BOOK OF ABSTRACTS

30th International Society of Heterocyclic Chemistry Congress

July 19-24, 2026, USP São Carlos, Brazil

WELCOME MESSAGE

30th ISHC Congress (19-24 July 2026, São Carlos, Brazil)

https://ishc-brazil2026.com/

Dear Colleagues,

Join us from July 19–24, 2026, at USP São Carlos, Brazil, for an exciting international meeting that brings together researchers from around the world to explore the latest advances and ideas in heterocyclic chemistry, featuring cutting-edge presentations, networking opportunities, and scientific excellence in a beautiful university setting. For the first time in its history, the traditional congress of the International Society of Heterocyclic Chemistry (ISHC) will be held in Latin America, marking a milestone for the region's growing scientific community. Inaugurated in 1967 in Albuquerque, New Mexico, with the 'First International Congress of Heterocyclic Chemistry,' this series of meetings has since evolved into a premier global forum. Today, the ISHC congresses continue to drive the advancement of the field, consistently drawing hundreds of researchers from around the world.

The event in Brazil will bring together leading scientists in synthetic and medicinal chemistry to present recent and creative advances in molecular design, catalysis, and the synthesis of complex heterocyclic systems and natural products. The program will feature new catalytic and radical-based strategies, as well as sustainable and photochemical methods that expand the chemist's toolkit for efficient molecular and heterocycle construction.

Several talks will highlight the development of stereoselective transformations, novel organocatalytic approaches, and modern redox processes that enable precise control over molecular and heterocyclic architecture. These advances reflect the growing emphasis on efficiency, selectivity, and environmental responsibility in synthetic chemistry.

In addition to methodological innovation, the event will explore the interface between chemistry and biology, showcasing how carefully engineered molecular scaffolds contribute to new discoveries in imaging, photodynamic therapy, and drug development. Collectively, the discussions will emphasize creativity, new methods in synthesis, sustainability, and translational potential as driving forces of contemporary chemical research.

Located in the heart of São Paulo state, São Carlos is a small, yet lively university city recognized for its strong research tradition and welcoming atmosphere. Known as Brazil's "Capital of Technology," it blends innovation with a touch of nature, offering great restaurants, cozy cafés, and nearby areas for eco-tourism and outdoor exploration. With its vibrant academic environment and relaxed charm, São Carlos provides an inspiring backdrop for this landmark international scientific gathering.

As the President of the International Society of Heterocyclic Chemistry (http://www.ishc-web.org/), it is with great pleasure that I welcome you to São Carlos to attend the ISHC congress 2026.

Antonio Burtoloso

University of São Paulo

SUPPORTERS & SPONSORS

ORGANIZING AND SCIENTIFIC COMMITTEE

Prof. Dr. Antonio Carlos Bender Burtoloso – General secretary and President of the International Society of Heterocyclic Chemistry (2025-2026) - http://www.ishc-web.org/

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ISHC BRIEF HISTORY AND PAST PRESIDENTS

The International Society of Heterocyclic Chemistry (ISHC) was established in August, 1968, in Albuquerque, New Mexico, in the USA by Dr. Raymond N. Castle (1916–1999). The function of the society is to promote heterocyclic chemistry, in particular by serving as the primary sponsoring agency for the ISHC Congress, a large biennial meeting attracting hundreds of participants. Further aims of the ISHC are to honor persons who have made outstanding contributions to the field with three distinguished Awards and the appointment of ISHC Fellows. The ISHC is also actively involved in the publication of "Progress in Heterocyclic Chemistry" (PHC) a major reference work on heterocyclic chemistry, and monthly bulletins providing updates on recent publications by ISHC members to the ISHC community.

The current president of the ISHC is **Antonio Burtoloso (2025–2026)**, University of São Paulo and the past presidents are:

1973 - 75 Raymond Castle (founder), Albuquerque, USA

1976 - 77 Edward Elslager, Warner–Lambert Parke–Davis Pharmaceuticals, USA

1978 - 79 Miha Tisler, University of Ljubljana, Slovenia

1980 - 81 Leroy Townsend, University of Michigan, USA

1982 - 83 Wolfgang Pfleiderer, University of Konstanz, Germany

1984 - 85 Stewart Schneller, University of South Florida, USA

1986 - 87 Henk van der Plas, University of Wageningen, Netherlands

1988 - 89 Yoshio Ban, Hokkaido University, Japan

1990 - 91 Victor Snieckus, University of Waterloo, Canada

1992 - 93 Jan Bergman, The Royal Institute of Technology, Sweden

1994 - 95 Albert Padwa, Emory University, USA

1996 - 97 Hal Moore, UC Irvine, USA

1998 - 99 Christopher Moody, University of Exeter, UK

2000 - 01 Yoshi Yamamoto, Tohoku University, Japan

2002 - 03 Steven Weinreb, Penn State, USA

2004 - 05 Marco Ciufolini, University of British Columbia, Canada

2006 - 07 Margaret Brimble, University of Auckland, NZ

2008 - 09 Jeffrey Aube, Kansas University, USA

2010 - 11 Richard Taylor, University of York, UK

2012 - 13 Dawei Ma, Shanghai Institute of Organic Chemistry, China

2014 - 15 Daniel Comins, NCSU, Raleigh NC, USA

2016 - 17 Oliver Reiser, University of Regensburg, Germany

2018 - 19 Masayuki Inoue, The University of Tokyo, Japan

2020 - 22 Christopher D. Vanderwal, of University of California, USA

2023 - 24 Teresa Pinho e Melo e Arthur Silva, Portugal

AWARDS

The International Society of Heterocyclic Chemistry (ISHC) created the ISHC Senior Award for outstanding heterocyclic chemists since 1981. The award started carrying the name E.C. Taylor in 2013 to honour the professor who received it in 1989. One person is chosen for the prize at the ISHC congress held once every two years.

In 1997, ISHC attributed the first A. R. Katritzky Junior Award, which is given to scientists 45 years of age or younger to recognize exceptional heterocyclic chemists. More recently, in 2017, the first ISHC Industrial Award was given, which is meant to distinguish any industrial scientist whose research has significantly impacted heterocyclic chemistry. The 2026 ISHC award winners are:

E. C. Taylor Senior Award – Peter Wipf, University of Pittsburgh

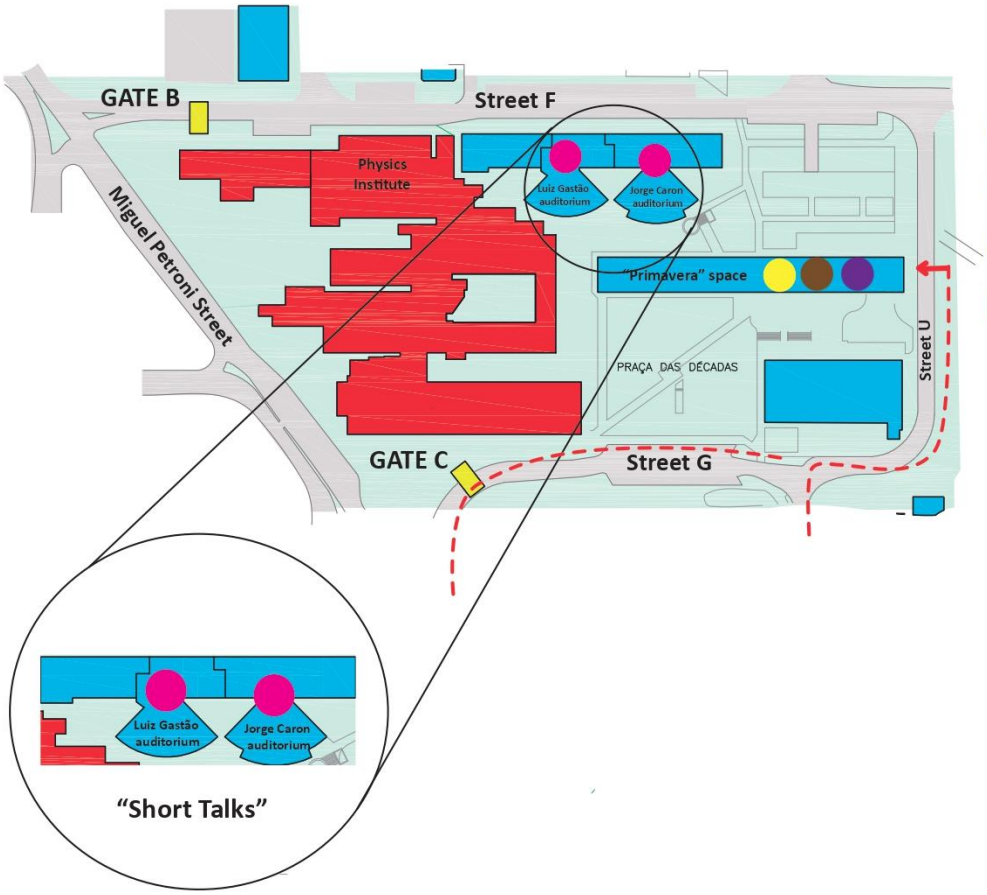
A. R. Katritzky Junior Award – Thomas Maimone, University of California–Berkeley

ISHC Industrial Award – Gregory Hughes – MERCK

Congratulations to the winners!

VENUE INFORMATION

VENUE MAP



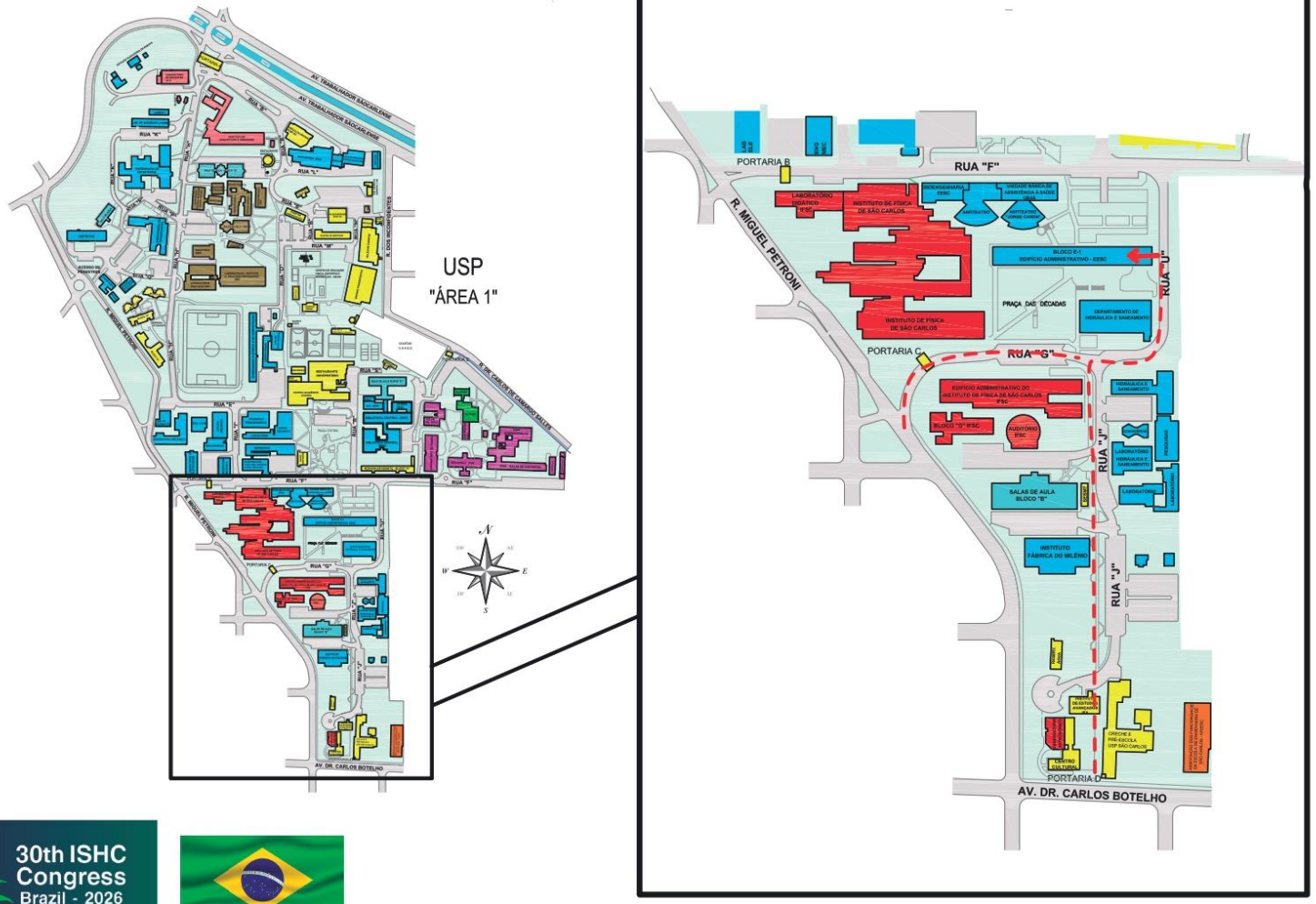
30th ISHC Congress
Brazil - 2026
INTERNATIONAL SOCIETY OF HETEROCYCLIC CHEMISTRY

- **Registration Desk – "Primavera" space**
- **Coffee Breaks – "Primavera" space**
- **Lunch – "Primavera" space**
- **Auditoriums – Seminar/Short talks**

Google Maps:

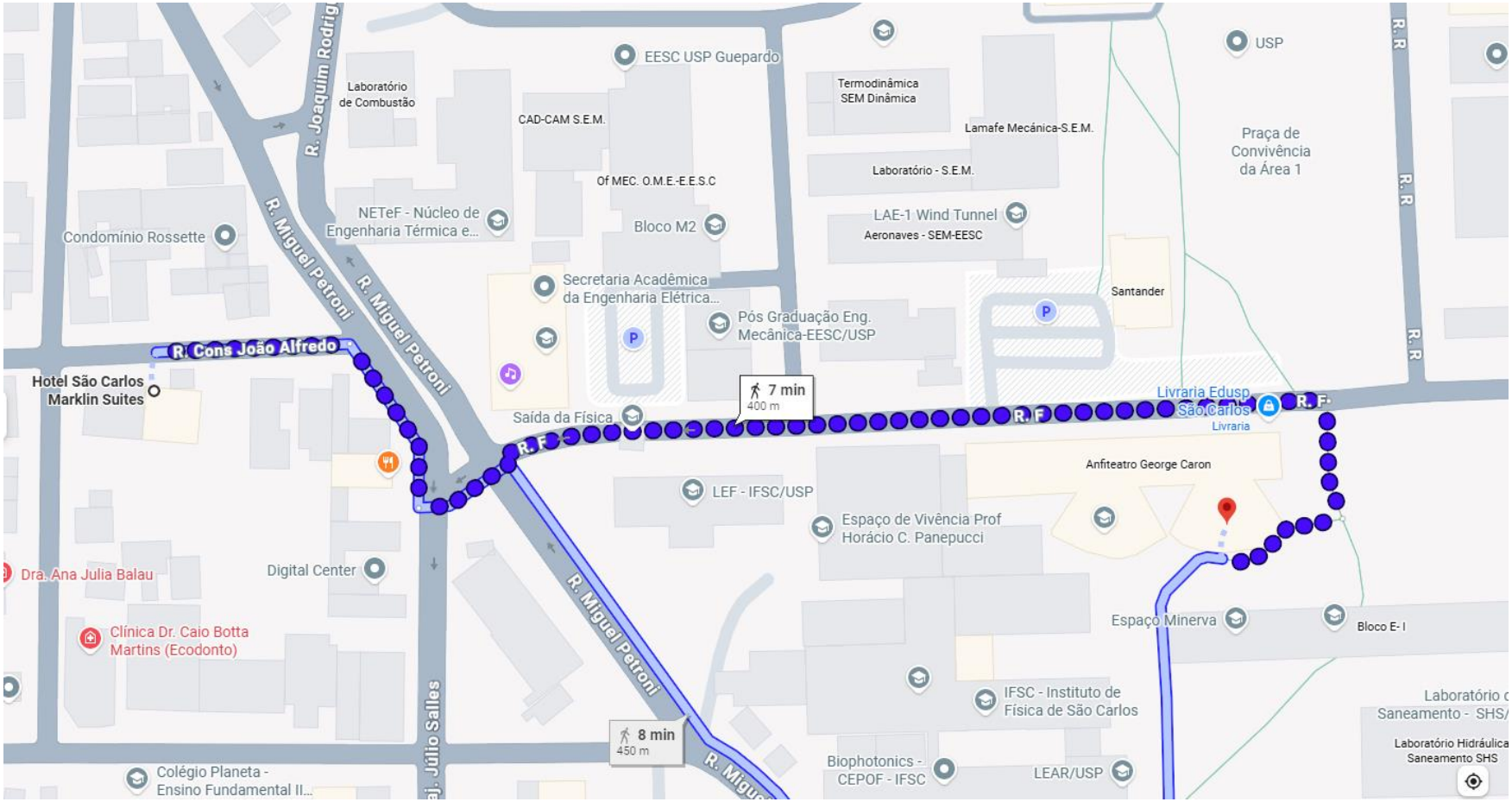
Universidade de São Paulo
Brasil

Venue Map

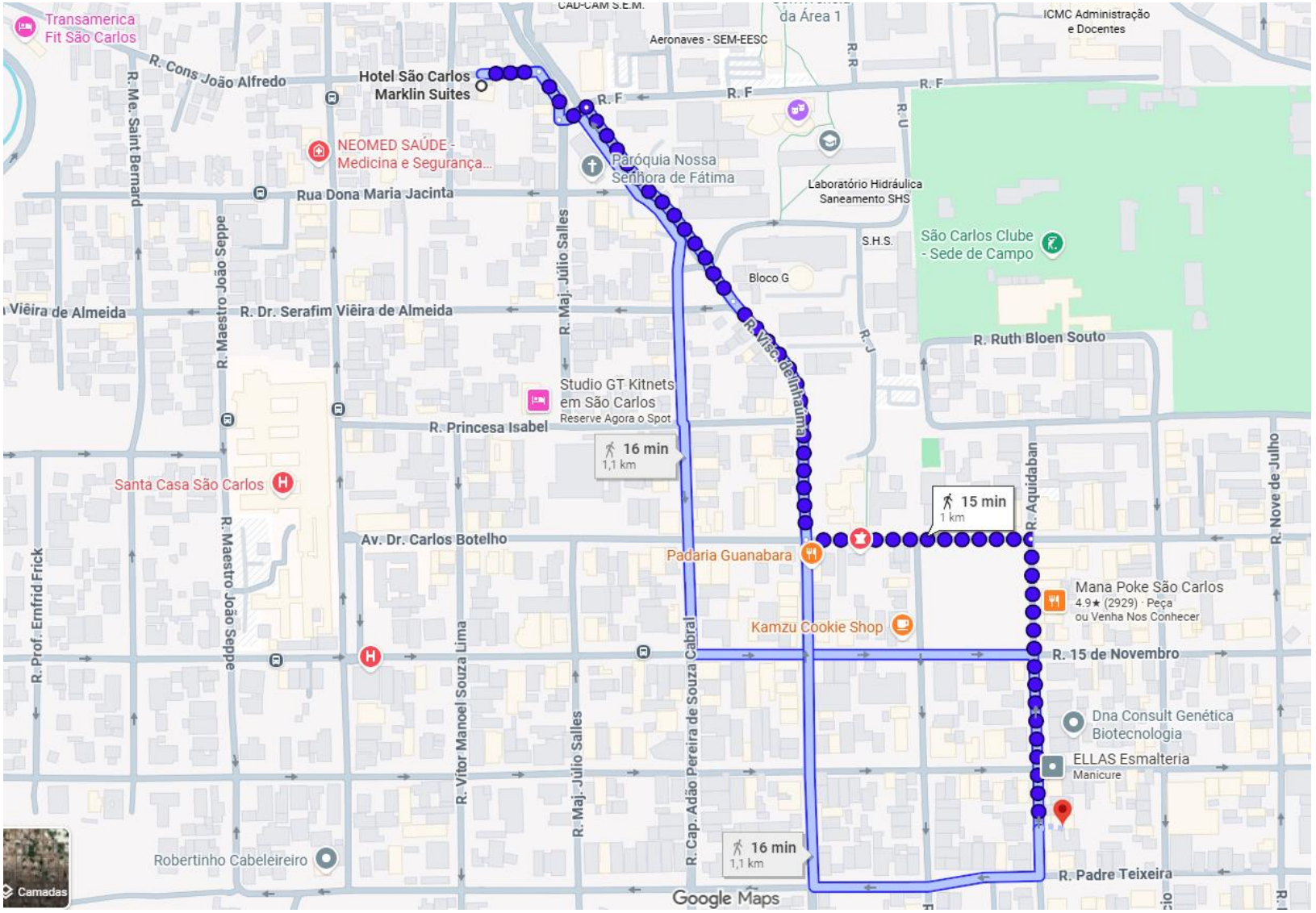


30th ISHC Congress
Brazil - 2026
INTERNATIONAL SOCIETY OF HETEROCYCLIC CHEMISTRY

Jorge Caron Auditorium from Marklin suites:



Casa Poá (registration and welcome reception) from Marklin suites:



CONFERENCE PROGRAM

	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday
	19/07/2026	20/07/2026	21/07/2026	22/07/2026	23/07/2026	24/07/2026
7:45-9:00		registration				
9:00-9:30		opening ceremony	PL4 Matthew Winston	PL7 Shigehiro Yamaguchi	PL8 Corinna S. Schindler	PL10 Magnus Rueping
9:30-10:00		PL1 Mingji Dai				
10:00-10:30			IL4 Eder Lenardão	IL6 Colleen Scott	IL10 Rene Koenigs	IL14 Oleg V. Larionov
10:30-11:00		*coffee break*	*coffee break*	*coffee break*	*coffee break*	*coffee break*
11:00-11:30		PL2 David J. Procter	PL5 Jianwei Sun	IL7 Vinh Nguyen	PL9 Teresa Pinho e Melo	IL15 Mario Waser
11:30-12:00				IL8 Susana Porcel		awards and closing remarks
12:00-12:30		IL1 Jun ZHU	IL5 Camilla Müller	IL9 Carlos Valdéz	IL11 Arlene Corrêa	
12:30-14:00		*lunch*	*lunch*	*lunch*	*lunch*	*departure*
14:00-15:30		Short Talks 1-6	Short Talks 7-12	SOCIAL PROGRAM	Short Talks 13-18	
15:30-16:00		*coffee break*	*coffee break*		*coffee break*	
16:00-17:00		Katritzky Junior Award PL3 Thomas Maimone	E. C. Taylor Senior Award PL6 Peter Wipf		IL12 G. Amarante	
					IL13 V. do Nascimento	
17:00-18:00		IL2 Ignacio Carrera	Poster Presentation		Poster Presentation	
		L3 Georg Manolikakes				
18:00-18:30		cultural presentation				
19:00-22:00	registration and welcome cocktail (casa Poá São Carlos)	PL - plenary lecture; IL - invited lecture			CONFERENCE DINNER (full Buffet + "rodízio" barbecue)	
22:00-23:00						

Presentation Index

Presentations are organized by category and date. The page column indicates the location of each abstract in the Book of Abstracts.

