medicinal chemistry screening campaigns. This poster presents a one-pot synthetic strategy to generate molecules containing an isocyanide warhead group using either a Ugi or Passerini multicomponent reaction. Many of the synthesized isocyanides demonstrated potent **antibacterial activity** against the dangerous, multidrug-resistant strain *Staphylococcus aureus* MU50, which is resistant to vancomycin, the antibiotic of last resort, without exhibiting toxicity towards mammalian cells. The poster highlights the development of both soft and hard drugs within this novel class of compounds, for topical or systemic infections.

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# α-KETOGLUTARIC ACID IN MULTICOMPONENT REACTIONS

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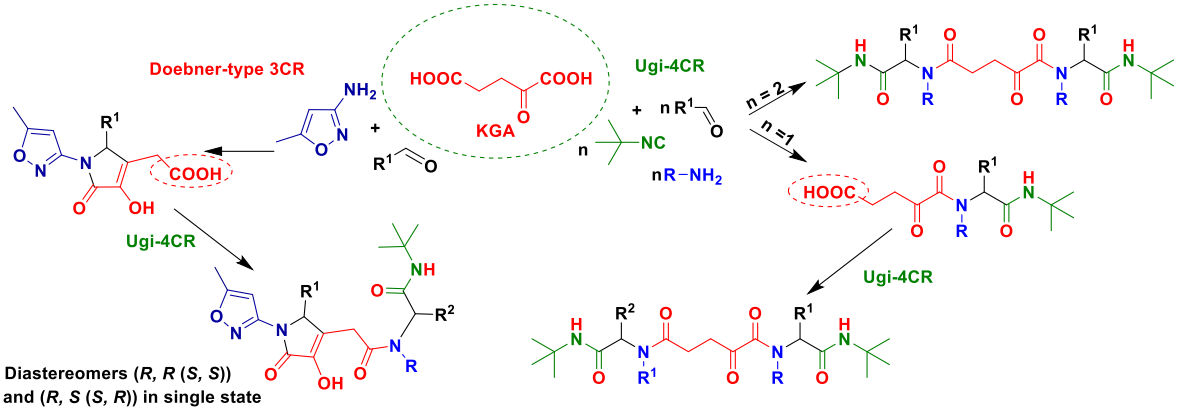
**Keywords:** *multicomponent reaction, α-ketoglutaric acid, Doebner reaction; Ugi reaction*

Multicomponent reactions (MCRs) based on α-ketoglutaric acid (KGA) and its derivatives are an effective and attractive tool for combinatorial, medicinal- and diversity-oriented synthesis. Ugi- and Doebner-type MCRs and the tandem combination of these reactions involving KGA are a way to increase the diversity of organic compounds and to obtain novel peptidomimetics, which were synthesized and studied in the present work. Substituted pyrrolidinones with a carboxyl-containing substituent in the 4th position derived from the Doebner-type reaction have been shown to be a privileged for increasing molecular diversity and have been introduced into Ugi-type MCRs.[1,2] The diastereoselectivity of this reaction can be controlled by the temperature mode, allowing the isolation of pyrrolone-containing peptidomimetics as both possible diastereomers in the single state.[2]




Both carboxylic groups of KGA can be involved in multicomponent Ugi reactions, and depending on the molar amounts of the starting materials in the Ugi reaction, products are formed in which only one carboxyl group is involved (near the keto group) or products in which both carboxyl groups react. The carboxyl group that is near the keto group is more reactive in the Ugi reaction. It should be noted that peptidomimetics with free carboxyl groups could further participate in the Ugi reaction to form diUgi products with different substituents in peptide chain.

The project of National Research Foundation of Ukraine "Polypharmacophoric organic compounds based on peptidomimetics and fused benzodiazepines" (2020.02/0023).

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# Heterocyclic scaffold synthesis through Enol-Ugi/Reduction/Cyclisation

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**Keywords:** *multicomponent reactions, isocyanides, heterocycles, Ugi reaction, coumarins, enols.*

The Ugi reaction has proved as a valuable tool for heterocycle construction, mainly through post-condensation transformations of the resulting adducts.[2] A particularly useful transformation is the Ugi/Reduction/Cyclisation sequence, usually involving a nitro group as a masked amine surrogate.[2]

The enol-Ugi condensation is a variation of the Ugi reaction, which uses enols as acid surrogates to afford a diversity of heterocyclic enamines. For example, the reaction of 4-hidroxi-3-nitrocoumarin with an aldehyde, an amine and an isocyanide readily affords peptidomimetic coumarin derivatives containing a potentially reducible nitro group.[3] Here we report a novel divergent enol-Ugi/Reduction/Cyclisation strategy selectively leading to chromenopiperazines (**7**) and imidazolocoumarins (**8**).

The electro-withdrawing nitro group on the coumarin is key to facilitate the enol-Ugi reaction. Then, reduction with iron in acetic acid leads to an amine (**6**) that can evolve in different ways. The enol-Ugi adducts of aliphatic amines are smoothly reduced and cyclised in one pot at room temperature to chromenopiperazines (**7**, *Figure 1*, path *a*).[4] Chromenopiperazines are privileged heterocycles, showing antimicrobial, anticancer and photobiological activities. The enol-Ugi adducts of aromatic amines can be also transformed to the corresponding chromenopiperazines, but in this case the reduction/cyclisation requires temperatures of 150ºC.

On the other hand, carful reduction of the enol-Ugi adducts (**5**) under ultrasound irradiation allows the isolation of amines (**6**). Then, amide-directed oxidative cyclisation with environmentally friendly hypervalent iodine reagents (PIDA) affords imidazolocoumarins (**8**, *Figure 1*, path *b*). This is driven by the relative acidic hydrogens on the C($sp^3$) asymmetric carbon. The directing effect of the amide group derived from the enol-Ugi condensation accounts for the complete regioselectivity of the cyclisation. Remarkably, the synthetised imidazolocoumarins are potential modulators of TLR7 receptor, showing high binding affinities in molecular docking studies.[5]

In conclusion, we have developed an efficient divergent multicomponent methodology to access coumarin-derived biologically relevant heterocycles in only two steps.