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PL2	11:00 - 12:00	From sulfonium salts to samarium catalysis: New radical chemistry for synthesis	David J Procter	2
PL3	16:00 - 17:00	Adventures in the Synthesis of Heterocyclic Natural Products	Thomas Maimone	3

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PL5	11:00 - 12:00	Development of Privileged Spirocycles for Asymmetric Synthesis	Jianwei Sun	5
PL6	16:00 - 17:00	Use of Enzymes in Pharmaceutical Manufacturing – From transaminases to an Enzymatic cascade For making Islatravir REPLACED	Greg Hughes REPLACED	6

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POSTER SESSION I

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Advancing Total Synthesis via Skeletal Editing

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This talk will focus on our recent efforts in using skeletal-editing retrosynthetic logic in natural product total synthesis (Figure 1).[1] Several examples[2] will be presented to illustrate how skeletal editing can streamline synthetic design and enable efficient access to complex natural product targets.

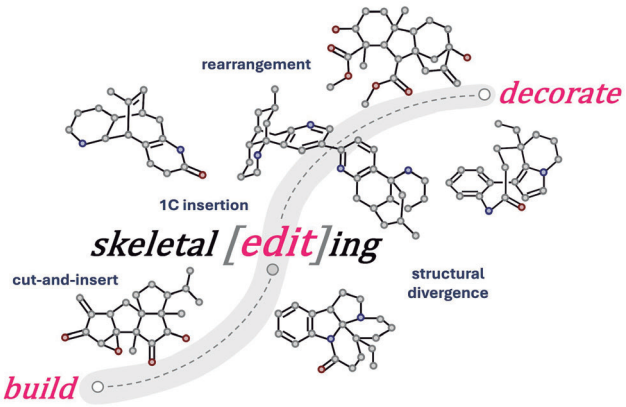

Figure 1: A build-edit-decorate approach for total synthesis.

Acknowledgements: We thank US National Institute of General Medical Sciences for financial support (R35 GM128570).

References:

1. a) Al-Ahmad, R.; Dai, M. *Acc. Chem. Res.* **2025**, *58*, 1392. b) Al-Ahmad, R.; de la Torre Roehl, I. M.; Liu, C.; Sarpong, R.; Dai, M. *J. Am. Chem. Soc.* **2026**, *148*, 21151.
2. a) Ma, D.; Martin, B. S.; Gallagher S. K.; Saito, T.; Dai, M. *J. Am. Chem. Soc.* **2021**, *143*, 16383. b) Li, L.; Liang, W.; Rivera, M. E.; Wang, Y.-C.; Dai, M. *J. Am. Chem. Soc.* **2023**, *145*, 53. c) Xu, B.; Zhang, Z.; Tantillo, D. J.; Dai, M. *J. Am. Chem. Soc.* **2024**, *146*, 21250. d) Cai, X.; Li, L.; Wang, Y.-C.; Zhou, J.; Dai, M. *Org. Lett.* **2023**, *25*, 5258.

From sulfonium salts to samarium catalysis: New radical chemistry for synthesis

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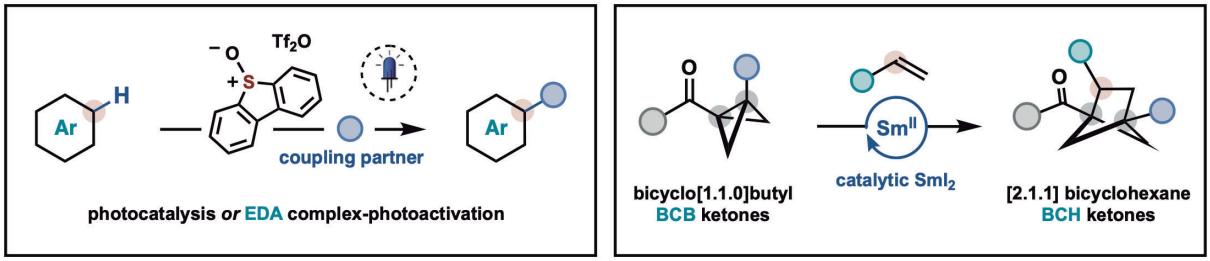
Part I – Our approach to the development of transition metal-free cross-coupling processes is based on using sulfur to replace metals in activating substrates and generating reactive intermediates for exploitation in carbon-carbon and carbon-heteroatom bond-formation. In particular, we use sulfoxides to activate substrates, for example, forming aryl sulfonium salts from arenes[1] and unusal sulfonium salts from alternative feedstocks.[2] These sulfonium salts are versatile partners in photocatalytic and photochemical radical cross-coupling processes.

Part II – Samarium(II) iodide is one of the most widely-used, stoichiometric, single electron transfer reductants in chemistry. We use a radical relay approach to carry out *catalysis* with SmI_2 alone.[3] The application of SmI_2 catalysis provides expedient access to bicyclic systems, including Csp^3-rich bioisosteres and scaffolds for use in medicinal chemistry.[3b,c]



References:

1. (a) Aukland, M. H.; Šiaučiulis, M.; West, A.; Perry, G. J. P.; Procter, D. J. *Nat. Catal.* **2020**, *3*, 163. (b) Dewanji, A.; van Dalsen, L.; Rossi-Ashton, J. A.; Gasson, E.; Crisenza, G. E. M.; Procter, D. J. *Nat. Chem.* **2023**, *15*, 43.
2. Zhao, H.; Filippini, D.; Chen, Y.; Gallego-Gamo, A.; Natrajan, L. S.; Pantaine, L.; Romano, C.; Procter, D. J. *Nat. Chem*, **2026**, *18*, 398.
3. (a) Mansell, J. I.; Yu, S.; Li, M.; Pye, E.; Yin, C.; Beltran, F.; Rossi-Ashton, J. A.; Romano, C.; Kaltsoyannis, N.; Procter, D. J. *J. Am. Chem. Soc.* **2024**, *146*, 12799. (b) Agasti, S.; Beltran, F.; Pye, E.; Kaltsoyannis, N.; Crisenza, G. E. M.; Procter, D. J. *Nat. Chem.* **2023**, *15*, 535. (c) Roy, D.; Mansell, J. I.; Barison, G.; Yu, S.; Katavic, R.; Romano, C.; Kaltsoyannis, N.; Procter, D. J. *Angew. Chem. Int Ed.* **2025**, e202512018.

Adventures in the Synthesis of Heterocyclic Natural Products

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Natural products continue to provide inspiration for improved synthetic design processes and serve as potential leads for drug discovery and chemical biology applications. This talk will highlight the development of efficient synthetic pathways toward biologically active natural products with a focus on the enabling synthetic strategies and tactics employed. In the spirit of the ISHC, nitrogen-containing heterocyclic targets will be the focus of the presentation.

Structurally unprecedented antibacterial alkaloids containing multiple electron-rich pyrrole units have been isolated from *Curvularia sp.* and *Bipolaris maydis* fungi (Figure 1). A synthetic program aimed at developing a family-level solution to curvulamine and related members will be discussed along with insight into the novel heterocyclic chemistry uncovered during this campaign.[1,2]

Next the evolution of a synthetic program aimed at accessing the unusual sulfonamide-containing natural product altemicidin will be discussed (Figure 1).[3] By leveraging a pyridine dearomatization/cycloaddition strategy we developed a concise pathway to the 5,6-fused bicyclic azaindane core, and after significant experimentation, an ultimate synthesis of altemicidin itself. Tactics to productively manipulate the multiple functional groups present on this highly polar scaffold proved challenging but were eventually realized via several carefully orchestrated and chemoselective transformations – Investments which paid dividends in the form of a significantly shorter chemical syntheses. Much to our surprise, the bond-forming logic between our synthetic strategy and a later identified biosynthetic pathway proved eerily similar.[4]

Finally, we will discuss synthetic efforts towards the family of structurally complex diterpene alkaloids, compounds with potent analgesic effects. We will highlight a recent synthesis of aconicarmisulfonine A.[5]

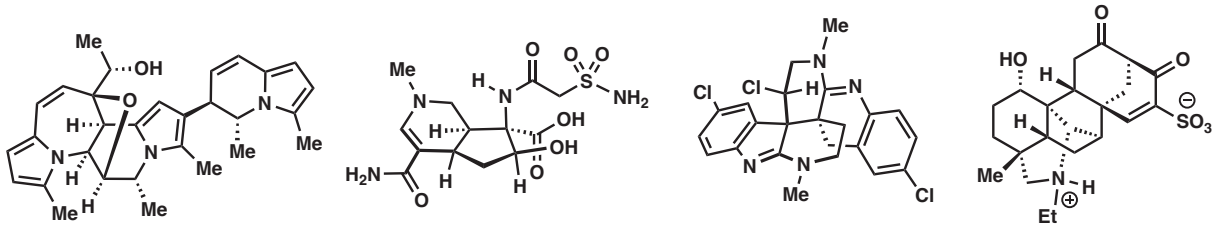

Figure 1: Heterocyclic alkaloids of interest.

References:

1. Haelsig, K. T.; Xuan, J.; Maimone, T. J. Total Synthesis of (–)-Curvulamine, *J. Am. Chem. Soc.* **2020**, *142,* 1206.
2. Xuan, J.; Haelsig, K. T.; Machicao P.A.; Sheremet, M.; Maimone, T. J. Evolution of a Synthetic Strategy for Complex Polypyrrole Alkaloids: Total Syntheses of Curvulamine and Curindolizine, *J. Am. Chem. Soc.* **2021**, *143*, 2970.
3. Harmange Magnani, C. S.; Maimone, T. J. Dearomative Synthetic Entry into the Altemicidin Alkaloids, *J. Am. Chem. Soc.* **2021**, *143,* 7935.
4. Harmange, C. S.; Hernandez-Melendez, J.; Tantillo, D. J.; Maimone, T. J. Total Synthesis of Altemicidin: A Surprise Ending for a Monoterpene Alkaloid, *JACS Au*, **2023**, *3,* 2883.
5. Ning, S., Maimone, T. J. Total Synthesis of Aconicarmisulfonine A, a Sulfonated Diterpene Alkaloid, *J. Am. Chem. Soc.* **2025**, *147,* 46800.

Leveraging Biocatalytic Selectivity for Heterocycle Synthesis in the Commercial Manufacturing of Pharmaceuticals

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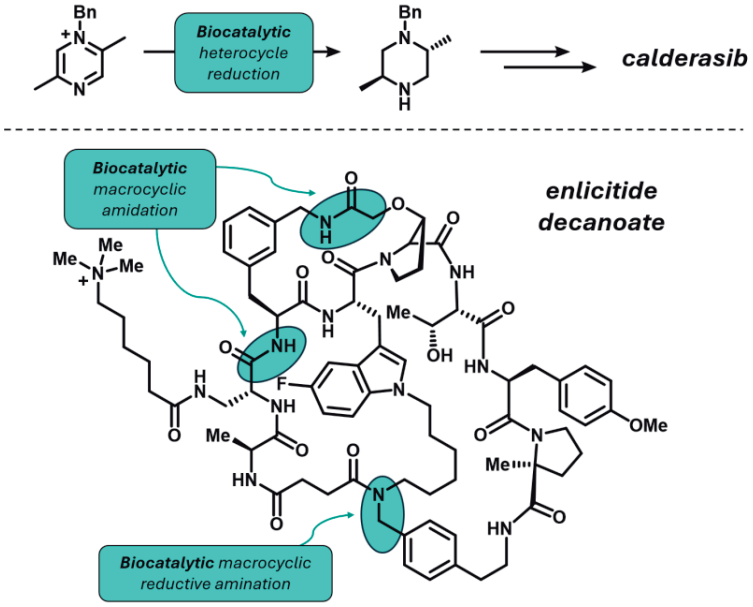
Enzymes catalyze biological reactions with exquisite selectivity and specificity in high activity through curated active site control. Wild-type enzymes can be engineered for alterations from their natural behavior, allowing specificity for synthetic, non-natural substrates often under decidedly non-natural reaction conditions. This is particularly powerful in the commercial manufacturing of pharmaceuticals, as the greenness and efficiency of biocatalysis is compounded at large reaction scales. Here we discuss applications of biocatalysis for the commercial synthesis of heterocycles in two drug substances: 1) an imine reductase engineered to catalyze a "new-to-nature" sequence of stereoselective reductions of a pyrazinium substrate to a fully saturated piperazine, and 2) a series of engineered oxidoreductases and ligases to selectively access macrocyclic peptides.



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References:
1. Klapars, A.; Fryszkowska, A.; Galanie, S. *et al. Science* **2026**, *392*, 643.

Development of Privileged Spirocycles for Asymmetric Synthesis

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The development of effective chiral catalysts continues to play an important role in modern asymmetric synthesis. While nature has provided a range of useful chiral catalysts (e.g., enzymes) for biosynthesis, rationally designed manmade chiral catalysts have often shown superb and complementary performance in a broad spectrum of asymmetric reactions. Specifically, chiral spirocyclic molecules have emerged as powerful privileged backbones for chiral catalysts. In particular, 1,1'-spirobiindane-7,7'-diol (SPINOL) has gained tremendous success in this regard owing to its rigid C_2-symmetric skeleton.

In this context, our laboratory has developed a new structure SPHENOL (2,2′,3,3′-tetrahydro-1,1′-spirobi[phenalene]-9,9′-diol) featuring two naphthol rings in a spirocyclic framework. It not only exhibits good performance as a chiral catalyst backbone, but more importantly, features convenient synthesis owing to the high nucleophilicity of the naphthol ring as well as the established enantiocontrol over the key *ortho*-quinone methide intermediate. More recently, we have further incorporated indole rings into spirocyclic frameworks, which have been demonstrated as another family of chiral catalyst backbone. The application of these related structures in asymmetric catalysis will be discussed in detail.

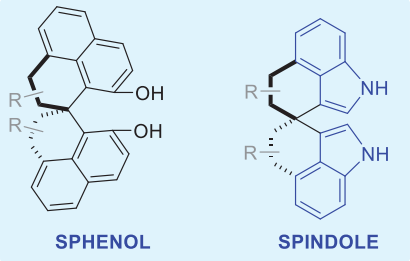

Figure 1: Representative Spirocycles.

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References:

1. R. Zhang, S. Ge, J. Sun, *J. Am. Chem. Soc.* **2021**, *143*, 12445.
2. H.-L. Xu, M. Zhu, H. H. Y. Sung, I. D. Williams, Z. Lin, C. Zhang, J. Sun, *J. Am. Chem. Soc.* **2025**, *147*, 3692.
3. L. Yang, K. L. Chan, K. K. Cheung, P. Chiu, Z. Lin, J. Sun, *Nat. Synth.* **2025**, 10.1038/s44160-025-00803-w.
4. X.-K. Qi, Q. Dai, Y. Gu, K. S. Lau, H. H. Y. Sung, I. D. Williams, Z. Lin, C. Zhang, J. Sun, *J. Am. Chem. Soc.* **2025**, *147*, 20225.
5. J.-Y. Wang, J. Lin, C. Zhang, J. Sun, *Angew. Chem. Int. Ed.* **2025**, *64*, e202507798.
6. C. Qian, Y. Chen, B. Wang, T. Wang, C. Zhang, Z. Lin, J. Sun, *Nat. Chem.* **2026**, 10.1038/s41557-026-02095-9.

Use of Enzymes in Pharmaceutical Manufacturing – From transaminases to an Enzymatic cascade For making Islatravir

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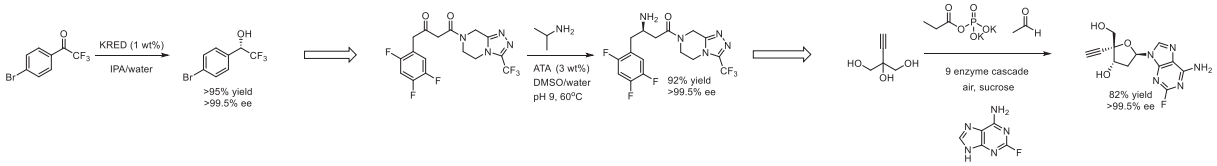
As protein engineering has become more widely used, our ability to leverage Nature's tools for the selective synthesis of compounds of industrial relevance has expanded rapidly. This presentation will provide an overview of our journey at Merck from simple early application of biocatalysis, through landmark commercial applications such as the use of a transaminase to prepare sitagliptin[1] and the development of a multi step enzymatic cascade for the production of islatravir[2].



Scheme 1: Applications of biocatalysis in the pharmaceutical industry.

Acknowledgements: We thank literally hundreds (thousands?) of scientists at Merck and our external partners who have enabled these developments.

References:

1. Biocatalytic Asymmetric Synthesis of Chiral Amines from Ketones Applied to Sitagliptin Manufacture. Savile, C.K.; Janey, J.M.; Mundorff, E.C.; Moore, J.C.; Tam, S.; Jarvis, W.R.; Colbeck, J.C.; Krebber, A.; Fleitz, F.; Brands, J.; Devine, P.N.; Huisman, G.; Hughes, G.J. *Science*, **2010**, *329*, 5989.
2. Design of an in vitro biocatalytic cascade for the manufacture of islatravir. Huffman, M. A.; Fryszkoswka, A.; Alvizo, O.; Borra-Garske, M.; Campos, K. R.; Canada, K. A.; Devine, P. N.; Duan, D.; Forstater, J. H.; Grosser, S. T.; Halsey, H. M.; Hughes, G. J.; Jo, J.; Joyce, L. A.; Kolev, J. N.; Liang, J.; Maloney, K. M.; Mann, B. F.; Marshall, N. M.; McLaughlin, M.; Moore, J. C.; Murphy, G. S.; Robaire, S. A.; Sherer, E. C.; Truppo, M. D.; Whittaker, A. M.; Verma, D.; Xiao, L. Xu, Y.; Yang, H. *Science* **2019**, *366*, 1255.

Main-Group Fluorophores with Environmental Responsiveness

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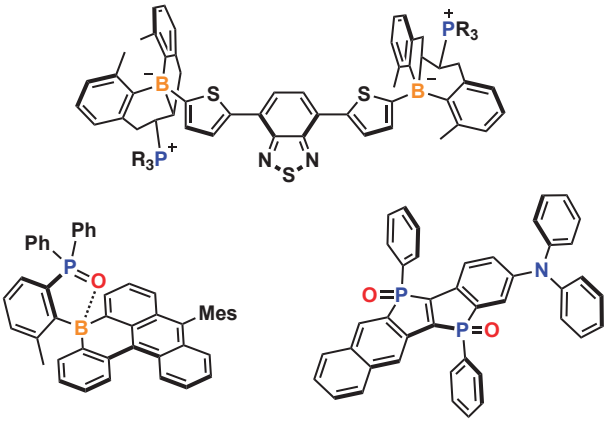
Incorporation of main-group elements into π-conjugated skeletons is a powerful strategy for creating new optoelectronic organic materials with unusual properties. A representative design principle is to exploit orbital interactions between a π-framework and a main-group moiety.[1] In particular, the introduction of electron-accepting or -withdrawing main-group moieties enables red-shifted emission without the need to expand the π-framework. A key challenge in this chemistry is to endow these fluorescent skeletons with responsiveness to environmental changes and external stimuli such as temperature and light. Overcoming this challenge would open new avenues for valuable molecular tools in various applications. In this presentation, we will highlight how the Lewis acidity of the boron atom can be harnessed to induce environment-responsive fluorescence changes,[2-4] and further discuss the potential of several main-group-based fluorophores for advanced fluorescent bioimaging.[5,6]



References:
1. K. Andoh, M. Murai, P.-A. Bouit, M. Hissler, S. Yamaguchi, *Angew. Chem. Int. Ed.*, **2024**, *63*, e202410204.
2. M. Kawashiro, T. Mori, M. Ito, N. Ando, S. Yamaguchi, *Angew. Chem. Int. Ed.*, **2023**, *62*, e202303725.
3. T. Mori, Y. Sano, T. Ikai, Y. Kawasaki, K. Tomooka, T. Sasamori, S. Yamaguchi, *Angew. Chem. Int. Ed.*, **2026**, *65*, e22746.
4. S. Kitamura, M. Sakai, S. Yamaguchi, *Angew. Chem. Int. Ed.,* **2026**, *65*, e23338.
5. J. Wang, M. Taki, Y. Ohba, M. Arita, S. Yamaguchi, *Angew. Chem. Int. Ed.*, **2024**, *63*, e202404328.
6. J. Wang, K. Kajiwara, M. Kesherwani, F. Tama, Y. Ohsaki, S. Yamaguchi, M. Taki, *J. Am. Chem. Soc.*, **2025**, *147*, 41514–41523.