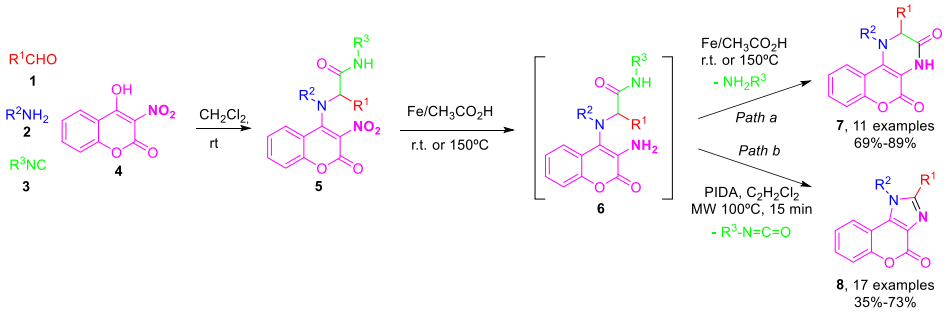


*Figure 1. Enol-Ugi/Reduction/Cyclization strategy to obtain chromenopiperazines (a)and imidazolocoumarins (b)*

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# $A_1$AR ANTAGONISTS WITH ENANTIOSPECIFIC RECOGNITION ASSEMBLED THROUGH A BIGINELLI-BASED APPROACH

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**Keywords:** *Biginelli reaction, $A_1$AR antagonists, Alzheimer's disease*

Since its early discovery and cloning the $A_1$AR has been considered an attractive target for therapeutic intervention. It is highly expressed in the central nervous system, participating within the development of several neurological and neurodegenerative disorders. Recent evidence supports that $A_1$AR blockade reduces amiloid toxicity, tau aggregation and enhances cognition in Alzheimer's disease.[1] In the frame of a program to develop $A_1$AR antagonists for the treatment of CNS diseases, herein we document the discovery of a novel family of potent and selective ligands derived of the alkyl 1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate scaffold.

A joint computational-experimental approach was used to redecorate this scaffold (present in the $A_{2B}$AR ligand **ISAM-140**), particularly at positions 3 and 4, to substitute the pharmacophoric elements responsible of the $A_{2B}$AR affinity. [2] A detailed exploration of diverse heterocyclic frameworks at position 4 and (alkyl, cycloalkyl, and benzyl) moieties within the ester group enabled to decipher the structural determinants for optimal binding within the $A_1$AR.[3] Library synthesis by combining optimal groups, using an efficient and environmentally friendly Biginelli-based approach, produced a focussed library of more than one hundred tricyclic derivatives, some of them eliciting excellent affinity ($K_i$ = 0.9-25 nM) and outstanding $A_1$AR subtype-selectivity (Figure 1). In the presentation we will discuss the main trends of the SAR and SSR in these series, but also the chiral separation of three representative racemates and its pharmacological characterization, thus providing the first evidence of enantiospecific recognition at the $A_1$AR.

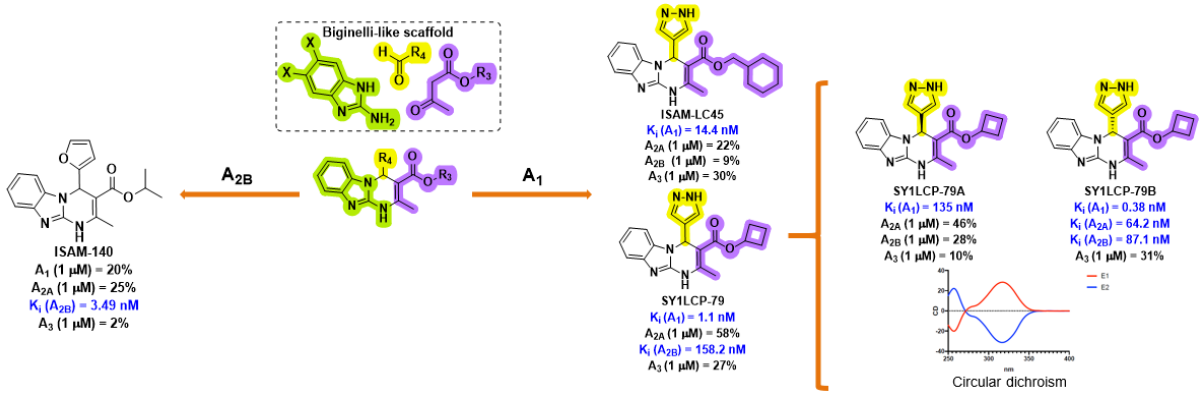


Figure 1. Structural decoration of the tricyclic scaffold for obtaining selective $A_{2B}$ or $A_1$ antagonists.

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# UDC strategy in the synthesis of pyrrolopiperazinones

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**Keywords:** *Multicomponent reaction, Ugi reaction, pyrrolopiperazinone*

The numerous biological activities of nitrogen heterocycles explain the relevance of these systems in the pharmaceutical industry. This is the case of pyrrolopiperazines, found in many natural products presenting different pharmacological activities, such as antibiotic, antibacterial or antitumoral agents.[1] Many synthetic strategies have been described for the synthesis of these systems, being multicomponent reactions (MCR) one of those that have demonstrated more versatility.[2] Herein, we describe two new simple methodologies for the synthesis of pyrrolopiperazinones based on the Ugi/deprotection/cyclization strategy (UDC). The Ugi reaction was carried out using three doubly functionalized reagents, 3-bromopropilamine, arylglioxals and *N*-Boc protected α-aminoacids, with isocyanides as the fourth component. Afterwards, the pyrrolo and the piperazinone systems were built at different stages, depending on the strategy followed, in order to evaluate the chemical and stereochemical outcome (**Figure 1**).

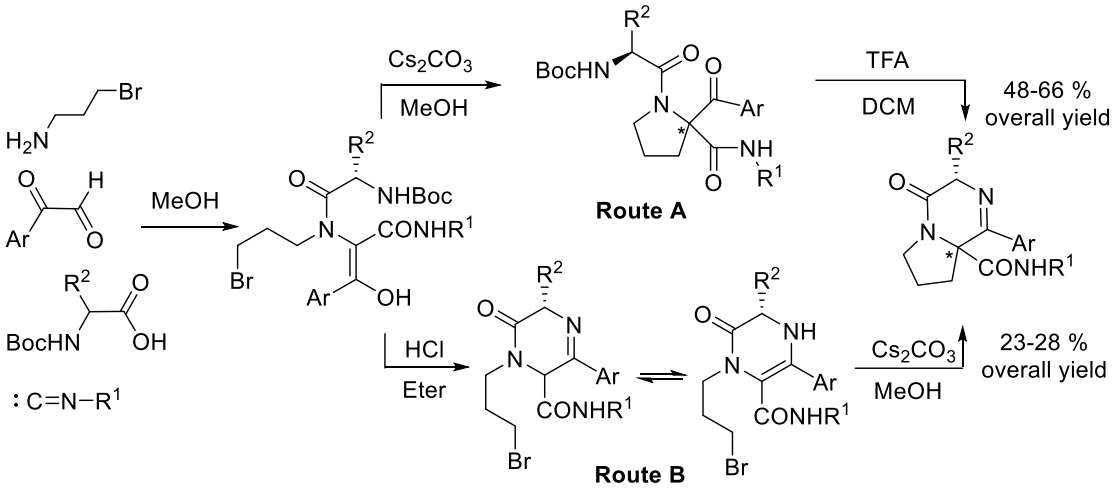


**Figure 1**. Synthesis of pyrrolopiperazinones by Ugi/post-condensation sequences

The Ugi/cyclization by intramolecular nucleophilic substitution/de-Boc/cyclization sequence (**Route A, Figure 1**) was chemically more efficient than the other one (**Route B, Figure 1**). However, both sequences present an important drawback, the low diastereoselectivity observed (d.e. < 5 %), despite the fact that the new stereogenic center was not generated during the Ugi reaction.[3]

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# MCR-ASSISTED DISCOVERY AND OPTIMIZATION OF NOVEL $A_{2A}$ ADENOSINE RECEPTOR ANTAGONISTS FOR CANCER IMMUNOTHERAPY

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**Keywords:** *UGI-reaction, adenosine, immunotherapy, $A_{2A}$ receptor*

Adenosine is a key immunosuppressive metabolite that regulates one of the major mechanisms supporting immune tolerance in tumors[1]. In normal cells, $A_{2A}$ and $A_{2B}$ receptors are engaged in the regulatory mechanisms that protects tissues against excessive immune reactions[1,2]. However, in the tumor microenvironment elevated adenosine concentration hijacks this protective pathway, hindering anti-tumor immunity[2]. Adenosine inhibits the biological functions of T lymphocytes, infiltrating the cancer tissue by binding to the $A_{2A}$ receptor. Similarly, activation of $A_{2A}$ receptor on Natural Killer cells leads to a loss of their effector capacity preventing, also, the elimination of cancer cells. $A_{2A}$ and $A_{2B}$ receptor antagonists constitute an emerging family of immunotherapeutic agents for cancer treatment. In this context, we herein document the design, synthesis, and SAR studies of a large collection of $A_{2A}$ receptor antagonists. Inspired by the Lundbeck 28 ligand[3], we carried out a pharmacomodulation process with the aim to improve the potency and selectivity of the series by introducing new diversities that potentiate non-orthosteric interactions. The classical UGI-4CR and several of its variants were employed for library synthesis, thus enabling to identify new ligands with excellent $A_{2A}$ affinity/selectivity profiles. The antiproliferative and antimetastatic effect observed for selected $A_{2A}$ antagonists will be presented.

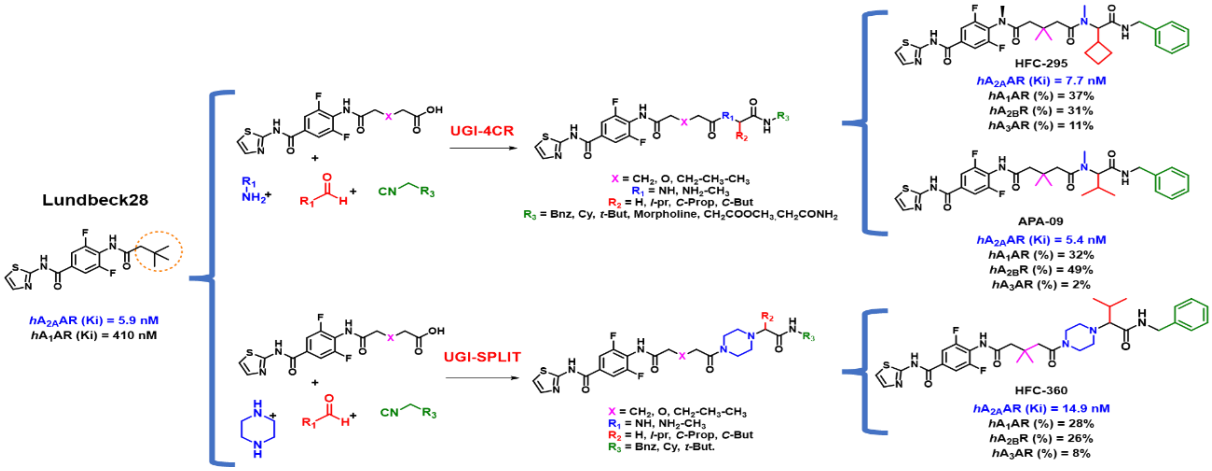


*Figure 1. MCR-assisted pharmacomodulation of Lundbeck28 and representative compounds obtained.*

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# DESIGN AND SYNTHESIS OF LIPID PEPTOID NANOPARTICLES FOR TARGETED DRUG DELIVERY VIA UGI REACTION