From [2+2]-Cycloadditions to In Situ Analytical Data-Driven Electrochemical Optimization

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Data-driven reaction optimization is limited by the scarcity of descriptors that are simultaneously information-rich and experimentally scalable. Electrochemical measurements offer a direct, physically grounded probe of reaction environments, but their integration into machine-learning workflows has been hindered by the lack of high-throughput hardware and automated analysis pipelines. Here, we introduce an in situ electrochemical optimization framework that combines custom parallelized hardware, automated data processing, and machine learning to enable high-throughput acquisition and encoding of electrochemical descriptors for reaction modeling. The platform centers on a miniaturized, parallel three-electrode array that performs non-destructive electroanalytical measurements prior to electrolysis within the same experimental configuration, ensuring that each reaction is represented by descriptors intrinsically tied to its operative electrochemical environment. When coupled with computer-vision–based feature extraction and Bayesian optimization, the framework enables efficient, data-efficient exploration of large reaction design spaces under tightly controlled conditions. Together, these elements establish a generalizable electrochemical machine-learning platform for scalable reaction optimization and predictive modeling.

New Synthetic Strategies for Tetrapyrrolic Macrocycles: Toward Improved Cancer Photodynamic Therapy and Imaging

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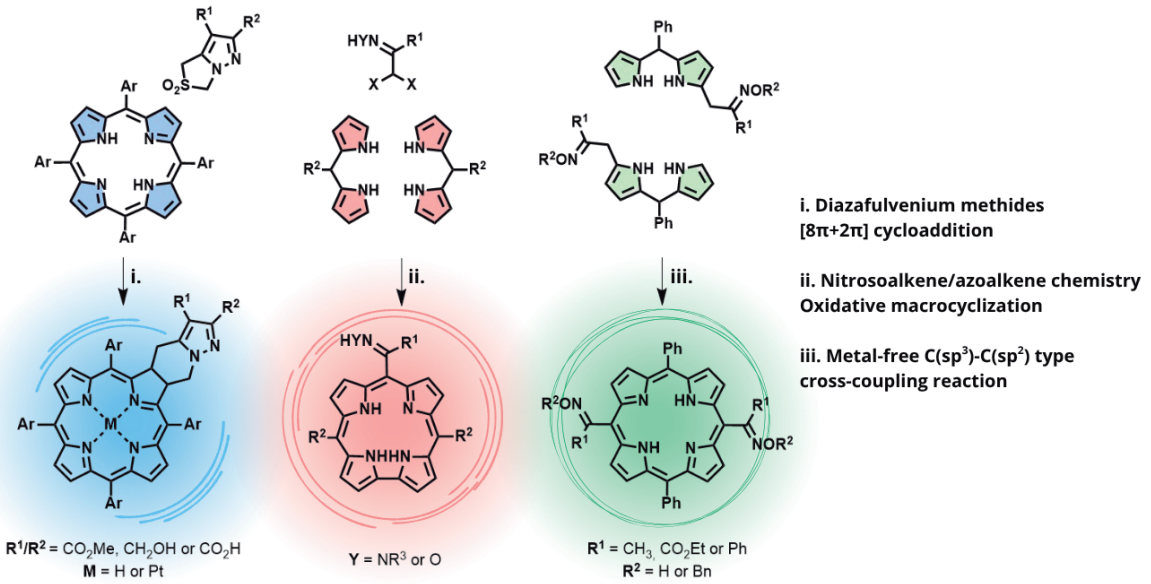
Photodynamic therapy (PDT) relies on the combined action of oxygen, light and a suitable photosensitizing molecule to destroy abnormal cancer cells selectively. The development of more efficient photosensitizers and diagnostic tools are crucial to improve the therapeutic outcome. Therefore, the focus of our research has been on the development of novel synthetic strategies for tetrapyrrolic macrocycles (ring-fused chlorins, corroles and porphyrins) for PDT and theranostics of cancer. New stable 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-fused chlorins, obtained via an unprecedented [8π+2π] cycloaddition of porphyrins with diazafulvenium methides, proved to be very active photodynamic agents against several types of cancer.[1] Moreover, *in vitro* and *in vivo* studies have demonstrated that the incorporation of platinum (II) into the structure of these macrocycles leads to molecules with theranostics features, acting as near-infrared luminescence probes as well as PDT photosensitizers.[2] A novel synthetic approach to *trans*-A_2B corroles, *meso*-substituted with either an oxime or a hydrazone group, was developed by exploring the reactivity of dipyrromethanes towards nitrosoalkenes or azoalkenes, respectively.[3] These contracted porphyrins have been shown to be very efficient photosensitizers for PDT of lung cancer. An unprecedented approach to *trans*-A_2B_2-porphyrins via DDQ-mediated metal-free C–C cross-coupling reactions of dipyrromethanes *alfa*-substituted with an oxime moiety has also been developed. Further details of this study will be disclosed, including the photophysical and photodynamic properties and the theranostic features of the studied tetrapyrrolic macrocycles.



Scheme: Synthetic Pathways to Tetrapyrrolic Macrocycles

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References:

1. Pinho e Melo et al. *Eur. J. Med. Chem.* **2015**, *103*, 374; *Eur. J. Med. Chem.* **2018**, *146*, 395; *ACS Omega* **2019**, *4*, 17244; *RSC Med. Chem.* **2021**, *12*, 615; *Front. Chem.* **2022**, *10*:873245; *Bioorg. Med. Chem.* **2023**, 93, 117443, 2. Pinho e Melo *et al. ACS Med. Chem. Lett.* **2017**, *8*, 310−315; *Eur. J. Med. Chem.* **2020**, *200*, 112468; 3. Pinho e Melo et al. *Chem. Rev.* **2018**, *118*, 11324; *J. Org. Chem.* **2020**, *85*, 3328; *J. Med. Chem.* **2024**, 67, 21934-21951; *Eur. J. Med. Chem.* **2025**, *298*, 117946.

The Dance of Rings: Orchestrating Molecular Complexity

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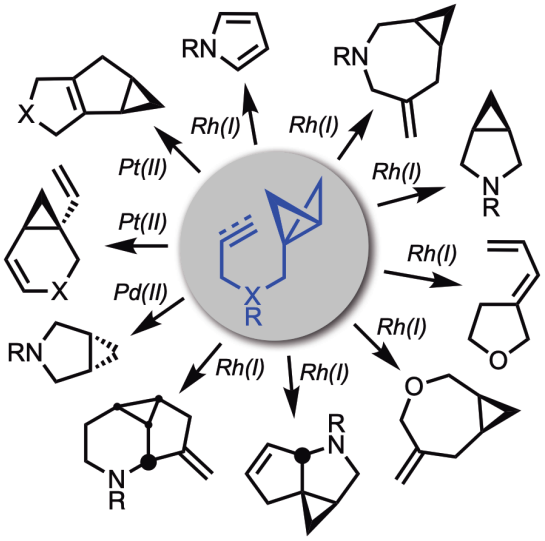
Strained carbo- and heterocyclic cyclic frameworks provide powerful opportunities to transform stored strain energy into molecular complexity through orchestrated bond reorganization. Central to our work are bicyclo[1.1.0]butanes and related compact ring systems, whose unusual bonding enables a distinctive choreography of bond cleavage and formation. Selective activation of the central bridgehead bond initiates strain-release cascades that convert these compact precursors into densely functionalized ring systems with high stereocontrol. These processes often resemble formal pericyclic rearrangements or cycloisomerizations, allowing rapid emergence of complex ring systems from deceptively simple starting materials. Systematic variation of substituents around the strained core reveals strong electronic and conformational effects that guide both reactivity and selectivity. Together, these studies illustrate how the deliberate choreography of ring breaking and ring forming can convert small, highly strained frameworks into versatile platforms for complexity generation in synthesis and discovery chemistry.



Scheme 1: Representative transition metal-catalyzed transformations of bicyclo[1.1.0]butanes.

References:

1. Borgini, M.; Huang, Q.-N.; Chen, P.-P.; Geib, S. J.; Houk, K. N.; Wipf, P. *J. Am. Chem. Soc.* **2024**, *146*(22), 14927–14934.
2. Milligan, J. A.; Wipf, P. *Nat. Chem.* **2016**, *8*(4), 296–297.
2. Walczak, M. A. A.; Krainz, T.; Wipf, P. *Acc. Chem. Res.* **2015**, *48*(4), 1149–1158.

Visible-Light Catalysis for the Synthesis and Functionalization of Heterocycles

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Visible-light catalysis has emerged as a powerful platform for enabling highly selective bond-forming reactions under mild and sustainable conditions. By harnessing the unique reactivity of photoexcited catalysts, previously inaccessible transformations can be achieved, providing efficient access to structurally complex heterocycles and other biologically relevant molecules.

This presentation will highlight our recent advances in visible-light-driven C–C and C–heteroatom bond formation. Particular emphasis will be placed on synergistic approaches that merge photoredox and transition-metal catalysis to access complementary reactivity. Representative examples include photocatalytic C–H functionalization and selective functional group interconversions, illustrating the versatility of these methods in heterocycle synthesis.

Mechanistic investigations have provided valuable insight into photoinduced electron-transfer processes, radical intermediates, and catalyst cooperation, guiding the rational development of highly selective transformations. These studies have enabled practical and broadly applicable methods for the efficient construction and late-stage diversification of heterocyclic frameworks.

The scope of these visible-light-driven transformations will be demonstrated through the synthesis of medicinally relevant heterocycles and natural product cores, illustrating how combining photochemistry with transition-metal catalysis provides new opportunities for the efficient synthesis of structurally complex molecules.

Adaptive Aromaticity in Heterocyclic Chemistry and Its Application to Singlet Fission

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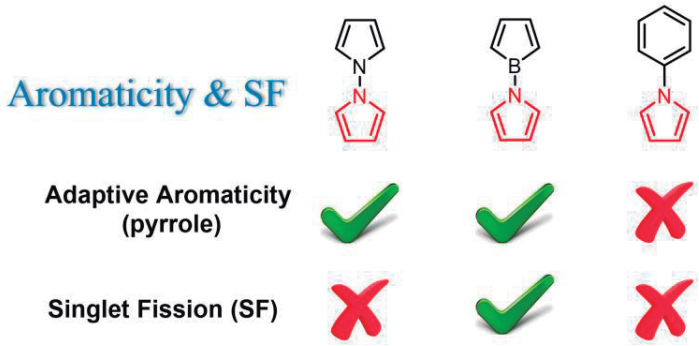
Adaptive aromaticity has attracted substantial attention due to its unconventional two-state aromaticity in both the lowest singlet state (S_0) and the lowest triplet state (T_1) and its application to singlet fission.[1] This concept denotes two-state aromaticity and thus stands in marked contrast to the traditional one-state aromaticity governed by the Hückel and Baird rules. Here, we carry out a comprehensive investigation on a series of pyrrole derivatives by density functional theory (DFT) calculations and machine learning (**Scheme 1**).[2] Various aromaticity indices including HOMA, NICS, EDDB, and MCI suggest that the pyrrole rings in these derivatives show adaptive aromaticity when the other ring of bicyclic systems has weaker (or comparable) aromaticity than the pyrrole ring among these pyrrole derivatives, which could be considered as a sacrificial reagent strategy to achieve adaptive aromaticity of these pyrrole rings. In contrast, when the other ring such as the phenyl ring has stronger aromaticity than the pyrrole ring, it cannot be sacrificed to achieve adaptive aromaticity of the pyrrole rings. More interestingly, a singlet fission chromophore is predicted when the other ring is an antiaromatic borole among these pyrrole derivatives. Additionally, principal component analysis (PCA, one of the most commonly used unsupervised machine learning algorithms) suggests that $\Delta NICS(1)_{zz}$ ($NICS(1)_{zz}(S_0) - NICS(1)_{zz}(T_1)$) of the other ring in these pyrrole derivatives can be an important factor in predicting $E(T_1)$ values, which is also supported by a strong correlation ($R^2 = 0.98$) between $\Delta NICS(1)_{zz}$ and $E(T_1)$. All these findings provide an alternative idea for the design of singlet fission chromophores.



Scheme 1: The proposed sacrificial reagent strategy to achieve adaptive aromaticity in the pyrrole rings.

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References:

1. a) Shen, T.; Chen, D.; Lin, L.; Zhu, J. *J. Am. Chem. Soc.* **2019**, *141*, 5720. b) Wang, L.; Lin, L.; Yang, J.; Wu, Y.; Wang, H.; Zhu, J.; Yao, J.; Fu, H. *J. Am. Chem. Soc.* **2020**, *142*, 10235. c) Lu, L.; Zhu, J. *Inorg. Chem. Front.* **2022**, *9*, 914.
2. Deng, Q.; Imran, S.; Qiu, Z.; Miyajima, D.; Zhu, J. *Org. Chem. Front.* **2026**, *13*, 484.

Iboga Alkaloids and Inspired Isoquinuclidines: Semi-synthetic Approaches, Reactivity, and Biocatalytic Strategies

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Iboga alkaloids are monoterpenoid indole alkaloids with remarkable pharmacological potential, most notably ibogaine, an atypical psychedelic currently being investigated for the treatment of substance use disorders and, more recently, traumatic brain injury-related neuropsychiatric symptoms.[1] Despite significant advances in total synthesis, semi-synthetic approaches remain the most practical route to access these complex natural products and their analogues. In this work, we described an optimized protocol to obtain voacangine and voacristine from *Voacanga africana* root bark, combining direct extraction with the efficient cleavage of iboga–vobasinyl dimers to nearly double the overall yield of voacangine (Figure 1A).[2] Furthermore, we investigated the oxidative reactivity of ibogaine and voacangine with different oxidants, uncovering regio- and stereoselective transformations that enabled late-stage functionalization strategies toward several analogues (Figure 1B).[3] In adittion, we developed a stereocontrolled C19 functionalization strategy starting from voacristine involving mesylation, intramolecular formation of a strained azetidinium intermediate, and nucleophilic ring opening to install diverse substituents through consecutive SN_2-type transformations (Figure 1C). Finally, inspired by the iboga scaffold, we also developed chemoenzymatic strategies to access novel isoquinuclidine-based heterocycles (Figure 1D).[3] Together, these studies provide practical access to structurally complex nitrogen heterocycles and establish new platforms for analogues generation, enabling biological evaluation as inhibitors of NMDA receptor function and the serotonin transporter (SERT), as well as inducers of glial cell line-derived neurotrophic factor (GDNF) release.[4,5]

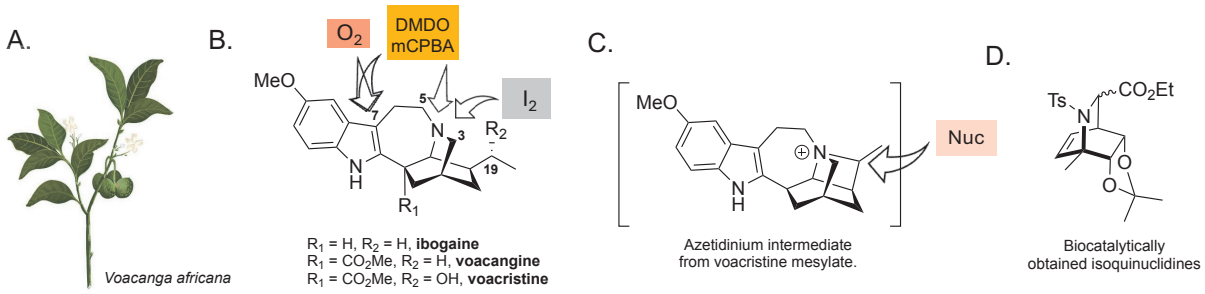

Figure 1: Late-stage functionalization and biocatalytic strategies for the preparation of iboga alkaloids analogues.

References:

1. a) Iyer, R. N.; Favela, D.; Zhang, G.; Olson, D. *Nat. Prod. Rep.* **2021**,38, 307-329 b) Cherian, K.N., Keynan, J.N., Anker, L. *et al. Nat. Med.* **2024**, 30, 373–381.
2. González,B.; Fagúndez, C.; Peixoto de Abreu Lima, A. *et al*. *ACS Omega* **2021**, 6, 16755–16762.
3. González, B.; Veiga, N.; Hernández, G. *et al. J. Nat. Prod.* **2023**, 86,1500–1511.
4. Pazos, M.; Dibello, E.; Mesa, J.M.; *et al. Molecules* **2022**, 27, 829.
5. Hwu, C.; Havel, V.; Westergaad, X.; *J. Am. Chem. Soc.* **2026**, 148, 1, 175–193

From Simple Enamide Building Blocks to Complex Heterocyclic Scaffolds and Beyond

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The stereoselective construction of three-dimensional heterocycles containing multiple stereogenic centers represents a key challenge in modern medicinal chemistry. Aliphatic heterocycles with a defined three-dimensional structure offer intriguing opportunities to improve the pharmacokinetic profile of potential drug candidates.[1] Hence, there is a sustained interest in the development of novel approaches for an efficient synthesis of 3D heterocyclic scaffolds.

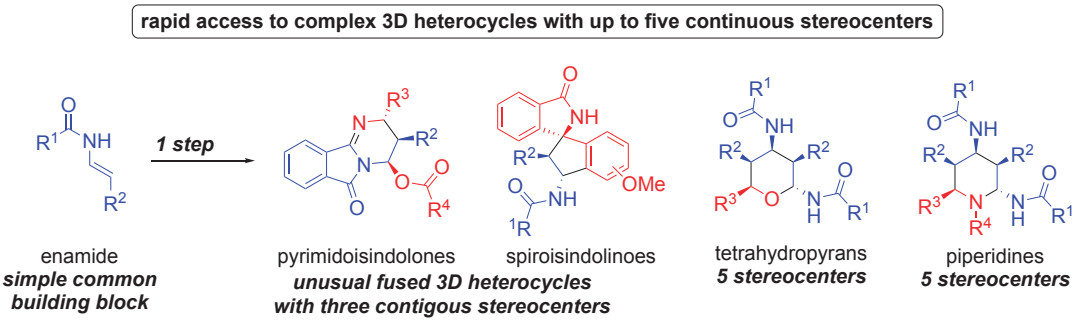
In the last years, enamides have emerged a versatile tools for the stereoselective synthesis of complex molecules containing multiple stereocenters.[2] Herein, novel methods for a rapid and highly modular synthesis of structurally divers 3D heterocyclic scaffolds from enamides as simple common building blocks will be presented:

i) the diastereoselective construction of pyrimido[2,1-a]isoindoles bearing three contiguous stereocenters, a so far difficult to access, heterocyclic scaffold, with three contiguous stereocenters.[3]

ii) approaches for the diastereo- and enantioselective synthesis of densely susbstituted spiroisoindolinones.[4]

iii) domino reaction for the synthesis of tetrahydropyrans and piperidines containing five contiguous stereogenic centers with an exceptionally high degree of diastereoselectivity.[5,6]

iv) one-pot ring-forming/ring opening of terathydropayrans to access acycli molecuels with five contiguous sterogenic centres.[7]



Graphical Abtract

References:

1. a) Lovering F.; Bikker J., Humblet C. *J. Med. Chem.* **2009**, *52*, 6752. b) Lovering F. *Med. Chem. Commun.* **2013**, *4*, 515.
2. a) Kramer, P; Manolikakes, G *Synlett* **2020**, 1027. b) Bouchet D.; Varlet T., Masson G. *Acc. Chem. Res.* **2022**, *55*, 3265.
3. Kramer, P.; Schönfeld, J.; Bolte, M.; Manolikakes, G. *Org. Lett.* **2018**, *20*, 178.
4. a) Halaczkiewicz, M.; Arianit, M.; Kelm, H.; Manolikakes, G. *Org. Lett.* **2024**, *26*, 2321-2325. b) M. Halaczkiewicz, A. Maraj, M. Riedel, L. Donner, H. Kelm, G. Manolikakes, *Chem. Eur. J.* **2025**, *31*, e202404223
5. Kramer, P.; Grimmer, J.; Bolte, M.; Manolikakes, G. *Angew. Chem. Int. Ed.* **2019**, *58*, 13056.
6. *manuscript in preparation*
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Synthesis of Chalcogen-Functionalized Heterocycles

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The combination of the heterocyclic unit with organochalcogen groups has been a promising strategy to prospect new bioactive compounds with a diversity of boosted activities.[1] Regarding organoselenium compounds, their role in organic synthesis has gradually migrated from their application in stoichiometric reactions, for example in the *syn* elimination of selenoxides, to their use as catalysts in oxygen transfer reactions, as Lewis base catalysts in the activation of electrophiles, or in Se-π-acid catalysis.[1] In recent years, the development of selective and efficient protocols to prepare chalcogen-containing heterocycles (S, Se and Te) has increased.[2] Considering the urgency for greener and efficient protocols to access organoselenium compounds, we have dedicated our efforts in the development of new strategies to access molecular hybrids of heterocycles and other active platforms with organoselenium moieties.[3-5] In this lecture, we present our recent results on the use of arylseleninic acids[3-5] and triselenium dicyanide (TSD)[6] as source of electrophilic selenium, both under thermal conditions or visible light irradiation (Figure 1).

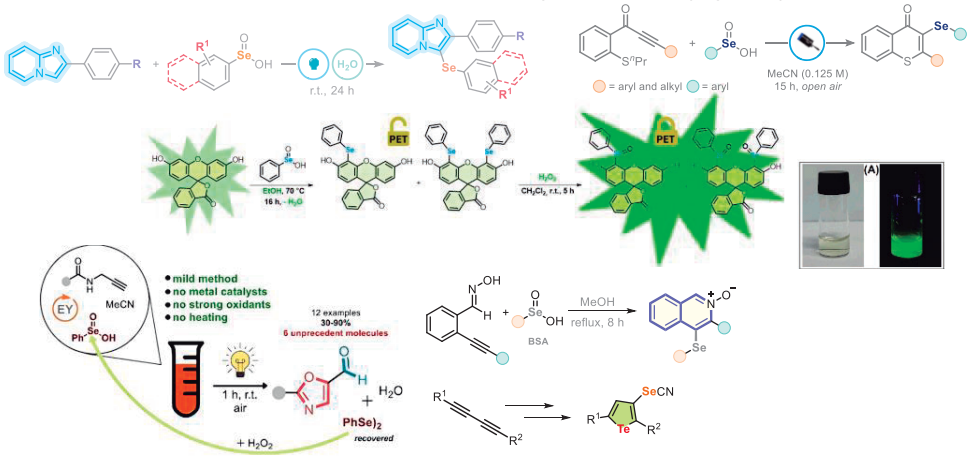

Figure 1: Some reactions to be discussed in this lecture.

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References:

1. Lenardão, E. J.; Santi, C.; Sancineto, L. *New Frontiers in Organoselenium Compounds*. Springer: Cham, 2018.
2. Bartz, R. H.; Hellwig, P. S.; Rosa, K. M.; Silva, M. S.; Lenardão, E. J.; Jacob, R. G.; Perin, G. *Org. Biomol. Chem.* **2025**, *23*, 2997-3028.
3. Abenante, L.; Quadros, G. T.; Perin, G.; Santi, C.; Penteado, F.; Lenardão, E. J. *Eur. J. Org. Chem.* **2022**, *2022*, e202200641.
4. Rosa, K. M.; Washio, N. M. N., Quadros, S.; Dreyer, J. P.; Machado, V. G.; Roehrs J. A.; Oliboni, R.; Lenardão, E. J. *J. Mol. Liq.* **2024**, *416*, 126528.
5. Anghinoni, J. M.; Ferreira, S. S.; Kazmierczak, J. C.; Perin, G.; Penteado, F.; Lenardão, E. J. *J. Org. Chem.* **2024**, *89*, 11272−11280.
6. Anghinoni, J. M.; Ferreira, S. S.; Penteado, F.; Lenardão, E. J.; Silva, M. S. *Molbank* **2022**, *2022*, M1485.

Expanding Discovery Chemistry Toolbox: From Concept to Practice

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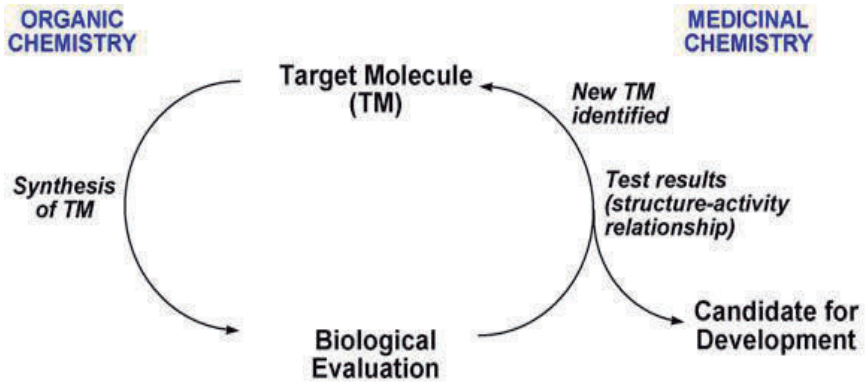
The pharmaceutical and chemical industry remains solely reliant on synthetic methodology to prepare drugs or drug like molecules for their discovery/process program. The expansion of synthetic methodology in recent years has greatly facilitated the preparation of heterocycles that would once have been considered an insurmountable synthetic challenge. In turn, the pharmaceutical industry, where large numbers of heterocycles are prepared and tested for their therapeutic use became the principal end-users and beneficiaries of this enlarged toolkit. Designing and discussing of Transition-Metal promoted various synthetic tools for the synthesis of pharmaceutically important heterocycles and generation of new chemotypes with translational potential will form the basic premise of my presentation.[1]



References:
1. a) Paul, S.; Talukdar, V.; Srivastava, D.; Patra, N.; Das, P. *Org. Lett.* **2025,** 27, *9987*. b) Iqubal, A.; Jash, A., Das, P. *Org. Lett.* **2025**, 27*,* 7643. c) Roy, T.; Jana, S.; Das, P. *J. Org. Chem. 2025*, 90, 9083. d) Patra, S.; Samata, S.; Talukdar, V.; Das, P. *J. Org. Chem.* **2025**, 90, 6261. e) Roy, T.; Mondal, K.; Halder, P.; Sengupta, A.; Das, P. *J. Org. Chem.* **2025**, 90, 6219. f) Iqubal, A.; Jash, A.; Halder, P.; Das, P. *J. Org. Chem.* **2025**, 90, 1571. g) Talukdar, V.; Mondal, K.; Halder, P.; Das, P. *J. Org. Chem.* **2024**, 89, 7455. h) Halder, P.; Mondal, K.; Jash, A.; Das, P. *J. Org. Chem.* **2024**, 89, 9275. i) Mondal, K.; Mukhopadhyay, N.; Patra, S.; Roy, T.; Das, P. *ACS Catal*. **2023**, 13, 11977. j) Roy, T.; Mondal, K.; Sengupta, A.; Das, P. *J. Org.. Chem.* **2023**, 88, 9, 6058.

Heterocycles in Materials Chemistry

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Organic dyes are of significant interest for diverse applications, including light-emitting diodes, organic photovoltaics, dye-sensitized solar cells, photodynamic therapy, and biological imaging. Among these materials, xanthene-based dyes are especially attractive because of their unique molecular switching behavior, excellent photophysical properties, and remarkably concise synthetic accessibility.[1] Polyaniline (PANI), by contrast, is a classical conducting polymer valued for its high electrical conductivity, redox reversibility, and electrochromic properties, which have enabled applications in hole-injection layers, anticorrosion and antistatic coatings, electrochromic devices, sensors, and catalysis.[2] Despite their utility, both organic dyes and PANI suffer from important limitations that our group has addressed through heterocyclic chemistry. Traditional xanthene dyes, such as rhodamine and fluorescein, typically absorb and emit in the visible region, which limits their effectiveness for biological imaging because visible light has poor tissue penetration and higher background interference. To overcome this challenge, our group uses heterocyclic structural modifications to shift xanthene dye absorption and emission into the far-red, near-infrared (NIR), and shortwave infrared (SWIR) regions for sensing and imaging in biological tissues.[1a, 1b, 3] Similarly, PANI is limited by poor solubility in common organic solvents and insufficient redox stability. Our group has applied heterocyclic design principles to address these challenges, developing PANI derivatives with improved processability and enhanced electrochemical stability while retaining desirable electronic properties.[4] (**Figure 1**),

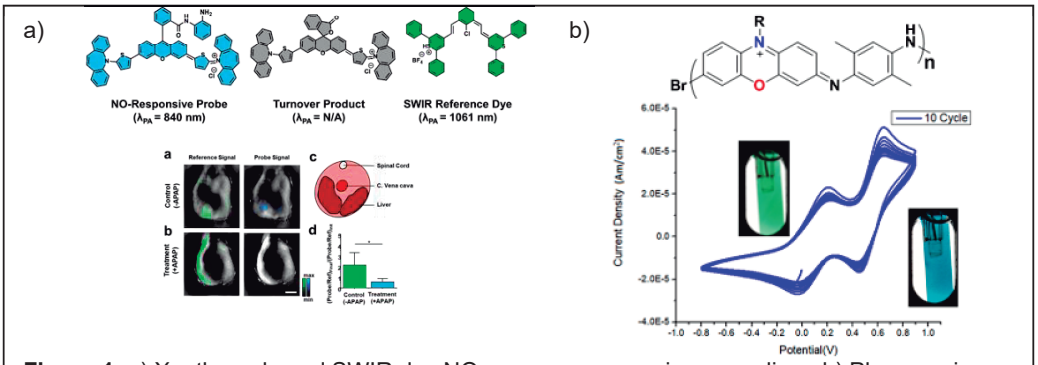

Figure 1. a) Xanthene-based SWIR dye NO-sensor response in mouse liver; b) Phenoxazine-based PANI derivative as redox stable electrochromic material.

This presentation highlights how heterocyclic chemistry can be used to tailor the properties of xanthene dyes and PANI derivatives. Specifically, I will discuss the use of heterocyclic structures to control the wavelength and molecular switching behavior of xanthene dyes for NIR and SWIR imaging applications, as well as the redesign of PANI to improve its redox stability, processability, and electrical conductivity. Together, these studies demonstrate the power of heterocyclic chemistry in developing advanced functional materials for bioimaging and organic electronics.

Acknowledgements: We thank the national Science foundation (OIA-1757220 and CHE-1945503) for funding these two projects as well as Mississippi State Unioversity College of Arts and Science and Department of Chemistry for support.

References:

[1] a) C. S. L. Rathnamalala, N. W. Pino, B. S. Herring, M. Hooper, S. R. Gwaltney, J. Chan, C. N. Scott, *Organic Letters* **2021**, *23*, 7640 7644; b) C. S. L. Rathnamalala, S. Hernandez, M. Y. Lucero, C. B. Swartchick, A. Kalam Shaik, N. I. Hammer, A. K. East, S. R. Gwaltney, J. Chan, C. N. Scott, *Angewandte Chemie International Edition* **2023**, *62*, e202214855; c) C. Liu, C. N. Scott, *Dyes and Pigments* **2021**, *196*, 109792.
[2] C. D. Pina, E. Falletta, *Current medicinal chemistry* **2022**, *29*, 329-357.
[3] a) I. Rajapaksha, H. Chang, Y. Xiong, S. Marder, S. R. Gwaltney, C. N. Scott, *The Journal of Organic Chemistry* **2020**, *85*, 12108-12116; b) C. S. L. Rathnamalala, J. N. Gayton, A. L. Dorris, S. A. Autry, W. Meador, N. I. Hammer, J. H. Delcamp, C. N. Scott, *The Journal of Organic Chemistry* **2019**, *84*, 13186-13193.

[4] a) M. Almtiri, T. J. Dowell, I. Chu, D. O. Wipf, C. N. Scott, *ACS Applied Polymer Materials* **2021**, *3*, 2988-2997; b) M. Almtiri, T. J. Dowell, H. Giri, D. O. Wipf, C. N. Scott, *ACS Applied Polymer Materials* **2022**, *4*, 3088-3097.

Creating Structural Diversity and Complexity via Carboborylation of Sulfonylhydrazones

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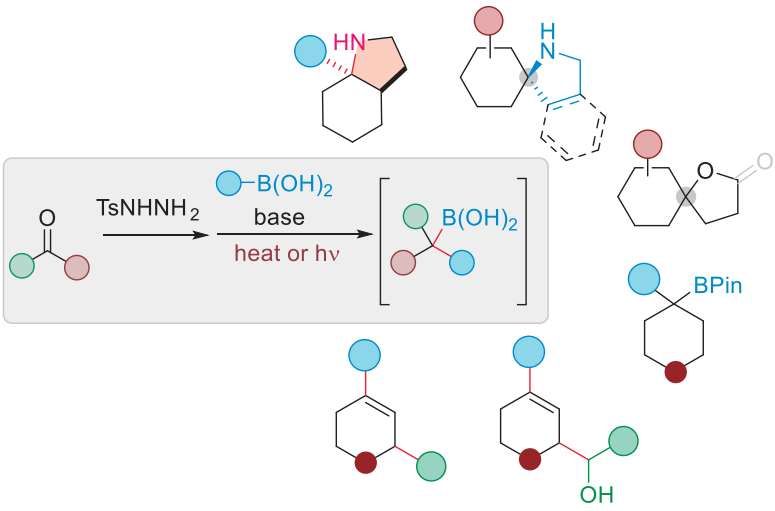
N-Sulfonylhydrazones, readily prepared from aldehydes and ketones, have become powerful reagents for carbonyl diversification and C–C bond formation.[1] Their reactivity is commonly initiated by in situ generation of diazo compounds that are intercepted under transition-metal-catalyzed or metal-free conditions, enabling a wide range of synthetic transformations. Moreover, the divalent nature of the diazo intermediate allows the formation of two new bonds through cascade or stepwise processes, providing efficient access to molecular complexity.

We have exploited this reactivity for the synthesis and late-stage modification of heterocycles aimed at the generation of structural diversity. This lecture will highlight recent contributions from our laboratory, with particular emphasis on thermal and photochemical carboborylation processes of *N*-tosylhydrazones.[2] Their application to the synthesis and functionalization of heterocyclic scaffolds will be discussed.



References:

1. X. Zhang, P. Sigavaru, Y. Pan, N. Wang, W. Zhang, X. Bi, *Chem. Rev.* **2025**, *125*, 1049.
2. (a) Á. Valdés-Maqueda, M. Plaza, C. Valdés, *ChemistryEurope* **2025**, *4*, 202500212. (b) Á. Valdés-Maqueda, M. Plaza, C. Valdés, *Chem. Sci.* **2024**, *15*, 19626–19633. (c) Á. Valdés-Maqueda, L. López, M. Plaza, C. Valdés, *Chem. Sci.* **2023**, *14*, 13765–13775. (d) L. López, M. Cabal, C. Valdés, *Angew. Chem. Int. Ed.* **2022**, *61*, 202113370.

Diverting Olefination Reaction to Deconstructive–Reconstructive Editing of Carbonyl Compounds

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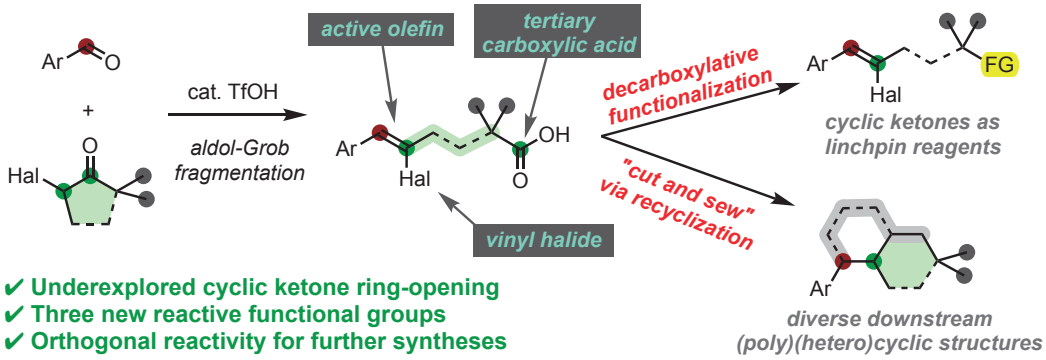
The construction of new C-C double bonds (olefination) is fundamentally important in organic chemistry and highly ubiquitous in the synthesis of materials and biologically relevant products. Many traditional olefination reactions, such as the Wittig, Julia, Peterson, Tebbe, Kauffmann and McMurry reactions, were carried out on carbonyl compounds as they are versatile organic precursors.[1] However, most of them use stoichiometric amounts of special reagents that pose issues with toxicity or product purification.[1] In this seminar, I would like to discuss our group adventure on the use of simple acid catalytic processes to promote interesting isodesmic reactions for the olefination of carbonyl compounds,[2-12] which eventually leads to the deconstructive-reconstructive editing of cyclic ketones.



[1] T. Takeda (ed.) "*Modern Carbonyl Olefination: Methods and Applications*", Wiley, **2004**.
[2] Tran, U. P. N.; Oss, G.; Pace, D. P.; Ho, J. and Nguyen T. V. *Chem. Sci.* **2018**, *9*, 5145-5151.
[3] Tran, U. P. N.; Oss, G.; Breugst, M.; Detmar, E. Pace, D. P.; Liyanto K. and Nguyen T. V. *ACS Catal.* **2019**, *9*, 912-919.
[4] Oss, G. and Nguyen T. V. *Synlett* **2019**, *30*, 1966-1970.
[5] To, T. A.; Pei, C.; Koenigs, R. M. and Nguyen, T. V. *Angew. Chem. Int. Ed.* **2022**, *61*, e202117366.
[6] To, T. A.; Mai, K. B. and Nguyen, T. V. *Org. Lett.* **2022**, *24*, 7237-724.
[7] Mann, J. S.; Mai, K. B. and Nguyen, T. V. *ACS Catal.* **2023**, *13*, 2696-2701.
[8] Ho, T. H.; To, T. A.; Mai, K. B. and Nguyen, T. V. *Org. Lett.* **2024**, *26*, 8842-8847.
[9] To, T. A.; Phan, N. T. A.; Mai, K. B. and Nguyen, T. V. *Chem. Sci.* **2024**, *15*, 7187-7197.
[10] To, T. A. and Nguyen, T. V. *Angew. Chem. Int. Ed.* **2024**, *63*, e202317003.
[11] Ton, N. N. H.; Mai, B. K.; Fallon, T. and Nguyen, T. V. *Angew. Chem. Int. Ed.* **2025**, *64*, e202502713.
[12] Lasch, D.; To, T. A.; Mai, K. B. and Nguyen, T. V. *Org. Lett.* **2026**, DOI = 10.1021/acs.orglett.6c02009

Gold-Redox Chemistry in the Synthesis of Valuable Heterocycles

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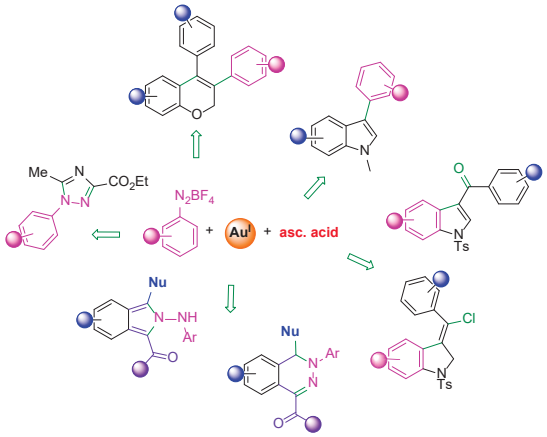
Aryldiazonium salts are strong electrophiles capable of triggering gold-redox transformations involving arylAu(III) intermediates.[1] The latter can address C-C and C-X cross-coupling reactions and promote multicomponent transformations, providing straightforward access to valuable heterocycles. Within this context, we have described the synthesis of alkylidenelactones, 3-aryl(3-acyl)indoles, 3-acylindoles, 3-(chloromethylene)indolines, 2*H*-chromenes, isoindoles, 1,2-dihydrophtalazines, and triazoles, among others (**Scheme 1**).[2] A key parameter that distinguishes our contribution to the field is the use of a biocompatible Au(I)-redox-activating agent, ascorbic acid. The former avoids the need to add a cocatalyst and/or irradiation, leading to readily accessible protocols that are easy to implement. Very recently, we have found that the combination of ascorbic acid with NHC^N ligands enables the activation of reluctant electron-rich aryldiazonium salts. EPR, NMR, and X-ray analyses reveal the reaction to be triggered by a radical pathway facilitated by the ligand-assisted stabilization of the Au(III) center.



Scheme 1: Synthesis of heterocycles by gold-redox transformations involving aryldiazonium salts.

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References:

1. a) Taschinski, S.; Döp, R.; Ackermann, M.; Rominger, F.; de Vries, F.; Menger, M. F. S. J.; Rudolph, M.; Hashmi, A. S. K.; Klein, J. E. M. N. *Angew. Chem. Int. ed.* **2019**, *58*, 16988-16993; b) Yuan, T.; Tang, Q.; Shan, C.; Ye, X.; Wang, J.; Zhao, P.; Wotjas, L.; Hadler, N.; Chen, H.; Shi, X. *J. Am. Chem. Soc.* **2021**, *143*, 4074-4082; c) Li, J.; Shi, H.; Zhang, S.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Org. Lett.* **2021**, *23*, 7713-7717.
2. a) Medina-Mercado I.; Colin-Molina, A.; Barquera-Lozada, J. E.; Rodríguez-Molina, B.; Porcel, S. *ACS. Catal*. **2021**, *11*, 8968-8977; b) Díaz-Salazar, H.; Ramírez-González, C. M.; Rosas-Ortega, M. A., Porcel, S. *Tetrahedron*, **2024**, *168*, 134358; c) Díaz-Salazar, H.; Osorio-Ocampo, G.; Porcel, S. *J. Org. Chem.* **2024**, 89, 10163-10174; d) López-Saladino, O. F.; Dusso, D.; Díaz-Salazar, H.; Martínez, B. A.; Rosas-Ortega, M. A.; Porcel, S. *Adv. Synth. Catal.* **2025**. DOI 10.1002/adsc.202500321.

Photochemistry as a tool for reaction discovery with reactive intermediates

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Photochemistry offers unique opportunities for reaction discovery by enabling the generation and control of highly reactive intermediates under mild conditions. Our research explores how visible-light activation can unlock novel reactivity modes of species such as carbenes, radicals and nitrenes, providing access to previously unattainable bond constructions and heterocyclic frameworks. This approach highlights photochemistry as a powerful platform for advancing modern synthetic methodology.