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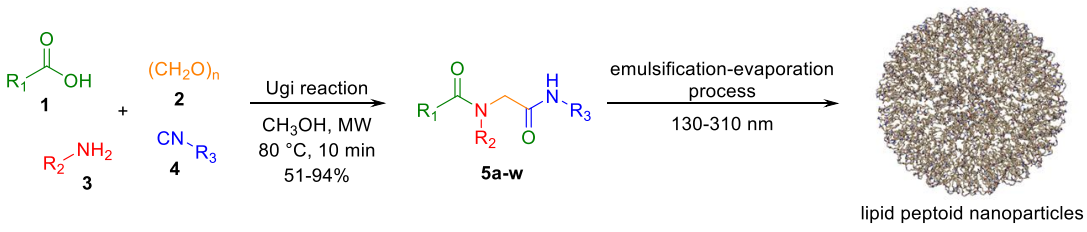
**Keywords:** *Ugi reaction, targeted drug delivery, nanoparticles*

Nanoparticles are nanometer-sized particles between 10 and 1000 nm. Nanotechnology is an important tool in the targeted delivery drugs as it helps to overcome the conventional methods limitations by using target-specific nanocarrier systems, such as lipid nanoparticles.[1] These nanocarriers can protect the drug molecules against hydrolytic and enzymatic degradation, prolong circulation time and cross various biological barriers.[2] In this work, lipid peptoid nanoparticles were obtained for the first time. In this new approach, we synthesized a diversity of lipid peptoids by varying the position ($R_1$, $R_2$, $R_3$), the size ($C_8$, $C_{12}$, $C_{18}$) and the number of long chains in the Ugi reaction, according to previously known conditions.[3] In total, more than 20 different adducts were isolated in good to excellent yields (51-94%). Then, all the products were submitted to the nanoparticle formation by the emulsification-evaporation process from lipophilic solution.[4] It was observed that the carboxylic acids **1** containing long chains of more than sixteen carbons ($R_1 \geq C_{16}$) are essential for the nanoparticle formation. Molecules with only one long chain ($R_1$, $R_2$ or $R_3$ = $C_9$, $C_{12}$ or $C_{18}$) afforded no nanoparticles (size above 1000 nm in all cases). On the other hand, molecules with two or three long chains yielded nanoparticles with sizes between 127 and 306 nm. Interestingly, when all the positions ($R_1$, $R_2$ and $R_3$) had $C_{18}$ chains, the result was not as good as expected (~600 nm), probably due to steric hindrance. In summary, we were able to achieve, for the first time, lipid peptoid nanoparticles, of which at least seven had size below 200 nm. One of the biggest advantages of our method is the easy incorporation of molecules on the surface of the lipid peptoid nanocarriers that can direct an active compound to reach a desired target. In this respect, an ongoing work in our lab is the functionalization of the lipid nanoparticles with folic acid to help in the systemic administration of antitumor drugs selectively to the tumor.




**Scheme 1.** Lipid peptoid synthesis via Ugi reaction and nanoparticles formation by the emulsification-evaporation process.

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# THE USE OF UGI FOUR-COMPONENT REACTION COUPLED WITH A Pd$^0$-CATALYSED DOMINO PROCESS FOR THE SYNTHESIS OF NOVEL HIGHLY CONJUGATED ORGANIC FLUOROPHORES

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**Keywords:** *Ugi reaction, one-pot domino process, fluorescence, heterocycles*

The synthesis of a novel class of heterocyclic fluorophores featuring the furo[2,3-*c*]isoquinoline core has been developed. The two key steps of the synthetic strategy consist of an **Ugi 4-component reaction** coupled with a subsequent ***one-pot* Pd$^0$-catalyzed domino process** named **HSCA**, which stands for *Heck-Sonogashira-Cyclization-Aromatization*. This versatile combination developed by our group successfully leaded to the synthesis of two generations of blue/green-fluorescent compounds[1,2]. Considering the application potential of fluorescent organic small molecules[3], this approach has been recently employed to obtain new furoisoquinolines with an extended π-electron conjugation, with the aim to achieve a red-shift both in the absorption and fluorescence bands (**Fig.1**).

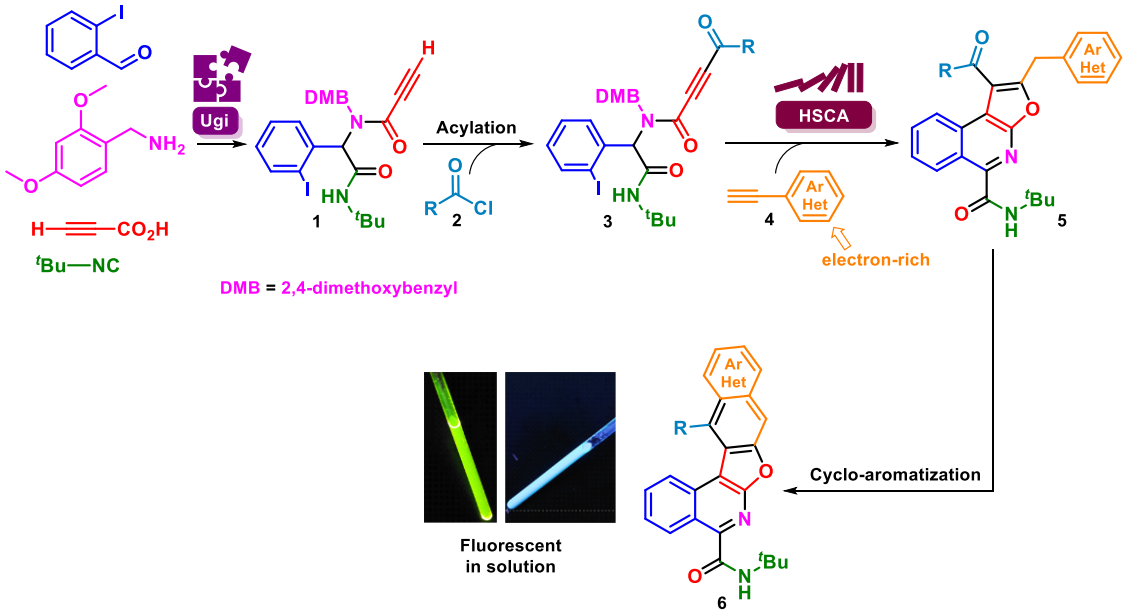


**Fig. 1:** the synthetic route for fused highly conjugated furo[2,3-*c*]isoquinolines.

The high structural complexity of our target molecules derives both from the acylation of **Ugi** product **1** to give **3**, both from the use of **electron-rich ethynyl arenes** **4** in the **HSCA**. In fact, the resulting compounds **5** are able to increase the overall conjugation through a further cyclo-aromatization, leading to fused highly conjugated furoisoquinolines **6**. These compounds, under UV excitation, exhibit an interesting fluorescence in solution ranging from the blue to the yellow region of the visible spectrum.

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# A Cobalt Mediated Nitrene Transfer aza-Wittig Cascade Reaction to access 1,3,4-Oxadiazole Scaffolds

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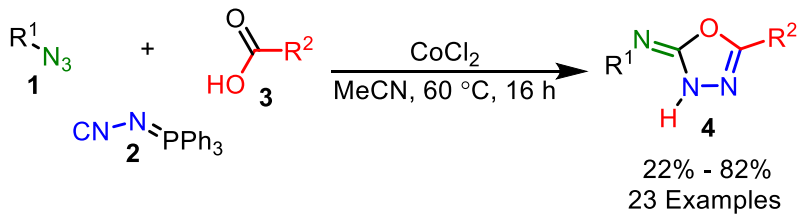
**Keywords:** *nitrene transfer, isocyanide, carbodiimide, oxadiazole, N-isocyaniminotriphenylphosphorane*

Abstract: Multicomponent reactions (MCRs) are highly desired synthetic tools to synthesize complex molecules from simple building blocks, in a single step[1]. A class of C1 building blocks that can be applied in MCR chemistry are isocyanides. Isocyanides possess unique reactivity that allows the possibility for late-stage structural diversification[2]. In addition, the combination of isocyanides with transition-metal (TM) chemistry catalysis has gained much attention in the past decade as an alternative for carbonylation chemistry. In our recently published manuscript[3], we present a Co(II) mediated 3-component synthesis of 2,5-disubstituted-1,3,4-oxadiazoles, **4**. The reaction consists of a nitrene transfer from sulfonyl azide **1** to N-isocyaniminotriphenylphosphorane (NIITP, **2**). Attack of the acid moiety **3** on the *in situ* generated carbodiimide, followed by an aza-Wittig provide the desired compounds in poor to good yields (22% - 82%). The reaction shows a wide tolerance for aliphatic carboxylic acids with different synthetic handles. To prevent to formation of a side product, a stoichiometric amount of cobalt chloride needs to be used, however the intermediate of the reaction can be achieved by using a catalytic amount of cobalt chloride.
The general reaction is presented in Scheme 1.




Scheme 1: General reaction scheme.

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# Synthesis of Highly Functionalized Heterocycles by Ugi/Nucleophilic Substitution/Ring Expansion Sequences

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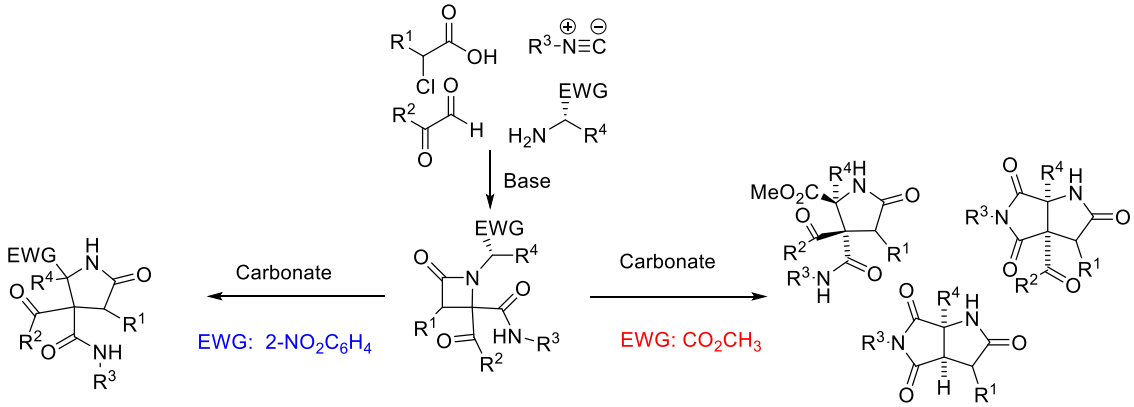
**Keywords:** *Multicomponent reaction, Ugi reaction, functionalized lactams.*

The biological activity displayed by nitrogen heterocycle compounds explains their relevance in the pharmaceutical industry [1] and in turn the increasing demand of efficient and simple methodologies for their syntheses. However, in many cases, the described methodologies present drawbacks such as the need for expensive reagents, specific substrates, harsh or sensitive conditions, or long synthetic sequences.[2]

Multicomponent reactions (MCR), as the Ugi reaction, have proven to be useful tools in the synthesis of these heterocycle systems.[3] In this work (Scheme 1), we report a novel methodology for the synthesis of lactams from Ugi/post-condensation sequences using simple, economical and low moisture-sensitive bases, in an air atmosphere and in a robust manner.[4] Selection of the appropriate reagents and bases allows the selective synthesis of different ring-size highly functionalized lactams.




**Scheme 1**. N-Heterocycles synthesized by Ugi/Nucleophilic substitution sequences.

## Acknowledgments

Funding from Consejería de Educación de la Junta de Castilla y León and European Regional Development Fund (ERDF) (project BU075G19 and project BU067P20) and MCIN/AEI/ 10.13039/501100011033 [grant PID2020-117610RB-I00] is gratefully acknowledged. B. G.-S., J. G.-A. and I. C.-B. thank Consejería de Educación de la Junta de Castilla y León, European Social Fund (ESF) and ERDF for their predoctoral (B. G.-S. and J. G.-A.) and postdoctoral (I. C.-B.) contracts.