Herein, we present our recent advances in photochemical and photocatalytic carbene and nitrene transfer reactions. Emphasis will be placed on strategies to access either singlet or triplet states and how this electronic control enables distinct applications in synthetic methodology.[1,2] Approaches to modulate nitrene reactivity via single-electron transfer pathways or direct photoexcitation will be highlighted, supported by mechanistic and computational studies that have guided the discovery of advanced cycloaddition chemistry.[3]

We further outline an international, collaborative research program that integrates fundamental reactivity studies, reaction development, and mechanistic insight with translational applications in drug discovery. This work demonstrates how photochemical methods can unlock the potential of reactive intermediates and convert fundamental discoveries into new strategies for the synthesis of therapeutic candidates.[4-6] Together, these studies highlight photochemistry as a powerful driver of innovation at the interface of fundamental and applied research.

References:

[1] (a) Empel, C.; Pham, Q. H.; Koenigs, R. M. *Acc. Chem. Res.*, **2024**, *57*, 2717-2727; (b) Jana, S.; Pei, C.; Empel, C.; Koenigs, R. M. *Angew. Chem. Int. Ed.* **2021**, *60*, 13271-13279; (c) Jana, S.; Yang, Z.; Li, F.; Empel, C.; Ho, J.; Koenigs, R. M. *Angew. Chem. Int. Ed.* **2020**, *59*, 5562-5566; (d) Hommelsheim, R.; Guo, Y.; Yang, Z.; Empel, C.; Koenigs, R. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 1203-1207.

[2] (a) Li, F.; Pei, C.; Koenigs, R. M.; *Angew. Chem. Int. Ed.* **2022**, *61*, e202111892; (b) Empel, C.; Jana, S.; Ciszewski, Ł.; Zawada, K.; Pei, C.; Gryko, D.; Koenigs, R. M. *Chem. Eur. J.* **2023**, e202300214. (c) De Angelis, L.; Pei, C.; Koenigs, R. M.; Doyle, M. P. *Nature Commun.* **2023**, *14*, 1109.

[3] (a) Guo, Y.; Pei, C.; Koenigs, R. M. *Nature Commun.* **2022**, *13*, 86; (b) Guo, Y.; Pei, C.; Jana, S.; Koenigs, R. M. *ACS Catal.* **2021**, *11*, 337; (c) Guo, Y.; Empel, C.; Pei, C.; Fang, H.; Koenigs, R. M. *Chem Catalysis,* **2022**, *2*, 2012; (d) Empel, C.; Koenigs, R. M.; *Chem Catalysis*, **2022**, *2*, 2506.

[4] Cai, B. G.; Empel, C.; Yao, W.-Z.; Koenigs, R. M.; Xuan, J. *Angew. Chem. Int. Ed.* **2023**, e202312031.

[5] Li, F.; Zhu, W. F.; Empel, C.; Datsenko, O.; Xu, Y.; Ehrler, J. M.; Atodiresei, I.; Knapp, S.; Mykhailiuk, P.; Proschak, E.; Koenigs, R. M. *Science*, **2024**, *383*, 498-503.

[6] Hussain, Y.; Prasanna R.; Empel, C.; Proschak, E.; Koenigs, R. M.; Chauhan, P. *Angew. Chem. Int. Ed.* **2025**, e202416956.

Greener synthesis of five-membered *N*-heterocycles

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Five-membered *N*-heterocycles are commonly found in a wide range of drugs and natural products, where they exhibit significant biological activity. The importance of these compounds has driven the development of greener synthetic methods to access this core structure.
In this presentation, we will discuss the photocatalysed synthesis of Δ¹-pyrrolines[1] and 2-pyrrolo[2,3-*b*]indoles (**Figure 1**) in batch or under continuous flow regime. Moreover, the one-pot synthesis of γ-lactams,[2] employing the Ugi multicomponent reaction followed by intramolecular Michael addition will be described.

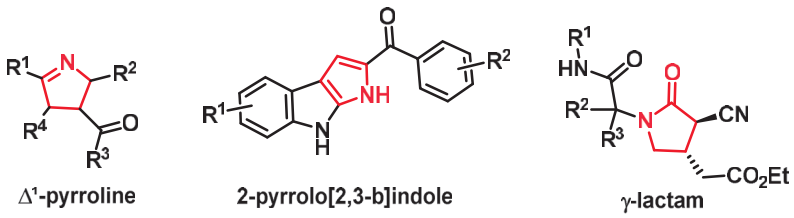

Figure 1: Five-membered *N*-heterocycles

Acknowledgements: We thank FAPESP (grant 2021/12394-0), GlaxoSmithKline, CAPES (Finance Code 001), and CNPq (303973/2023-4) for financial support and fellowships.

References:

1. Martelli, L. S. R.; Furniel, L. G.; Santiago, P. H. O.; Ellena, J.; Corrêa, A. G., *ACS Omega* **2025**, *10*, 18017.
2. Vidal, H. D. A.; Nunes, P. S. G.; Martinez, A. K. A.; Januário, M. A. P.; Santiago, P. H. O.; Ellena, J.; Corrêa, A. G., *Chem. Asian J.* **2025**, *20*, e202400917.

New catalytic methods for efficient organic synthesis

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Catalytic functionalizations present new avenues for the construction of carbon–carbon and carbon–heteroatom bonds from readily available and abundant feedstocks. We have been developing new catalytic systems as versatile synthetic tools that enable efficient conversion of a variety of precursors to functionalized products. Additionally, we have been pursuing the development of asymmetric catalytic strategies to understudied stereogenic functional groups. The talk will highlight the progress in the development of new catalytic approaches to challenging synthetic targets and their potential applications in organic synthesis.

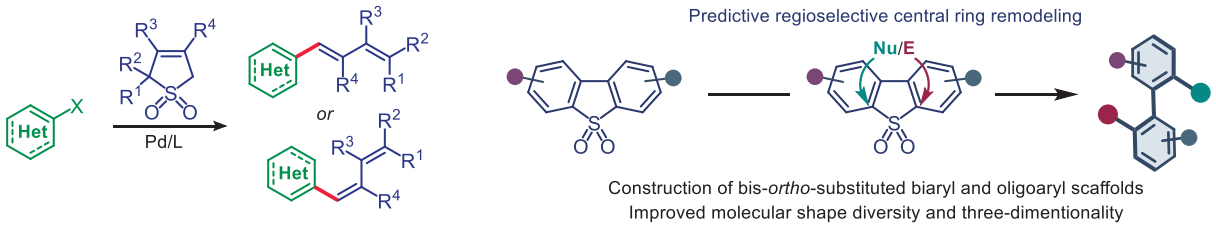

Figure 1: Examples of developed catalytic methods.

References:

Nguyen, V. D.; Nand, S.; Trevino, R.; Porey, A.; Thompson, W. T.; Haug, G. C.; Fremin, S. O.; Dhakal, S. K.; Hughes, W. B.; Moran, D. P.; Lakey-Beitia, J.; Giri, C. K.; Manning-Lorino, P.; Greco, S. G.; Arman, H. D.; Larionov, O. V. *Nat. Commun.* **2026**, 10.1038/s41467-026-74669-7.

2. guyen, V. T.; Dang, H. T.; Pham, H. H.; Nguyen, V. D.; Flores-Hansen, C.; Arman, H. D.; Larionov, O. V. *J. Am. Chem. Soc.* **2018**, *140*, 8434−8438.

Chiral Isochalcogenourea Lewis Base Organocatalysis

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Abstract

Chiral Isochalcogenoureas (IChU) are versatile Lewis base (LBs) organocatalysts that allow for numerous highly enantioselective transformations. Over the last years our group had a strong interest in the utilization of these chiral LBs for the covalent activation, control and utilization of simple carboxylic acid derivatives (via in situ C1 ammonium enolate formation) and allenoates (via in situ betaine formation). Furthermore, we are also interested in the design and use of new catalyst derivatives and in the elucidation of their key properties such as nucleophilicity and basicity. In this presentation I will give an overview of our most recent results focusing on the development and mechanistic understanding of new catalysts and new transformations.

Selected recent contributions related to this topic:

- M. Piringer, A. Scheucher, M. Hofer, M. Bechmann, A. R. Ofial, L. Stockhammer, Mario Waser *ChemistryEurope.,* **2026**, *4*, e202500443.
- L. Stockhammer, K. Kasten, A. Eitzinger, L. S. Vogl, M. Piringer, D. Weinzierl, A. R. Ofial, A. D. Smith, Mario Waser *Angew. Chem. Int. Ed.,* **2025**, *64*, e202514865.
- Lukas S. Vogl, Peter Mayer, Raphaël Robiette, Mario Waser *Angew. Chem. Int. Ed.,* **2024**, *63*, e202315345.
- Magdalena Piringer, Mario Hofer, Lukas S. Vogl, Peter Mayer, Mario Waser *Adv. Synth. Catal.* **2024**, *366*, 2115-2122.
- David Weinzierl, Magdalena Piringer, Paul Zebrowski, Lotte Stockhammer, Mario Waser *Org. Lett.,* **2023**, *25*, 3126-3130.
- Lotte Stockhammer, Rebecca Craik, Uwe Monkowius, David B. Cordes, Andrew D. Smith, Mario Waser *ChemistryEurope,* **2023**, *1*, e202300015

Lighting Up the Synthesis of Sulfur-Based Heterocycles: A Continuous Flow Photochemical Approach Leading to 3-Sulfenylthiochromones

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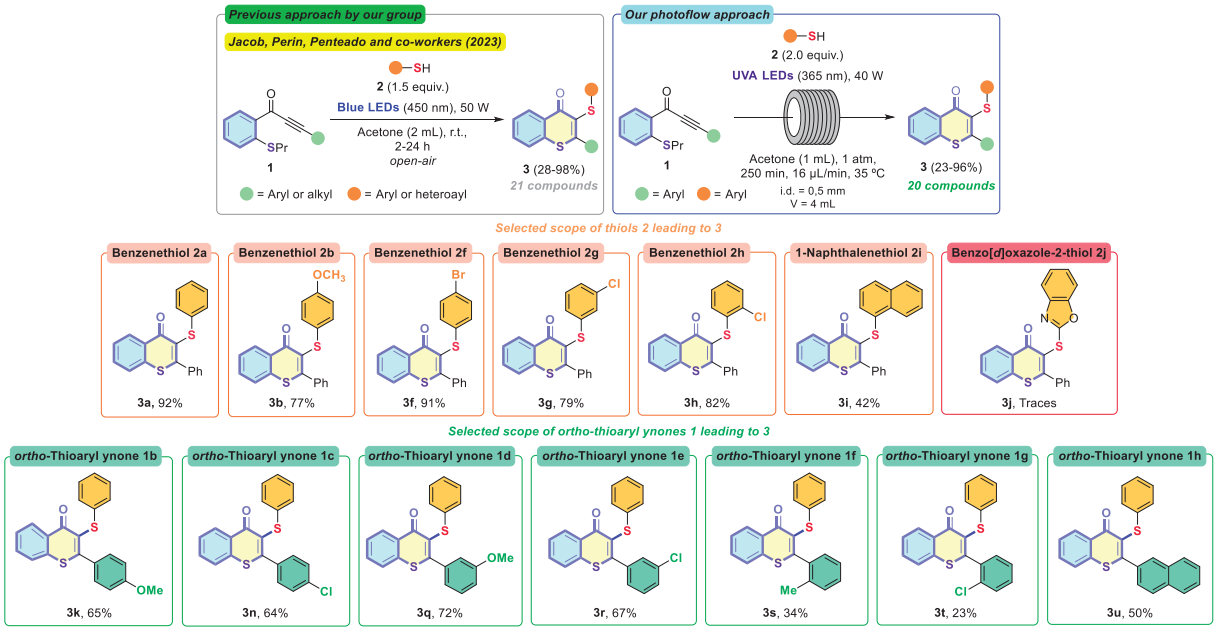
Flow chemistry is increasingly important for industrial applications because it enables continuous and well-controlled reactions with improved safety, efficiency, and reproducibility compared to traditional batch processes.[1] In this context, this enabling technology has been employed in the development of methodologies for the synthesis of chalcogen-substituted heterocycles via electrophilic chalcogenation/cyclization reactions.[2] Accordingly, based on a previous report from our research group,[3] this work aims to develop a protocol for the continuous flow photoinduced synthesis of 2-aryl-3-(arylthio)-4*H*-thiochromen-4-ones **3** through radical annulation of *ortho*-thioaryl ynones **1** in the presence of thiols **2** as reaction partners (**Scheme 1**). Our approach enabled the synthesis of twenty compounds **3** in yields ranging from 23 to 96%, using a solution of 0.25 mmol (0.25 M) of *ortho*-thioaryl ynone **1** and 0.50 mmol (0.50 M) of thiol **2** in acetone (1.0 mL) under irradiation with UVA light (365 nm, 40 W) at 35 °C and 1 atm. The reactions were conducted with a residence time of 250 minutes and a flow rate of 16 µL/min.



Scheme 1: Selected results of this work

Acknowledgements: We thank CAPES, CNPq, FAPERGS and FINEP for financial support.

References:

1. a) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. *Chem. Rev*. **2017**, *117*, 11796. b) Hughes, D. L. *Org. Process Res. Dev*. **2020**, *24*, 1850. c) Capaldo, L.; Wen, Z.; Noël, T. *Chem. Sci*. **2023**, *14*, 4230. d) Essel, V.; Mukherjee, S.; Mitra, S.; Goswami, A.; Tran, N. N.; Ferlin, F.; Vaccaro, L.; Malekpour, G. F.; Nguyen, N.-T.; Escribà-Gelonch, M. *Green Chem*. **2024**, *26*, 9503.
2. a) Alzaidi, O.; Wirth, T. *ACS Org. Inorg. Au* **2024**, *4*, 350. b) Arepally, S.; Gieman, H.; Wirth, T. *Angew. Chem. Int. Ed*. **2025**, *64*, e202509811.
3. Bartz, R. H.; Silva, K. B.; Santos, R. R. S. A.; Peglow, T. J.; Lenardão, E. J.; Iglesias, B. A.; Penteado, F.; Perin, G.; Jacob, R. G. *ChemCatChem* **2023**, *15*, e202201557.

SYNTHESIS AND CHARACTERIZATION OF DENSELY FUNCTIONALIZED PIPERIDINES

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Multicomponent synthesis represents a versatile and efficient approach for constructing complex molecular architectures, including densely functionalized piperidines, which are of considerable interest in pharmacology due to their potential as bioactive compounds. In this study, the synthetic route to the parent molecule, ethyl-(2*S*,6*R*)-1,2,5,6-tetrahydro-1,2,6-triphenyl-4-phenylalanine-3-pyridinecarboxylate, was investigated, and four derivatives were obtained by varying the benzaldehyde component. The methodology involved a multicomponent reaction in which ethyl acetoacetate (1 mmol), aniline (2 mmol), and acetic acid (3 mL) were stirred at room temperature for 20 min. Subsequently, 2 mmol of the appropriate benzaldehyde, - 2-chlorobenzaldehyde (B1), 2-fluorobenzaldehyde (B2), 4-fluorobenzaldehyde (B5), or 3-fluorobenzaldehyde (B6) (Fig. 1) - was added, and the reaction mixture was stirred for an additional 90 min. The resulting products were washed, filtered, and dried, affording yields of 82%, 83%, 81%, and 79%, respectively. The structures of the synthesized compounds were confirmed by ^{1}H and ^{13}C NMR spectroscopy. Overall, the proposed methodology proved to be efficient for the synthesis of these compounds and represents a promising strategy for the preparation of new piperidine derivatives.

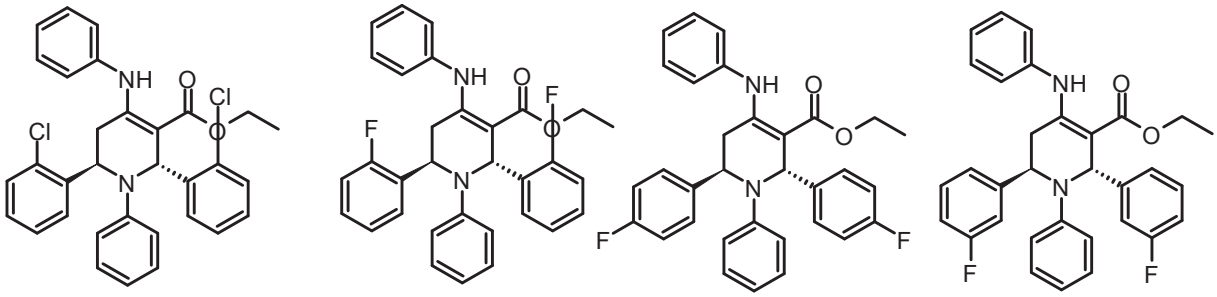

Figure 1. Structures of compounds B1, B2, B5 and B6

Acknowledgements: We thank to FAPEMIG; FAPESP, CNPq and CAPES, also UFLA and UFABC

Reference:

1. BALIJAPALLI, Umamahesh; MUNUSAMY, Sathishkumar; NATESAN, Karthikeyan; SUNDARAMOORTHY, Sundaramoorthy; IYER, Sathiyanarayanan Kulathu. Metal-free, one-pot, rapid synthesis of tetrahydropyridines using acetic acid as solvent and catalyst at room temperature. Synthetic Communications, 44, 7, 943–953, 2014. https://doi.org/10.1080/00397911.2013.838266

Visible-Light-Driven Pd-Catalyzed Heck Reaction for C3 Alkylation of Coumarins

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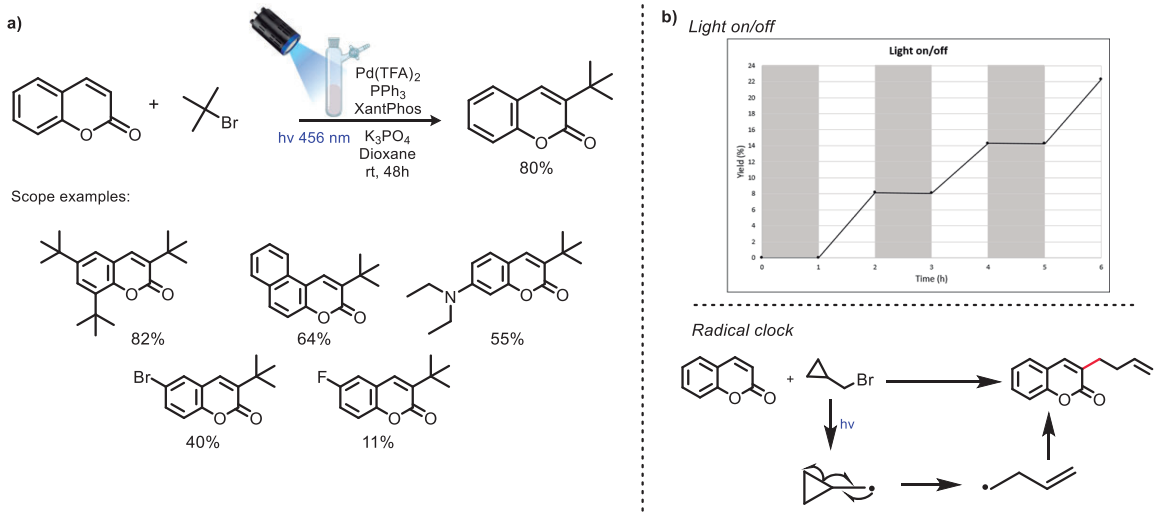
Coumarin derivatives are widely recognized for their diverse biological activities and remain as privileged molecules in medicinal chemistry.[1] Functionalization at the C3 position constitutes a powerful strategy to advance in their physicochemical and pharmacological properties. Despite this relevance, general metal-catalyzed methods for the direct and regioselective alkylation at C3 position are underdeveloped, and classical cross-coupling protocols often rely on high temperatures and stoichiometric oxidants, which may restrict functional group tolerance.[2] Herein, we report the C3-alkylation of coumarins via a palladium-photoredox Heck reaction using alkyl bromides as radical precursors under visible-light irradiation. After full optimization of the reaction parameters, the desired products were obtained in up to 80% yield. The methodology exhibits a broad substrate scope, where electron-rich derivatives and π-extended systems were well tolerated. Besides, halogenated substrates remained compatible, while strongly electron-withdrawing substituents led to diminished reactivity (**Scheme 1a**). Mechanistic investigations, including light on/off experiments and radical clock studies, support a radical pathway and indicate that the transformation does not proceed through a radical chain mechanism (**Scheme 1b**).[3]



Scheme 1: Optimized conditions, selected scope examples, and mechanistic studies (light on/off and radical clock) for the Pd-photoredox C3-alkylation of coumarins.

Acknowledgements: We thank the following funding agencies,

(2025/12870-7); (2023/05757-4); (2020/10246-0); (2022/11314-5); (2021/12394-0); (2022/14197-0).

References:

[1](a) Matos, M. J.; Vazquez-Rodriguez, S.; Santana, L.; Uriarte, E.; Fuentes-Edfuf, C.; Santos, Y.; Muñoz-Crego, A. *Med. Chem.* **2012**, *8*, 1140. (b) Matos, M. J.; Vazquez-Rodriguez, S.; Santana, L.; Uriarte, E.; Fuentes-Edfuf, C.; Santos, Y.; Muñoz-Crego, A. *Molecules* **2013**, *18*, 1394. (c) Gualandi, A.; Rodeghiero, G.; Della Rocca, E.; Bertoni, F.; Marchini, M.; Perciaccante, R.; Jansen, T. P.; Ceroni, P.; Cozzi, P. G. *Chem. Commun.* **2018**, *54*, 10044. [2](a) Min, M.; Kim, Y.; Hong, S. *Chem. Commun.* **2013**, *49*, 196. (b) Jafarpour, F.; Hazrati, H.; Mohasselyazdi, N.; Khoobi, M.; Shafiee, A. *Chem. Commun.* **2013**, *49*, 10935. (c) Zhu, Y.-F.; Wei, Y.-Y. *Chem. Sci.* **2014**, *5*, 2379. (d) Niu, B.; Zhao, W.-N.; Ding, Y.-C.; Bian, Z.-G.; Pittman, C. U., Jr; Zhou, A.-H.; Ge, H.-B. J. *Org. Chem.* **2015**, *80*, 7251. (e) Dian, L.-Y.; Zhao, H.; Zhang-Negrerie, D.; Du, Y. F. *Adv. Synth. Catal.* **2016**, *358*, 2422. [3]G. A. M. Jardim, J. A. Dantas, A. A. Barboza, M. W. Paixão, M. A. B. Ferreira, *Synthesis* **2022**, *54*, 4629–4645.

C-3 and N-1 Functionalization of the 4-Quinolone Core: Access to Acylhydrazone and Acyclonucleoside Derivatives

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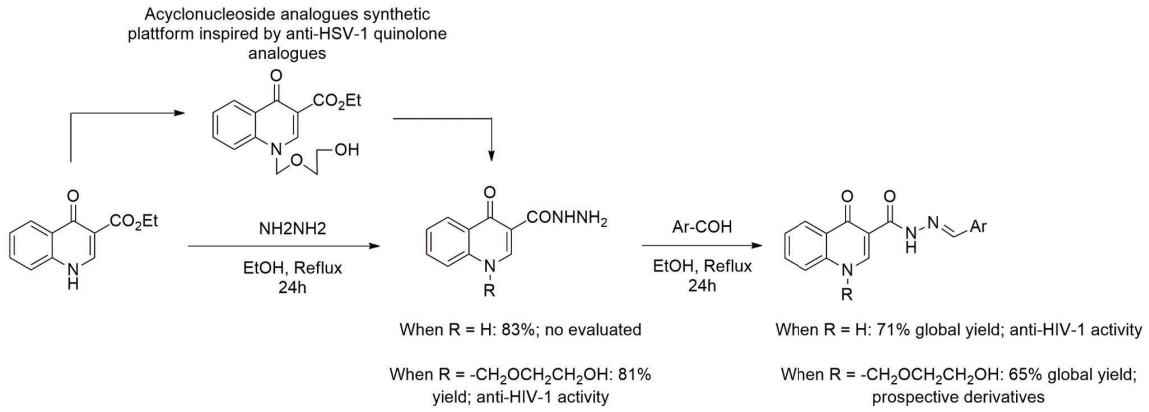
The modification of heterocyclic scaffolds remains an important strategy in synthetic chemistry, enabling the preparation of structurally diverse compounds. In this context, the 4-quinolone framework represents a versatile system, particularly due to the reactivity of the C-3 and N-1 positions. In this work, we investigated different synthetic approaches for the functionalization of the C-3 and N-1 positions of the 4-quinolone scaffold, aiming to access structurally distinct derivatives. Initially, a series of acylhydrazone derivatives was obtained using reproducible synthetic methodologies from carbohydrazide-type precursors, allowing the introduction of conjugated groups onto the 4-quinolone scaffold. In parallel, acyclonucleoside analogues were synthesized through functionalization at the N-1 position of the quinolone core, aiming at the incorporation of structural fragments inspired by nucleosides, whose antiviral activity is well established. This approach enabled the exploration of different substitution patterns from the same heterocyclic nucleus. In addition, selected derivatives were evaluated for antiviral activity in preliminary assays, showing promising initial results. Overall, these findings reinforce the usefulness of the 4-quinolone scaffold as a synthetic platform for the preparation of functionalized derivatives, contributing to the expansion of the set of bioactive compounds available for further studies.



Scheme 1: Divergent C-3 functionalization of the 4-quinolone core affording biologically evaluated acylhydrazone derivatives and prospective acyclonucleoside analogues.

Acknowledgements: UFF, CAPES(fiance code 001), CNPq, FAPERJ.

References:

1. Høiby, N. Pandemics: past, present, future. APMIS. 2021; 129, 352–371.

2. Amorim, L. S. C.; STEPHENS, P. R. S.; et al, Braz. J. Pharm. Sci., 2026, accepted for publication.

3. Silva, Y. I. M.; Yoneda, J.; et al., Braz. J. Pharm. Sci., 59, e227838, 2023.

SYNTHESIS OF HYBRID TRIHETEROCYCLIC 4*H*-PYRIMIDO[2,1-*a*]BENZIMIDAZOLE DERIVATIVES CATALYZED BY IONIC LIQUIDS

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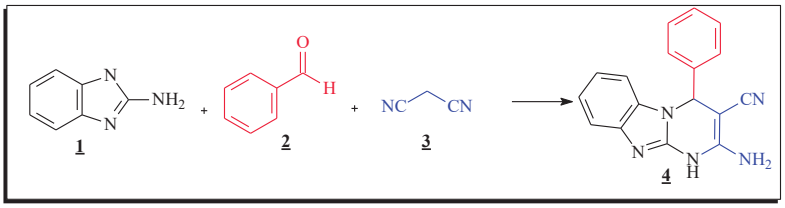
Keywords: heterocycles, green chemistry and multicomponent reaction.

Benzimidazole and its derivatives are aromatic heterocyclic compounds present in the structure of several drugs due to their biological and pharmacological properties, including antimicrobial, anticancer, antifungal, antileishmanial, and antituberculosis actions.[1] Among the structurally modified subclasses, the substituted 2-aminobenzimidazoles stand out, which have been used as new inhibitors of acetylcholinesterase and butyrylcholinesterase enzymes, in addition to acting as potent glucagon receptor antagonists.[2] Due to this pharmacological and biological relevance, the present work aims at the synthesis of benzimidazole hybrids through multicomponent reactions (MCRs) in ionic liquids, with the objective of developing an efficient synthetic strategy that allows obtaining structurally complex molecules, with high atom economy, reduction in the number of reaction steps, minimal waste generation, and alignment with the principles of green chemistry.3 In the synthesis of the hybrids 4*H*-pyrimido[2,1-*a*]benzimidazole **4** (Scheme 1), a round-bottom flask adapted for reflux was used, where 1 mmol of 2-aminobenzimidazole **1**, 1 mmol of aldehyde **2** and 1 mmol of malononitrile **3** were added under constant temperature and magnetic stirring.

Scheme 1. Synthesis of a benzimidazole derivative.



The synthesis of 4*H*-pyrimido[2,1-*a*]benzimidazole hybrids proved efficient with yields of 20-80%. It was possible to apply a synthesis with a catalyst and solvent with low toxicity that fits within the parameters of Green Chemistry, since the synthesis of this class of compounds has immense biological and pharmacological applicability.

Acknowledgements: We thank CNPq, FINEP, CAPES, UEG and LaQuiMeSO.

References:

1. Moosavi-Zare, A. R.; Darvishi, Z.; Goudarziafshar, H.; Zabardasti, A.. *RSC Adv.* **2025**, *15* (22), 17503–17515.

2. Bansal, Y.; Silakari, O. *Bioorg. Med. Chem.* **2012**, *20* (21), 6208–6236..

3. Ferreira, J. G. L.; Ramos, L. M.; de Oliveira, A. L.; Orth, E. S.; Neto, B. A. D. *J. Org. Chem.* **2015**, *80* (11), 5979–5983.

One-pot synthesis of *N*-(hetero)arylsuccinimides from activated (hetero)arenes: the full use of NBS

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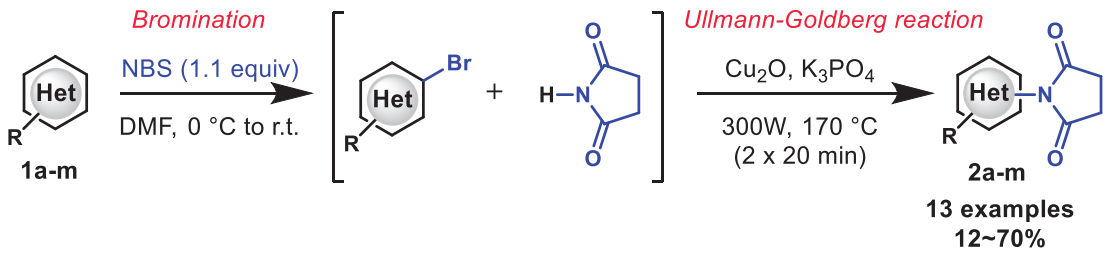
N-bromosuccinimide (NBS) is a versatile brominating reagent. It is used not only in radical bromination but also in electrophilic addition and electrophilic substitution reactions. NBS can be used to obtain aryl bromides, which are useful for further functionalization, such as coupling reactions for C/N/O/S-aryl bond formation.[1] However, the succinimide group of NBS is poorly explored and is often treated as a waste. Because of this, and considering the biological potential of succinimide derivatives,[2] some research groups have demonstrated that the succinimide moiety of NBS can act as a nucleophile. For instance, the imidation of α-bromo (di)ketones.[3]

Although the synthesis of *N*-arylsuccinimides can be easily carried out from anilines,[4] direct imidation of aromatics leading to *N*-arylsuccinimides is still challenging. To date, Baran and colleagues developed a methodology for obtaining *N*-(hetero)arylsuccinimides from (hetero)arenes, however, their approach requires multiple reagents and, also requires the formation of a specific reagent separately.[5] Alternatively, the Ullmann-Goldberg reaction allows the coupling of imides with only aryl halides mediated by copper or copper salts.[6] However, this reaction is known for harsh conditions (excess amount of metal, high temperatures, long reaction times). Currently, catalytic conditions[7] and the use of greener methods, such as microwave irradiation[8] are available, which it is still considered a very attractive reaction.

In this work, we propose the full use of NBS, both for a brominating agent of arenes and for the incorporation of the succinimide group in a one-pot sequence (**Scheme 1**). Using low-cost reagents such as Cu_2O and K_3PO_4, *N*-arylsuccinimides were obtained in moderate to good yields directly from non-halogenated aromatics. It was observed that microwave irradiation was crucial to circumvent the low nucleophilicity of succinimide.



Scheme 1: One-pot bromination/Ullmann-Goldberg coupling sequence for the synthesis of *N*-arylsuccinimides

Acknowledgements: CAPES (Finance Code 001), FAPESP (Grant Number 2021/13573-5 and 2017/18007-2), CEM-UFABC.

References:

1. Saikia, I.; Borah, A. J.; Phukan, P.; *Chem. Rev.* **2016**, *116*, 6837.
2. Zhao, Z.; Yue, J.; Ji, X.; Nian, M.; Kang, K.; Qiao, H.; Zheng, X.; *Bioorg. Chem.* **2021**, *108*, 104557
3. a) Wei, Y.; Lin, S.; Liang, F.; *Org. Lett.* **2012**, *14*, 4202. b) Zou, L. H.; Li, Y. C.; Li, P. G.; Zhou, J.; Wu, Z.; *Eur. J. Org. Chem.* **2018**, *2018*, 5639.
4. a) Rad-Moghadam, K.; Kheyrkhah, L.; *Synth. Commun.* **2009**, *39*, 2108. b) Bozdoğan, B.; Erşatır, M.; Demirkol, O.; Akbaşlar, D.; Giray, E. S.; *Synth. Commun.* **2017**, *47*, 217.
5. Foo, K.; Sella, E.; Thomé, I.; Eastgate, M. D.; Baran, P. S.; *J. Am. Chem. Soc.* **2014**, *136*, 5279.
6. Yamamoto, T.; Kurata, Y.; Can. *J. Chem.* **1983**, *61*, 86.
7. Sperotto, E.; van Klink, G. P. M.; van Koten, G.; de Vries, J. G.; *Dalton Trans.* **2010**, *39*, 10338.
8. Yashwantrao, G.; Saha, S.; *Tetrahedron* **2021**, *97*, 132406.

Visible-Light Catalyzed Access to Fluorescent 3-Aryl-2-Quinolones

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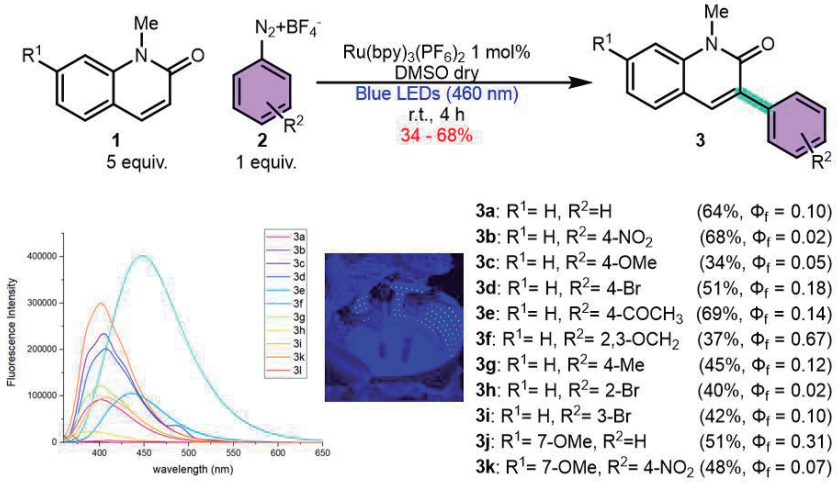
Quinolones are a well-established scaffold for molecules with diverse biological activities, however, their fluorescent properties remain relatively underexplored. This dual functionality combines biological activity and real-time molecular tracking in biological systems, enabling the monitoring of their distribution, transport, and metabolism within cells.[1] Despite their relevance, the direct arylation of 2-quinolones remains underexplored, with only limited examples reported in the literature.[2] In this context, the present study focuses on the optimizing the photoredox-catalyzed arylation of 1-methyl-2-quinolone **1** and on the photophysical characterization of the resulting compounds **3**, with the aim of future biological applications. Similar to our previous work on the photoredox catalysis of 3-aryl-*N*-aryl coumarins [3] ,a methodological study was conducted. The reaction conditions were systematically optimized by varying solvent, reaction time, catalyst loading, concentration, and substrate ratios. The optimal conditions consisted of dry DMSO, 1 mol% of $Ru(bpy)_3(PF_6)_2$, and five equivalents of quinolone. Under these conditions, the desired products were obtained in moderate yields (34%-69%), with relative fluorescence quantum yields reaching up to 69%, relative to anthracene in ethanol. The quinolones derivatives displayed absorption maxima around 340 nm and emission maxima near 450 nm. Notably, substituents at the C3 aryl group (R^2) and the C7 position (R^1) significantly influenced their fluorescence properties. (**Scheme 1**). These results underscore the potential of this class of coumpounds as fluorescent probes for biological applications.



Scheme 1: Synthesis of fluorescent 3-aryl-1-methyl-2-quinolones via photoredox catalysis and their quantum yields.

Acknowledgements: We thank CNPq, CAPES, CAPES-Cofecub, FAPERJ, CNAM, ESPCI, PUC-Rio.

References:

1. a) Toshiko T. et al., *Journal of Molecular Structure,* **2026**, 1349,143921. b) Yiwei X. et al., *Chin. J. Chem,* **2025**, *43*, 1239—1245.
2. a) Yuan et al., *RSC Adv*., **2016**, 6, 35936. b) Dixit et al., *Asian J. Org. Chem.*, **2025**, 14, e202400684.
3. a) Carneiro et al., *Bioorg. Med. Chem.,* **2021**, 114, 105141.

Trifluoromethylation of Tryptophan Derivatives via Photoelectrochemical Strategy

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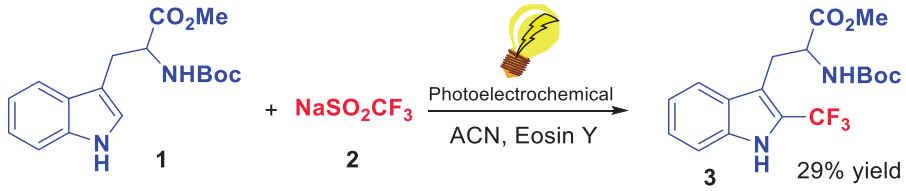
The functionalization of tryptophan derivatives is widely explored in organic synthesis and medicinal chemistry, since this moiety is directly associated with critical biological functions.[1] *L*-tryptophan is a precursor of essential metabolites such as serotonin and melatonin, and is also present in drugs such as sumatriptan and zolmitriptan, acting in the modulation of serotonergic targets.[2]

Additionally, the introduction of the trifluoromethyl group (CF_3) is a strategic approach for adjusting pharmacokinetic and electronic properties, increasing lipophilicity and metabolic stability.[3] However, direct trifluoromethylation of tryptophan derivatives remains limited, especially under conditions compatible with late functionalization.[4] Notably, there are no established drugs containing trifluoromethylated tryptophans, which reinforces the unexplored nature of this modification.

In this project, we are developing a methodology for the trifluoromethylation of tryptophan derivative **1**, employing $NaSO_2CF_3$ (**2**) as the CF_3 source under combined anodic and photochemical activation in the presence of Eosin Y as a photocatalyst (Scheme 1). Applying ACN, light, electric current, and electrolyte, the desired product **3** was obtained with a yield of 29%, demonstrating a synergistic effect between the electric current, the photocatalyst, and light irradiation.

The methodology, currently under development, shows potential for extension to other amino acids and peptide systems, enabling access to fluorinated heterocyclic scaffolds relevant to medicinal chemistry.



Scheme 1: Trifluoromethylation of Tryptophan Derivatives.

Acknowledgements: The authors gratefully acknowledge the financial support from CNPq (G.M.M., Process nº 446457/2024-8), FAPEMIG (P.P.C., Grant nº APQ 01259/24), FAPESP (K.T.O, Grant n° 2025/14388-8).

References:

1. Zhao, J.; X. Bai; J. Du; Y. Chen; X. Guo; J. Zhang; J. Gan; P. Wu; S. Chen; X. Zhang; J. Yang; J. Jin; L. Gao. *Oncol. Rep.* **2025**, *54*, 1–16.
2. Goads, P. J.; C. J. Boes. *Curr. Med. Res. Opin.* **2001**, *17*, s46.
3. Novás, M.; M. J. Matos. *Molecules* **2025**, *30*, 3009.
4. Gregorc, J.; N. Lensen; G. Chaume; J. Iskra; T. Brigaud. *J. Org. Chem.* **2023**, *88*, 13169.

Design and Synthesis of Novel 4-Quinolone-Based Hydroxamic Acids: Structural Functionalization at C-3 of a Privileged Heterocyclic Scaffold

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The 4-quinolone nucleus is a privileged heterocyclic scaffold widely explored in medicinal chemistry due to its structural versatility and synthetic accessibility. In this work, we report the design and synthesis of a series of novel 4-quinolone-3-hydroxamic acid derivatives, aiming to investigate the functionalization of the quinolone core at the C-3 position through the incorporation of a hydroxamic acid moiety. The synthetic approach involved thermal cyclization to construct the 4-quinolone framework, followed by *N*-alkylation to introduce an ethyl substituent and improve solubility. Subsequent transformation of the C-3 carbonyl group was achieved *via* nucleophilic acyl substitution using hydroxylamine generated *in situ* from $NH_2OH \cdot HCl/KOH$, enabling the efficient preparation of seven novel hydroxamic acid derivatives in moderate to good yields (34–83%). All compounds were fully characterized by IR, ^1H and ^{13}C NMR spectroscopy, high-resolution mass spectrometry, and melting point analysis, confirming the successful modification of the heterocyclic core. The synthetic methodology proved to be robust and versatile, allowing access to structurally diverse derivatives from a common intermediate. Preliminary biological evaluation against HSV-1 revealed moderate antiviral activity (3.25–42.27%) combined with low cytotoxicity (CC_{50} > 300 μM), suggesting that the introduction of hydroxamic acid functionality may influence interaction of the quinolone scaffold with biological targets. Overall, this study highlights the potential of C-3 functionalization of the 4-quinolone nucleus as a strategic approach for the generation of new heterocyclic derivatives, providing a valuable platform for further structural optimization and exploration of structure–activity relationships in the search for bioactive compounds.

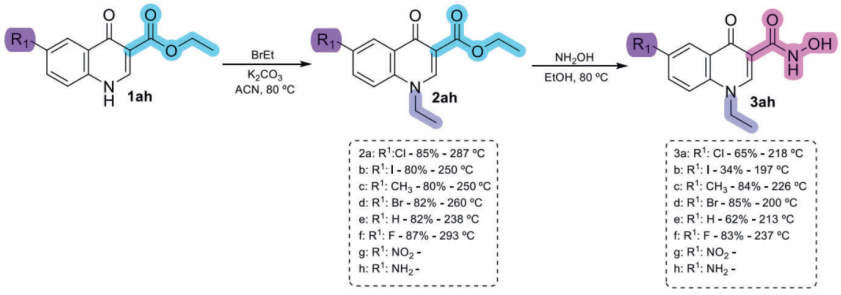

Figure 1: Synthetc methodology for obtaining the results of 4-quinolone-3-hydroxamic acids **3ah**

Acknowledgements: We thank CNPq, FAPERJ, CAPES (Finance Code 0001)

References:

1. BOECHAT, F., et al. 1,2,3-Triazolyl-4-oxoquinolines: A feasible beginning for promising chemical structures to inhibit oseltamivir-resistant influenza A and B viruses. Bioorganic & Medicinal Chemistry, **2015**, v. 23, p. 7777–7784.
2. ANDRADE, J. C. O. Síntese e prospecção antiviral de novos derivados ácidos 4-oxoquinolino-3-hidroxâmicos. **2024**. Dissertação (Mestrado em Química) – Universidade Federal Fluminense.