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# PREPARATION OF MORE LIPOPHILIC ANTIMYCOLATA AGENTS BY MODIFICATION OF KNOWN ANTIBIOTICS THROUGH MULTICOMPONENT REACTIONS

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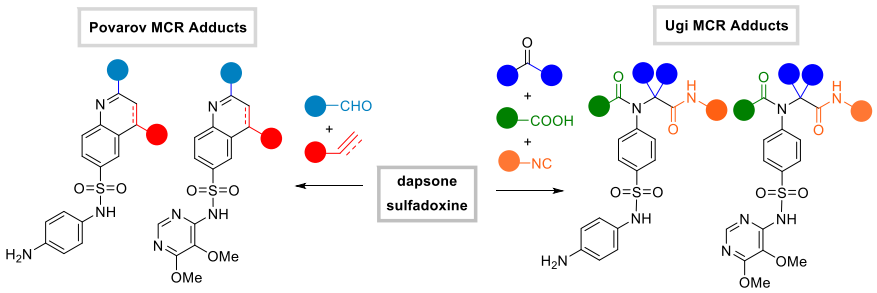
**Keywords:** *multicomponent reactions, drugs, antibiotics, resistant bacteria, mycobacteria*

The modification of existing drugs has become a powerful tool for the development of new pharmacologically active derivatives, being successfully used by the pharmaceutical industry. In this sense, the Late-Stage Functionalization approach allows the introduction or modification of certain connectivities found in drugs.[1] Thus, the use of this methodology may be particularly relevant in the development of new antibiotics.[2]

Some antibiotics display a high potency against their target but their clinical use is diminished due to their poor absorption by the targeted microorganisms. Specifically, the bacteria belonging to *Mycolata* group, which causes severe health problems, for instance tuberculosis, contains an external lipophilic layer that further prevents the penetration of many drugs.[3]

Following with previous works, based on the reactivity of some of the functional groups present in the structure of initial drugs for its transformation through multicomponent reactions,[4] new active derivatives have been designed to obtain compounds with an increase lipophilicity to facilitate crossing the membranes in mycolata. Particularly, we chose a couple of WHO-listed essential medicines, the known antibiotics dapsone and sulfadoxine, which display in their structure an aniline group able to take part in different multicomponent reactions, such as, Povarov and Ugi (Scheme 1).




**Scheme 1.** Multicomponent Ugi and Povarov reactions with dapsone and sulfadoxine to afford active derivatives.

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# PREPARATION OF NOVEL TOPOISOMERASE I INHIBITORS THROUGH MULTICOMPONENT REACTIONS

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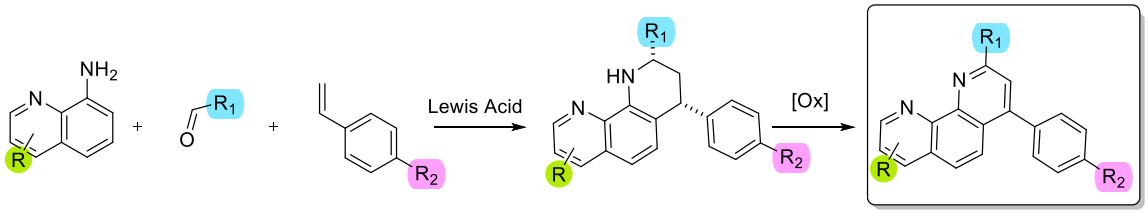
**Keywords:** *multicomponent reactions, 1,10-phenantrolines, TopI inhibitors, antiproliferative effect*

Among the nitrogen-containing heterocycles, the phenanthroline ring has aroused great interest due to its presence in several biologically important products.[1] Particularly, 1,10-phenanthrolines have gained great attention due to their ability to form complexes with metal ions, which makes them especially attractive for the development of new metallodrugs with applicability in different diseases, for instance, cancer.[2] For this reason, the development of new synthetic strategies to access substituted 1,10-phenantrolines would be of great interest in order to provide SAR profiles of these heterocycles.

On the other hand, topoisomerase I inhibitors, such as camptothecin, have several limitations that make it necessary to search for new compounds that act against this target.[3] Based on previous experience in our group, regarding to the synthesis of non-CPT like TopI inhibitors, including quinoline and naphthyridine derivatives,[4,5] we recently decided to explore the applicability of our methodologies on the design and preparation of new heterocyclic compounds containing the 1,10-phenantroline moiety as potential TopI inhibitors.

Herein, we report the synthesis of 2,4-substituted-1,10-phenanthroline derivatives, using the multicomponent Povarov reaction (Scheme 1). Moreover the inhibition against human TopI enzyme of 1,10-phenanthroline derivatives and their cytotoxic effect against several cell lines have been studied.




**Scheme 1.** Synthesis of 2,4-disustituted-1,10-phenanthrolines by multicomponent Povarov reaction.

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# Synthesis and biological evaluation of fused heterocycles derivatives as human topoisomerase I inhibitors

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**Keywords:** *naphthyridines, pyrimidines, Povarov reaction, topoisomerase I, enzyme inhibition, antiproliferative effect*

Povarov reaction[1] can be considered as an example of HDA reactions and represents an excellent method for the preparation of nitrogen-containing heterocyclic compounds,[2] where aldimines derived from aromatic amines and aldehydes react with electron-rich alkenes in the presence of a Lewis acid. Povarov reaction can take place intramolecularly[3] when the imine bears both the diene and the dienophile moieties connected by a chain. As a result, fused polycyclic adducts are obtained.

Thus, this work describes the reaction of aminopyridine derivatives **I** and aromatic aldehyde derivatives **II** in the presence of two different catalysts to perform intramolecular Povarov reaction (Figure 1). On the one hand, using a Lewis acid such as $BF_3{\cdot}Et_2O$ fused chromeno[1,8]naphthyridines **III** were obtained. On the other hand, using a Brønsted acid such as trifluoroacetic acid (TFA), fused chromenopyridopyrimidines **IV** were obtained as the only product.

Finally, and due to their structural analogy with camptothecin (CPT), the biological activity of derivatives **III** and **IV** obtained was studied. In this way, some of the obtained compounds showed inhibition against human topoisomerase I enzyme and cytotoxicity against different cancerous cell lines.

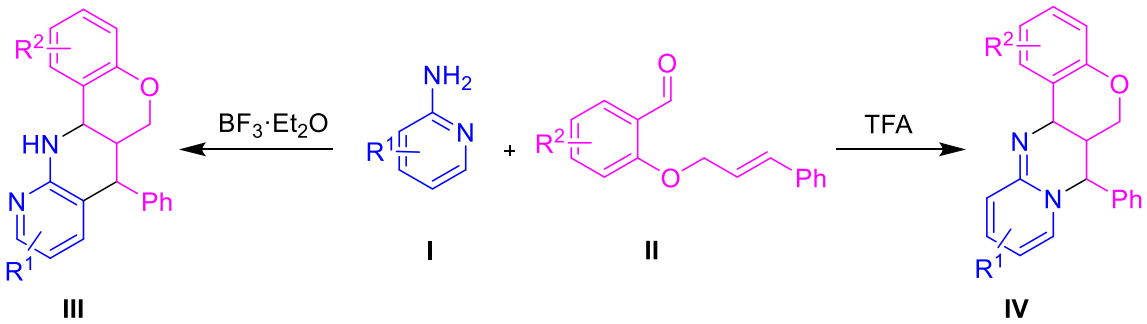


**Figure 1.** Scheme of intramolecular Povarov reaction study with different catalysts.

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# THE JOULLIÉ-UGI THREE-COMPONENT REACTION AS A SYNTHETIC TOOL FOR THE DIASTEROSELECTIVE PREPARATION OF HIGHLY FUNCTIONALIZED *N*-ACYLAZIRIDINE DERIVATIVES

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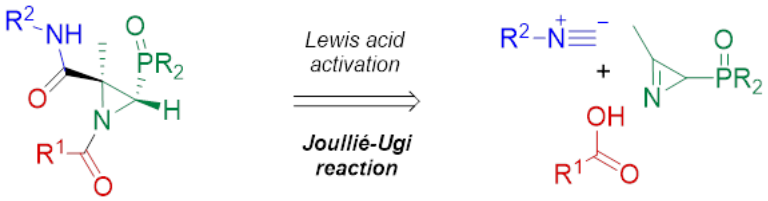
**Keywords:** 2*H-Azirines, phosphorus substituted aziridines, Joullié-Ugi three-component reaction*

Although covalent binding drugs have always been part of the therapeutic battery, in the recent years, new effective therapeutic agents with this binding mechanism have been developed. Understanding of its action mechanism and implementation of new rational design instruments has allowed the inclusion of reactive motifs or electrophilic groups. For that reason, research and discovery of new electrophilic synthons is receiving increasing attention in the field of medicinal chemistry. The aziridine ring strain makes this heterocycle a perfect candidate as electrophilic warhead. Moreover, its presence in natural and therapeutic compounds is related with their antitumor, antibacterial, or antimicrobial activity, as is the case of mitomycin and azinomycin derivatives.[1] Furthermore, our research group has designed phosphorous substituted aziridines [2] that showed cytotoxic effect against human lung adenocarcinoma (A549) and human embryonic kidney (HEK293) cancer cell lines.

In this research work, the Joullié-Ugi three-component reaction has been used as synthetic tool for the preparation of phosphorous substituted *N*-acylaziridines. Phosphorylated 2*H*-azirines (used as preformed cyclic imines), reacted easily with carboxylic acids and isocyanides in THF at room temperature, using catalytic amounts of $ZnCl_2$ as Lewis acid. Through this methodology, the Joullié-Ugi adducts can be obtained in yields up to 85% and very good diastereoselectivity. Moreover, the reaction procedure is equally efficient when different aliphatic or aromatic carboxylic acids or even amino acids are used. Furthermore, the obtained *N*-acylaziridines can be used as synthetic precursors for the preparation 5-membered oxygen- and nitrogen-containing heterocycles.




**Scheme 1**. Joullié–Ugi retrosynthetic pathway.

**Acknowledgments**

Financial support from the *Ministerio de Ciencia, Innovación y Universidades (MCIU)* (PID2021-122558OB-I00, UE), by *Gobierno Vasco, Universidad del País Vasco* (GV, IT1701-22; UPV) and by Fundación Vital (VITAL23/28) is gratefully acknowledged. The authors thank the technical and human support provided by SGIker (UPV/EHU/ERDF, EU).

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# MULTICOMPONENT SYNTHESIS OF THE SARS-COV-2 MAIN PROTEASE INHIBITOR NIRMATRELVIR

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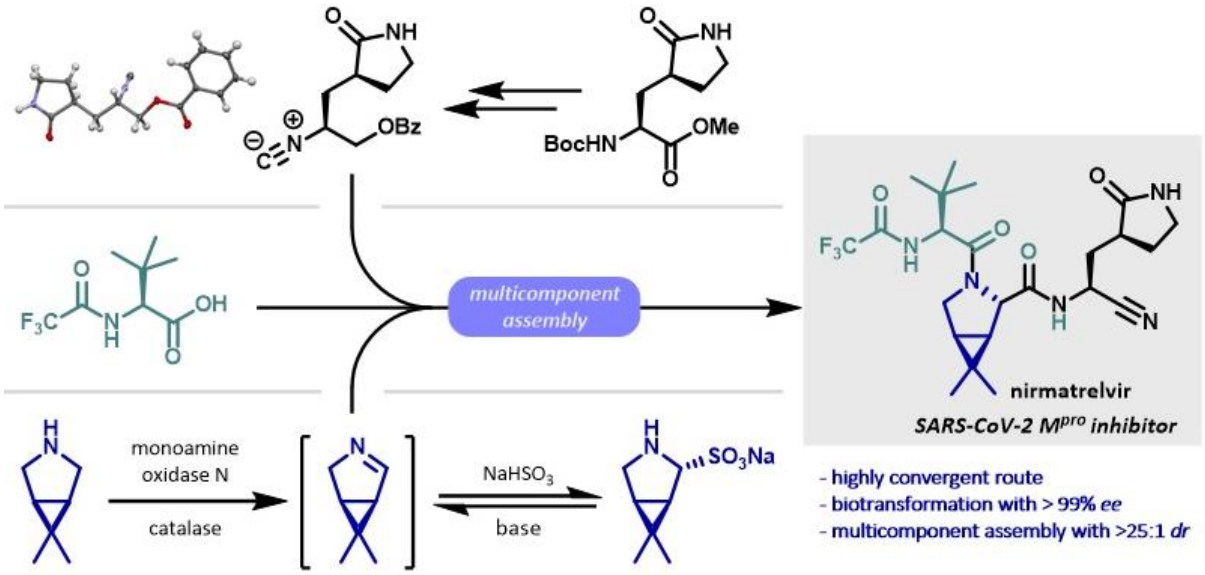
**Keywords:** *SARS-CoV-2, nirmatrelvi, desymmetrization*