N-Heterocyclic Peptidomimetics as Cysteine Protease Inhibitors

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Six-membered aromatic N-heterocycles are widely found in bioactive molecules due to their ability to engage in diverse noncovalent interactions and modulate physicochemical properties. As such, they are considered privileged scaffolds in medicinal chemistry.[1,2] In parallel, unnatural amino acids (UAAs) have emerged as valuable tools in drug design, enabling improved metabolic stability, tunable reactivity, and enhanced molecular recognition.[3] Herein, we report the design and synthesis of peptidomimetic compounds incorporating new UAA building blocks bearing pyrimidine and pyrazine moieties. The general structure consists of side chains containing N-heterocycles incorporated into a dipeptidomimetic framework previously explored for cysteine protease inhibition[4] (Figure **1**). Selected analogues were further modified to include trifluoromethyl (CF_3) substituents via reductive amination, aiming to modulate electronic properties and lipophilicity. The synthetic strategy for accessing these UAAs relies on $Pd(AmPhos)_2Cl_2$-catalyzed Negishi cross-coupling reactions, enabling efficient C–C bond formation between organozinc intermediates and (hetero)aryl halides under mild conditions, and providing access to structurally diverse intermediates that were subsequently incorporated into the target peptidomimetics. The resulting compounds were evaluated for inhibitory activity against cruzain (Cz), a key cysteine protease associated with Chagas disease, as well as against human cathepsin L (hCatL), a cysteine protease involved in SARS-CoV-2 entry into host cells. Initial biochemical data indicate that the incorporation of these UAAs enhances inhibitory affinity and may contribute to improved selectivity and target interactions. The obtained compounds showed promising activity, with several analogues exhibiting pK_i values above 9.0, supporting their potential as cysteine protease inhibitors suitable for cell-based assays.

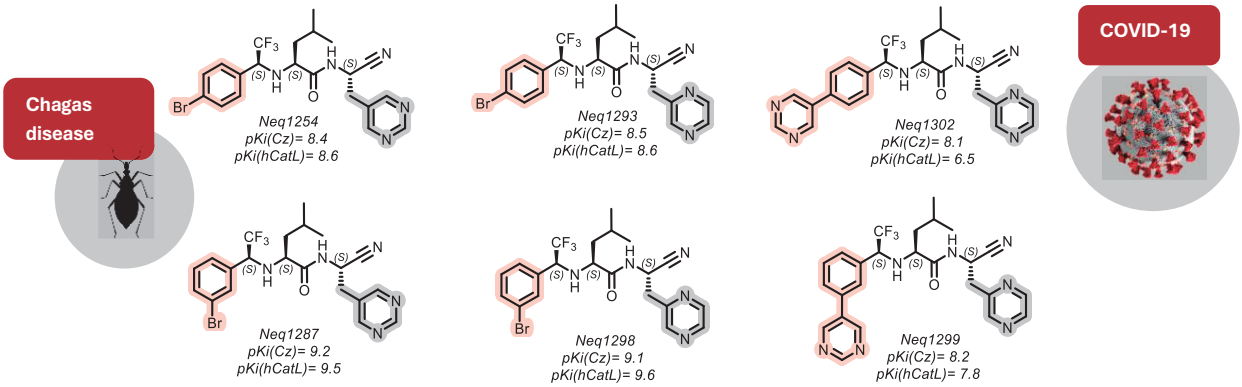

Figure 1: Design of N-heterocycles peptidomimetics incorporating unnatural amino acids and their biological targets.

Acknowledgements: We thank the University of São Paulo for institutional support, as well as FAPESP (São Paulo Research Foundation, PhD grant #2025/16319-3 and FAPESP grant #2024/10359-0 for financial support. We also thank all collaborators involved in this work.

References:

1. Barbosa, P. L.; Imperatori, A.; Gomes, P. L. A.; Batalha, P. N.; Muri, E. M. F.; Fiorot, R. G. *Tetrahedron* 2026, 195, 135240.
2. Marshall, C. M.; Federice, J. G.; Bell, C. N.; Cox, P. B.; Njardarson, J. T. *J. Med. Chem*. 2024.
3. Blaskovich, M. A. T. *J. Med. Chem*. 2016.
4. Cianni, L.; Rocho, F. D. R.; Rosini, F.; Bonatto, V.; Ribeiro, J. F. R.; Lameira, J.; Leitão, A.; Shamim, A.; Montanari, C. A. *Bioorg. Chem*. 2020, 101, 104039.

Synthesis of 1,2,3-triazoles from enantioenriched intermediates by enzymatic kinetic resolution

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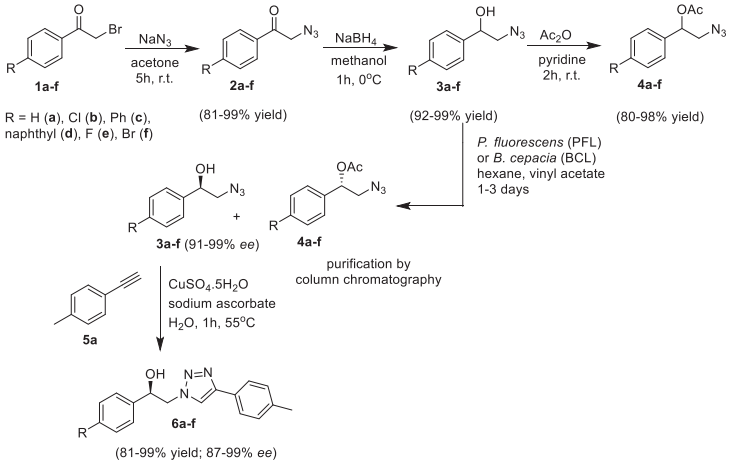
In this study, six 2-azido-1-phenylethanones (**2a-2f**) were synthesized from commercial 2-bromo-1-phenylethanones (**1a-1f**) and sodium azide, with yields of 81-99%. Subsequently, (±)-2-azido-1-phenylethanols (**3a-3f**) were synthesized from the reduction of azidoketones (**2a-2f**) with sodium borohydride, with yields of 92-99%. The compounds were characterized by NMR, IR, and melting point. Racemic acetates (**4a-4f**) were synthesized from azido-alcohols (**3a-3f**) with acetic anhydride and pyridine, with yields of 80-98%. Subsequently, the (±)-2-azido-1-phenylethanols (**3b-3f**) and racemic acetates (**4b-4f**) were analyzed by HPLC-UV/Vis on a chiral AS-H column. Compounds **3a** and **4a**, in turn, were analyzed on a chiral OD-H column. The racemic azido-alcohols (**3a-3f**) were subjected to Enzymatic Kinetic Resolution with *Pseudomonas fluorescens* (PFL) and *Burkholderia cepacia* (BCL) lipases in hexane (1-3 days), and the products were obtained in enantiomerically enriched form and purified by chromatography.[1] Enriched azido-alcohols (**3a-3f,** 91-99% *ee*) were used for the synthesis of enriched β-hydroxy-1,2,3-triazoles (**6a-6f**) via a Cu(I)-catalyzed 1,3-dipolar cycloaddition click reaction.[2] Racemic compounds (**6a-6f**) were also synthesized under the same reaction conditions starting from racemic azido-alcohols (**3a-3f**) to be used as standards in chromatographic separations (UV/Vis HPLC) using a chiral column (AS-H or OD-H). The absolute configurations of compounds (**3a-3f**) and (**4a-4f**) were obtained by measuring the optical rotations using a polarimeter.



Scheme 1: Steps in the reactions for the synthesis of enantiomerically pure or enriched hydroxy-1,2,3-triazole compounds.

Acknowledgements: The authors thank FAPESP and CNPq for the grants and financial support for the development of this research.

References:

1. Rocha, L. C.; Rosset, I. G.; Melgar, G. Z.; Raminelli, C.; Porto, A. L. M., Jeller. A. H. *J. Braz. Chem. Soc.,* **2013,** *24*,1427.
2. Zanin, L. L.; Jimenez, D. E. Q.; Birolli, W. G.; Venâncio, T.; Valdes, T. A.; Leitão, A.; Porto, A. L. M. *Curr. Bioact.Compd.*, **2021**, *17*, 1.

Exploring Heterocyclic Chemical Space from Brazilian Biodiversity: ADMET Driven Multi-Parameter Optimization for Virtual Screening of Antifungal Candidates

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Fungal infections are an increasing global health concern, particularly among immunocompromised patients, and are associated with approximately 3.8 million deaths annually, while treatment options remain limited and resistance to current antifungal agents (e.g., *Candida albicans* resistance to fluconazole, amphotericin B, and caspofungin) continues to rise, underscoring the need for compounds with new mechanisms of action. In this context, Brazilian biodiversity offers a rich source of chemical diversity. This study explored the heterocyclic chemical space of the Brazilian Natural Products Database (BRNPDB) through an ADMET-driven multi-parameter optimization strategy. A dataset of 9,865 compounds was processed using Python (Anaconda/Spyder) and the RDKit toolkit, yielding 4,983 heterocyclic structures, which were filtered according to ADMET criteria (MW 200–600 Da, logP ≤ 5, HBD ≤ 5, HBA ≤ 10, TPSA < 140 Å²) and structural toxicity alerts, encoded with Morgan fingerprints, and projected into chemical space using t-SNE (Figure 1A), resulting in 1,371 compounds selected for virtual screening. Molecular docking was carried out with GOLD with the validated ERG10 target (PDB ID: 6L2C), an enzyme involved in ergosterol biosynthesis. The analysis revealed marked structural diversity and progressive refinement following ADMET-guided filtering, while differences in physicochemical properties, particularly TPSA, hydrogen bond donation, and logP, suggested distinct pharmacokinetic profiles across classes such as alkaloids, polyketides, flavonoids, and phenylpropanoids (Figure 1B). Docking indicated key interactions within the active site, including hydrogen bonds, hydrophobic contacts, and π-stacking. Model performance assessed by k-fold cross-validation showed strong predictive ability (ROC-AUC = 0.915), indicating that molecular descriptors and fingerprints capture structural features associated with docking scores, while the F1-score (0.605) suggests that high-affinity compounds form a distinct subset within the chemical space, further supported by their clustering in specific regions. Together, these results show that combining chemical space exploration with ADMET-guided optimization enables the identification of promising antifungal candidates, selected for subsequent in vitro and in vivo validation.

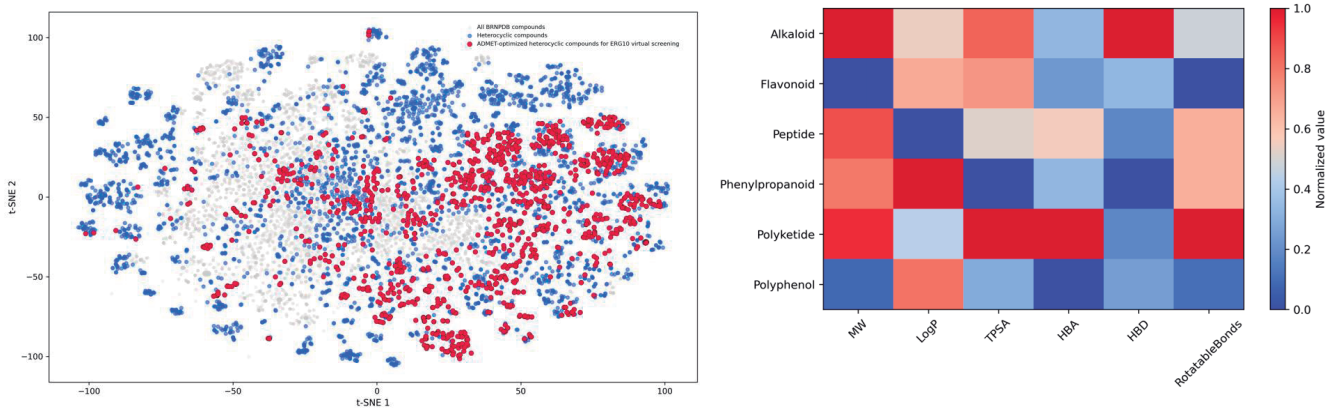

Figure 1: (A) Heterocyclic Chemical Space of Brazilian Biodiversity; (B) ADME profile in different chemical classes of candidates

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References

1. Denning D.W. Global incidence and mortality of severe fungal disease. The Lancet Infectious Diseases. 2024, 24(7), e428-e438.
2. Zhang Y.; Wei W.; Fan J.; Jin C.; Lu L.; Fang W. Aspergillus fumigatus mitochondrial acetyl coenzyme A acetyltransferase as an antifungal target. Appl Environ Microbiol, 2020, 86(7): e02986-19.

Di-Fluoroalkylated Pyrazolo[1,5-*a*]pyrimidines: Three-step Synthesis and BSA Binding Profiling

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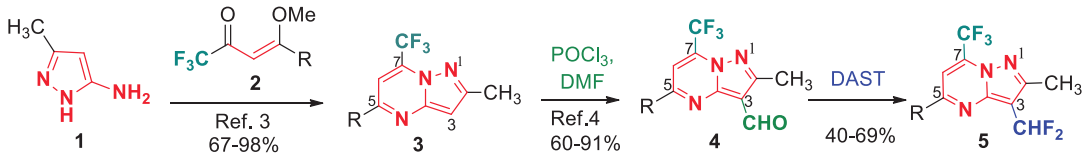
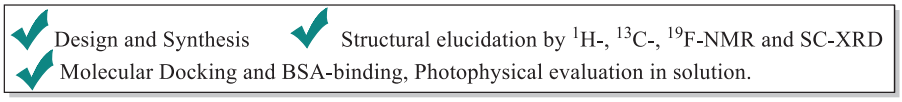
The pyrazolo[1,5-*a*]pyrimidine scaffold, a purine analog, has attracted considerable attention due to its biological activity and photophysical properties[1]. The incorporation of fluorine atoms or fluoroalkyl groups into organic molecules is known to significantly modulate their physicochemical, pharmacokinetic, and pharmacodynamic properties[2]. Given the relevance of fluorinated pyrazolo[1,5-*a*]pyrimidine derivatives in medicinal and photophysical applications, our research group has focused on investigating their interactions with plasma proteins, particularly bovine serum albumin (BSA).
A novel series of six 5-aryl(heteroaryl)-3-difluoromethyl-7-(trifluoromethyl)-2-methylpyrazolo[1,5-*a*]pyrimidine derivatives (**5**) was synthesized through a sequential three-step approach. The synthetic route started from a [3+3] cyclocondensation reaction of selected 4-methoxy-4-aryl(heteroaryl)-1,1,1-trifluorobut-3-en-2-ones (**2**) with 5-amino-3-methyl-1*H*-pyrazole (**1**), yielding 5-aryl(heteroaryl)-2-methyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidines (**3**). In a second step, a Vilsmeier–Haack formylation reaction functionalized the C-3 position of compounds **3**, affording the corresponding 3-formyl derivatives (**4**). Subsequently, difluorination of aldehydes (**4**) using diethylaminosulfur trifluoride (DAST) converted the CHO group into the CHF_2 moiety (Scheme 1). Furthermore, molecular docking simulations were performed and predicted that the substitution of the aldehyde by the difluoromethyl group did not significantly alter the molecular conformations. Finally, the interactions of series **4** and **5** with BSA, show the best results were obtained with the aldehyde derivatives **4e** and **4f**, as well as with the CHF_2-substituted heterocycles, **5d** and **5f**, where the **5d** derivative showed the best interaction with albumin site III.



R= Ph (**a**); 4-$NO_2C_6H_4$ (**b**); 4-FC_6H_4 (**c**); 4-BrC_6H_4 (**d**); 2-thienyl (**e**); 1-naphthyl (**f**); 4-MeC_6H_4 (**g**); 4-$OMeC_6H_4$ (**h**)



Scheme 1: General view and scope of the present study.

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References:

1. Rammohan A.; Nagajyothi P.C.; Zyryanov G.V.; Prasad P.D.; Shim J. Dyes Pigm. **2025,** 241, 112896.
2. Banks R. E.; Smart B. E.; and Tatlow J. C. Organofluorine Chemstry: Principles and Commercial Applications. New York, **1994**.
3. Stefanello F.S.; Vieira J.C.B.; Araújo J.N.; Souza V.B.; Frizzo C.P.; Martins M.A.P.; Zanatta N.; Iglesias B.A.; Bonacorso H.G. Photochem **2022**, 2, 345–357.
4. Araújo J.N.; Stefanello F.S.; Machado É.O.T.; Luz F.M.; Gritzenco F.; Nogara P.A.; Martins M.A.P.; N. Zanatta, Deflon V.; Iglesias B.A.; Bonacorso H.G. J. Photochem. Photobiol. A Chem. **2026,** 475, 117024.

Synthesis and stability tests of decahydroacridines

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Multicomponent reactions (MCRs) are a versatile and efficient way to obtain complex and bioactive molecules, often showing higher yields when compared to linear and convergent methodologies.[1]
Among the heterocyclic molecules that can be obtained through MCRs are the decahydroacridines, a class of compounds with a variety of biological and pharmaceutical applications. These molecules can be obtained by mixing cyclohexane-1,3-dione, benzaldehyde and ammonium acetate in a single reaction flask, using ethanol under reflux as the solvent. However, the contact of the final product with oxygen can initiate an oxydation process of the central ring (Figure 1), which makes it necessary to understand the stability of these compounds when applied in the pharmaceutical industry.[2]
With this objective, the synthesized molecule was subjected to severe conditions to evaluate its resistance to degradation. Tests were carried out at high temperatura (150ºC) for 72h, with samples collected every 24h, as well as exposure to ultraviolet radiation under acidic, neutral and basic conditions for 12h, with sampling at 1, 2, 3, 6, 9 and 12h.
The synthesized molecule was characterized by ^{1}H NMR, while the degradation analyses were performed using ultraviolet spectroscopy.
It was observed that exposure to high temperature did not induce oxidative processes in the sample. When exposed to ultraviolet radiation, no changes were observed under neutral conditions, whereas in acidic and basic media, oxidation of the molecule is observed.
This is an ongoing work and further testing is necessary to deepen the understanding of the degradation profile of the molecule.

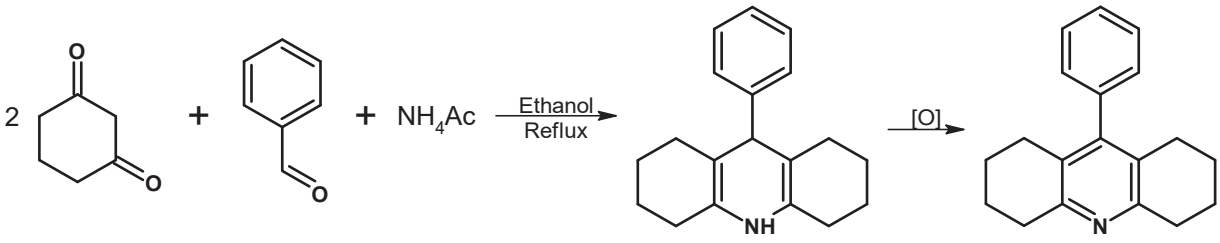

Figure 1: Synthesis and oxidation of decahydroacridine

Acknowledgements: We thank FAPEMIG, CNPq, CAPES and UFLA.

References:

1. Ranjbar, S.; Najmeh, E.; Firuzi, O.; Khoshneviszadeh, M.; Miri, R. *Mol Divers.* **2019**, *23*, 471-508.
2. a) Kaur, R.; Chaudhary, S.; Kumar, K.; Gupta, M. K.; Rawal, R. K. *European Journal of Medicinal Chemistry*, 2017, 132, 108-134.
b) De Alvarenga, B. R.; Carneiro, R. L. *Molecules*, 2019, 24, 3804.

Selenium-functionalized pyrazoles as promising antiviral agents against ZIKV and MAYV

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Arboviroses represents a major group of emerging diseases that recurrently threaten global health[1]. Thus, Zika (ZIKV) and Mayaro (MAYV) have emerged primarily due to negligence that disproportionately impacts vulnerable populations. This gap necessitates the discovery of novel bioactive scaffolds, where the combination of organoselenium compounds with heterocyclic frameworks such as pyrazoles can represent a promising key for the development of antiviral agents[2]. Drawing inspiration from a recently documented one-pot selenium functionalization of pyrazoles[3], this research evaluates the inhibitory potential of these synthesized analogs against ZIKV and MAYV. Compound **9n** stood out due to their superior balance between potency (EC_{50} = 1.3 μM) and low cytotoxicity (CC_{50} = 403 μM), showing strong antiviral and virucidal activity against ZIKV, inhibition of MAYV adsorption, and a favorable selectivity index. *In silico* ADMET analysis indicated suitable drug-like properties, including high gastrointestinal absorption and, in most cases, blood-brain barrier permeability. PASS predictions suggested chemoprotective, redox-related, and anti-inflammatory activities, along with moderate potencial to interfere with viral replication. Overall, results support a multifactorial antiviral mechanism involving redox modulation and direct viral inhibition, highlighting compound **9n** as a promising candidate for futher development.