In the wake of the Covid-19 pandemic, it has become clear that global access to efficacious antiviral drugs will be critical to combat future outbreaks of SARS-CoV-2 or related viruses. The orally available SARS-CoV-2 main protease inhibitor nirmatrelvir has proven an effective treatment option for Covid-19, especially in compromised patients. We report a new synthesis of nirmatrelvir featuring a highly enantioselective biocatalytic desymmetrization (>99% ee) and a highly diastereoselective multicomponent reaction (>25:1 dr) as the key steps. Our route avoids the use of transition metals and peptide coupling reagents, resulting in an overall highly efficient and atom-economic process.



# TOTAL SYNTHESIS OF COMPLEX INDOLE ALKALOIDS BY A NITROARYL TRANSFER CASCADE REACTION

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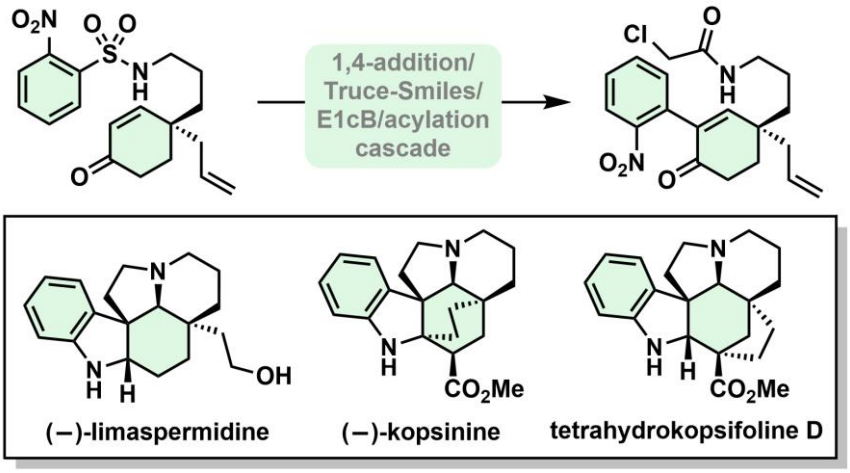
**Keywords:** *Indole alkaloids, cascade reaction*

The medicinally relevant alkaloids of the *Aspidosperma* and *Kopsia* genera of flowering plants show high structural complexity, thus forming a challenging target for synthetic chemists.[1] Most syntheses rely on an indole starting material, necessitating the use of protecting groups. An alternative approach involves a late-stage Fischer indole synthesis, which may, however, result in low yields due to poor regioselectivity. In this work, we present a solution to both problems by making use of cascade chemistry.[2] This allows the combination of multiple elementary reaction steps in a single process, and thus inherently contributes to enhanced synthetic efficiency.




We report an intramolecular conjugate addition/Truce-Smiles/E1cB cascade of 2-nitrobenzenesulfonamide-functionalized cyclohexenones as a new entry to the core scaffold of monoterpene indole alkaloids. The method was applied to the asymmetric total synthesis of (−)-limaspermidine, (−)-kopsinilam, and (−)-kopsinine, as well as the framework of the kopsifoline alkaloids. Furthermore, we show that the cascade tolerates various substituents on the nitroarene, opening the way to other natural products as well as non-natural analogues.

## References

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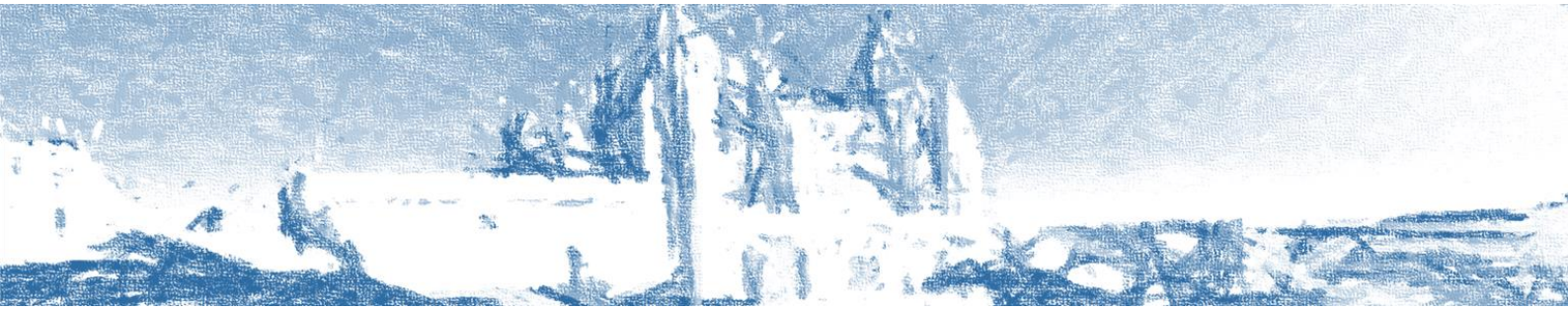

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