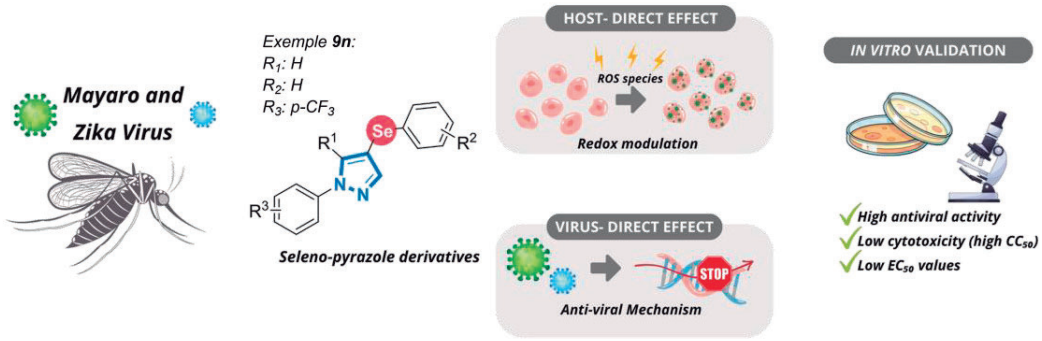

Figure 1: Activity of 4-selanylpyrazoles against Arboviruses.

Acknowledgements: We thank UFF, CNPq, CAPES and FAPERJ.

References:

1. C. H. Calisher, N. Karabatsos, Arbovirus serogroups: definition and geographic distribution, in: T. P. Monath (Ed.), The Arboviruses: Epidemiology and Ecology, CRC Press (2020) 19–58.
2. V.K. Jain, K.I. Priyadarsini, Selenium compounds as promising antiviral agents, New J. Chem. 48 (2024) 6534–6552.
3. Peglow, T. J.; Thomaz, J. P. S. S. C.; Gomes, L. S.; Nascimento, V. Potassium Persulfate Promoted the One-Pot and Selective Se-Functionalization of Pyrazoles under Acidic Conditions. *ACS Omega* **2024**, *9* (52), 51295–51305.

Synthesis of Selenated Chromenes via Electrochemical Cyclization of Propargylic Ethers

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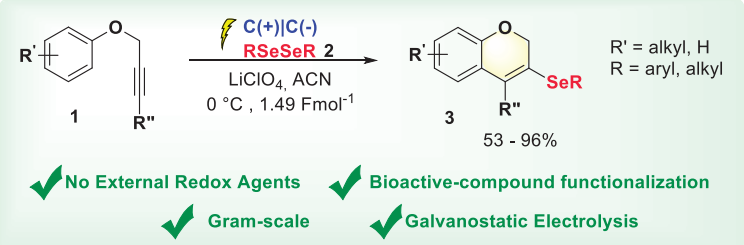
Chromenes constitute an important class of oxygen-containing heterocycles widely found in numerous natural products and biologically active molecules. Compounds containing the chromene core have attracted significant attention due to their broad range of biological activities, including anticancer, antimicrobial, antiviral, anti-inflammatory, and antioxidant properties.[1] These features have driven the development of synthetic strategies for the synthesis and functionalization of chromene derivatives.

Additionally, synthetic methods for the incorporation of selenium into organic cores are a well-established strategy to enhance biological activity, largely due to its distinctive redox properties.[2] However, the use of traditional selenation reagents, such as selenols (RSeH) or selenenyl bromides (RSeBr), is often limited by their high toxicity and low stability.

In line with the pursuit of more sustainable and less toxic methodologies, organic electrosynthesis has emerged as a robust and environmentally benign approach to perform chemical transformations.[3] In this context, we propose the synthesis of selenated chromenes via electrochemical cyclization of propargylic ethers, employing low-potential electric current and eliminating the need for external oxidizing or reducing agents.

The optimized reaction conditions for the electrochemical cyclization of propargylic ether derivatives (**1**) with diphenyl diselenide (**2**) were developed by using an undivided cell equipped with graphite electrodes under constant current (10 mA), using acetonitrile as solvent, and lithium perchlorate as supporting electrolyte. The transformation was developed at 0°C to afford the corresponding selenated chromenes (**3**) in yields of up to 96% (Scheme 1).



Scheme 1. Selenated Chromenes via Electrochemical Cyclization.

Acknowledgements: The authors gratefully acknowledge the financial support from CNPq (G.M.M., F. de L., Process nº 446457/2024-8), FAPESP (K.T.O., Grant n° 2025/14388-8), and FAPEMIG (P.P.C., Grant nº APQ 01259/24).

References:

1. Costa M.; Dias T. A.; Brito A.; Proença F. *Eur. J. Med. Chem.* **2016**, *123*, 487-507.
2. a) Nogueira C. W.; Zeni G.; Rocha J. B. T.; *Chem. Rev.* **2004**,*104*, 6255−6285. b) Gallo-Rodríguez C.; Rodríguez J. B.; *ChemMedChem* **2024**, *19*. e202400063.
3. a) Ma Y. T.; Liu M. C.; Zhou Y. B.; Wu H. Y.; *Adv. Synth. Catal*. **2021**, *363*, 5386–5406. b) Martins G. M.; Meirinho A. G.; Ahmed N.; Braga A. L.; Mendes S. R.; *ChemElectroChem* **2019**, *6*, 1300–1315.

Continuous flow synthesis of buclizine under photo and electrochemical conditions

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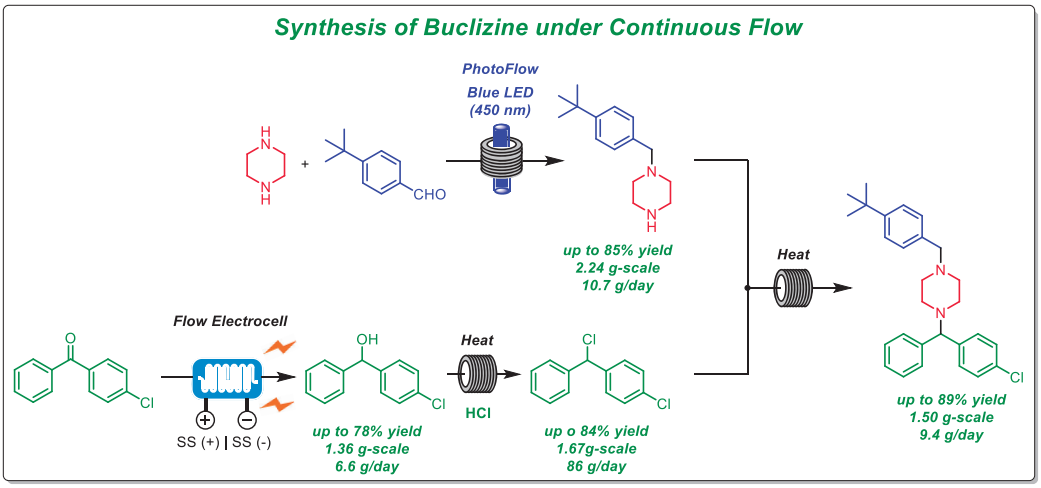
Buclizine is an antihistaminic and antiemetic drug present as the API in numerous medicines. The use of this compound was approved by the FDA (Food and Drug Administration) in 1957, and nowadays, this API is also repositioned as an appetite stimulator. Structurally, buclizine consists of a central piperazine core, which is present in various pharmaceutical formulations. Attached to this core are a *tert*-butylbenzyl group and a diphenylmethyl group (**Scheme 1**).

In this study, we present the gram-scale synthesis of the API buclizine enabled by continuous flow technologies, integrating both photochemical and electrochemical strategies. Starting from the commercially available and inexpensive building blocks (4-(*tert*-butyl)benzaldehyde, piperazine, and 4-chlorobenzophenone), we utilized a photocatalytic reductive amination and an electrochemical reduction to assemble the key intermediates for the final nucleophilic substitution. In our approach, continuous flow conditions were successfully implemented across all the reaction steps, and this methodology afforded significant overall yields while ensuring enhanced safety, straightforward scalability, shorter reaction times, and reduced solvent consumption, thus demonstrating the robustness of continuous flow technologies for the synthesis of high-value-added APIs.[1]



Scheme 1: Continuous flow protocol for the synthesis of Buclizine.[1]

Acknowledgements: We thank the São Paulo Research Foundation FAPESP (grants 2023/04020-8, 2025/14388-8 and T.O.R. fellowship 2024/07235-8), CNPq (K.T.O. research fellowship 3033333/2022-7), and CAPES Financial CODE 001.

References:

[1] Ramos, T. O.; Brocksom, T. J.; Oliveira, K. T. *Tetrahedron*, **2026**, 195, 135241

Multicomponent synthesis of [3,2-c]thienocoumarins and evaluation of their activity against *Mycobacterium tuberculosis*

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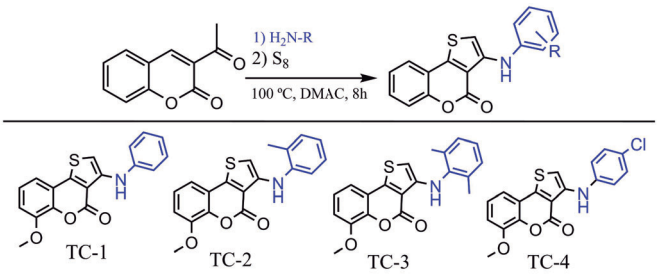
Tuberculosis isthe leading cause of death among the infectious diseases, with an estimated 1.3 million deaths worldwide, surpassing COVID-19 and HIV [Trajman, 2025]. Approximately 10.6 million cases were reported in 2023, including both diagnosed and undiagnosed cases. Moreover, 275 thousand people were diagnosed with drug-resistant tuberculosis, highlighting the urgent need for new drugs and treatments. Coumarins are naturally occurring natural products abundant in medicinal plants. These phenylpropanoids are widely explored due to their importance in biological systems [Gupta, 2023]. Recent studies have shown that triazole and thiazole derivatives exhibit promising minimum inhibitory concentrations (MICs) of 100 μM and 60 μM, respectively.Therefore, a multicomponent synthesis will be employed to access [3,2-c]thienocoumarins, aiming to evaluate their inhibitory activity against *Mycobacterium tuberculosis*.

Using the Farapjour method, we were able to obtain four analogs (this research is ongoing), as outlined in Scheme 1. These scaffolds are of interest due to their potential biological activity and structural versatility. Compound TC-1 is the only derivative previously reported in the literature and was used as a reference for comparison. The reaction employing heteroaromatic arylamines was not successful under the tested conditions, possibly due to electronic or steric effects. Nevertheless, new arylamines are being explored to expand the scope of the reaction and improve its applicability. The yields range from 8% to 31%, which are lower than those reported in the literature. We are currently investigating the cause.



Scheme 1: Synthesis procedure and obtained scaffolds.

The biological assays are being conducted in the Department of Pharmacology, the method for inhibition evaluation is Resazurin Microtiter Assay, and the expected date for the results is May 5. We will continue synthesizing compounds to expand the scope, and once all reactions are completed, if an active compound is identified, the final step will be to understand its mechanism of inhibition in the pathogen.

Acknowledgements: We would like to thank UFSC, CAPES, CNPq and ISHC.

References:

1. Trajman, A.; Campbell, J. R.; Kunor, T.; Ruslami, R.; Amanullah, F.; Behr, M. A.; et al. The Lancet **2025**, 405, 850.
2. Gupta, V.; Ambatwar, R.; Bhanwala, N.; Khatik, G. L. *Curr. Top. Med. Chem.* **2023**, *23*, 1489–1502.
3. Farajpour, B.; Heydarzadeh, R.; Hussain, F. H. S.; Notash, B.; Mirzaei, P.; Shiri, M. *J. Org. Chem.* **2024**, *89*, *Issue* 7.
4. Palomino, J.-C.; Martin, A.; Camacho, M.; et al. Antimicrob. Agents Chemother. **2002**, 46, 2720.

Two-step Electrochemical Synthesis of Glibenclamide

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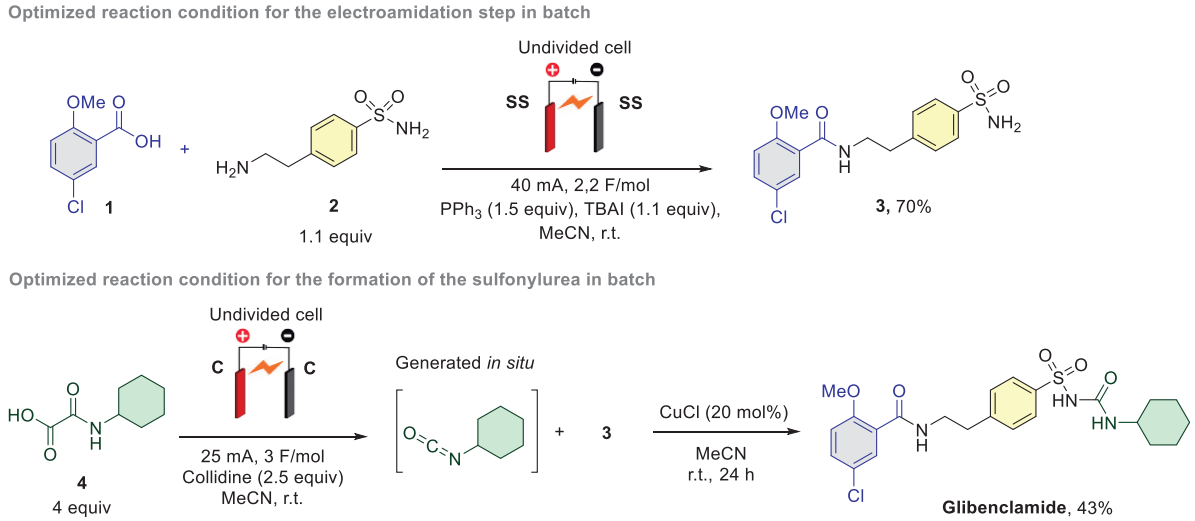
According to the International Diabetes Federation (IDF), approximately 415 million adults aged 20 to 79 years worldwide were affected by diabetes mellitus in 2015. Estimates suggest that this number will rise to more than 640 million by 2040, making diabetes mellitus (DM), particularly type 2 diabetes, a major global public health concern.[1] Glibenclamide, an active pharmaceutical ingredient (API) for medicines that treat DM, was developed by Pfizer and Remedy Pharmaceuticals Inc. and approved by FDA in 1984.[2] It is one of the sulfonylureas available through Brazil's universal public healthcare system (SUS), and is included in the emergency medication kit for public calamity situations, according to regulations of the Brazilian Ministry of Health.

Although several strategies have been reported for its synthesis, most rely on extensive routes, long reaction times, the direct handling of highly toxic reagents, and often expensive starting materials.[3] In this context, we have developed an innovative route to glibenclamide based on a two-step protocol consisting of an electroamidation followed by addition to the corresponding isocyanate, also generated *in situ* by electrosynthesis (Scheme 1). After optimizations, starting from the commercially available carboxylic acid **1** and amine **2**, the intermediate **3** was obtained in 70% yield in batch conditions. In the second step, an *in situ* protocol for the generation of cyclohexyl isocyanate from the corresponding oxamic acid **4** was applied, which, upon reaction with intermediate **3**, afforded glibenclamide in 43% yield. The yields of batch conditions are under final investigation, and we intend to transpose both steps to continuous-flow conditions, in order to improve the reaction conditions, yields, sustainability and scalability.



Scheme 1: Glibenclamide synthesis under batch electrochemical conditions.

Acknowledgements: The authors wish to acknowledge São Paulo State Research Foundation - FAPESP for financial support to K.T.O. (2025/14388-8) and fellowship to M.P.J. (2025/002014-6). We also thank the National Council for Scientific and Technological Development (CNPq) for a research productivity fellowship to K.T.O (303333/2022-7) and the Coordination for the Improvement of Higher Education Personnel (CAPES - Financial Code 001).

References:

1. Zheng Y.; Ley S. H.; Hu F. B. *Nat. Rev. Endocrinol.* **2018**, 14, 88.
2. Guo Y.-Y.; Zhang J.-Y.; Sun J.-F.; Gao H. *Eur. J. Med. Chem.* **2024**, 267, 116185.
3. a) Sagandira C. R.; Khasipo A. Z.; Watts P. *Chem. -Eur. J.* **2021**, 27, 16028. b) De Ventura T.; Zanirato V. *Eur. J. Org. Chem.* **2021**, 1201.

Design of Experiments-Guided Optimization of Midazolam Precursor Oxidative Aromatization under Continuous Flow

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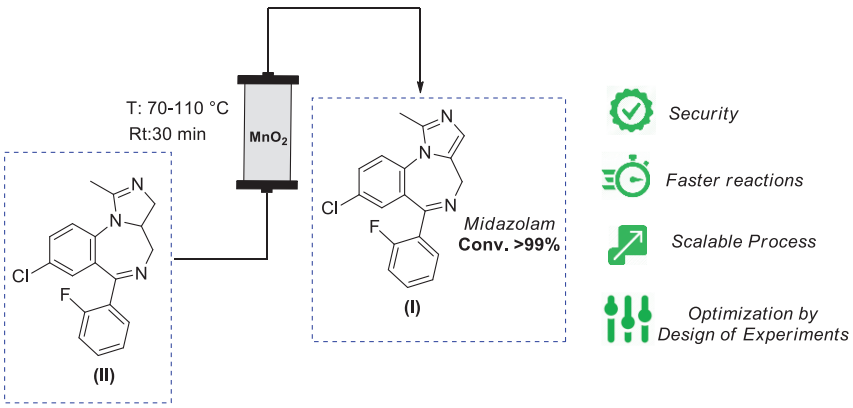
Midazolam (I) is a benzodiazepine derivative widely employed as a sedative, anxiolytic, and anesthetic induction agent.[1] Its conventional synthesis involves construction of the 1,4-benzodiazepine core, followed by a key oxidative aromatization step that provides the stability and bioactivity required for the final active pharmaceutical ingredient.[1–3] In this work, a continuous-flow process for the oxidative aromatization of the non-aromatic precursor of midazolam (II) was developed using a packed-bed reactor containing Manganese dioxide (MnO_2) as a heterogeneous oxidizing agent.[4] A process optimization was development applying a full factorial 2^3 design of experiments (DoE) and the evaluating variables were: substrate concentration (0.017–0.025 g mL^{-1}); temperature (70–110 °C); MnO_2 mass (4–6 g), at a fixed residence time of 30 min. The conversion was determined by HPLC-PDA and NMR spectroscopy. All investigated variables showed statistically significant effects on the process, with temperature being the most influential factor. Under the optimized conditions (0.017 g mL^{-1} substrate concentration, 110 °C, 6 g MnO_2), conversions higher than 99% were achieved with a residence time of only 30 min. Compared with the corresponding batch process (97% conversion in 12 h), the continuous method provides higher productivity, shorter reaction times, and reduced waste generation.



Scheme: Reactional scheme for base Midazolam obtention.

Acknowledgements: We thank CAPES, CNPq, FAPERJ, UFRJ, and collaborating institutions for financial support.

Reference:

1. Taghizadeh, M. J. et al. *J. Iran. Chem. Soc.* **2019**, *16*, 785–794.
2. Wang, Y.-Q. et al. *Org. Process Res. Dev.* **2023**, *27*, 2374–2384.
3. Javad, M. and Reza, G. *Iran. J. Chem. Chem. Eng.* **2022**, *41*, 853 – 865.
4. Zhao, J. et al. *Sci. Total Environ.* **2021**, *753*, 141835.

Visible-Light Photocatalytic Oxidative Dehydrogenation toward Midazolam under Continuous Flow

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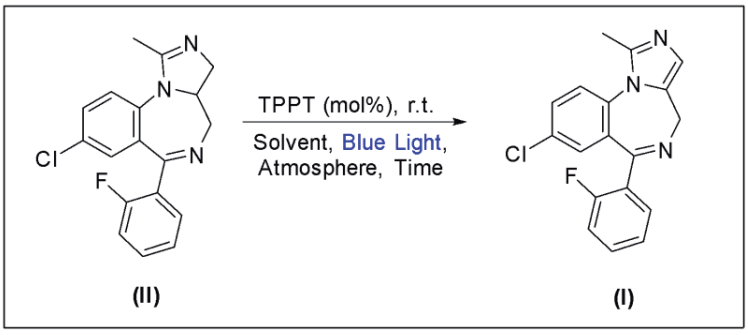
Midazolam (**I**) is a benzodiazepine widely used in clinical practice, whose pharmacological activity depends on the presence of a conjugated heteroaromatic system. The final step of its synthesis involves the oxidative dehydrogenation of a non-aromatic intermediate, which is critical for obtaining the active compound.[1] Conventional methods employ stoichiometric oxidants, such as manganese dioxide and permanganates, which present limitations related to waste generation, low sustainability, and the need for additional purification steps.[2] In this context, more sustainable approaches have been investigated, including the use of molecular oxygen and catalytic processes under milder conditions, providing higher selectivity and efficiency.[3] However, the application of this step in continuous flow systems remains limited and highlights a significant gap, representing a major challenge for the implementation of more modern and integrated synthetic routes.[3,4] This work proposes an innovative continuous process for the synthesis of midazolam base (**I**) through photocatalysis-mediated oxidative dehydrogenation under visible light irradiation.[3] The method employs tetrafluoroborate of 2,4,6-triphenylpyrylium (TPPT) as a photocatalyst, capable of promoting electron transfer reactions leading to the formation of the heteroaromatic system (Scheme). The reaction is carried out using an imidazo-benzodiazepine precursor (**II**) under controlled conditions of irradiation, solvent, and reaction atmosphere. The continuous flow strategy provides improved operational control, reduced reaction time, and decreased use of conventional oxidizing agents. Reaction progress was monitored by HPLC, confirming the formation of midazolam base. Although feasibility was demonstrated, the initial results showed low yields and limited purity, indicating the need for optimization of reaction parameters. Nevertheless, this study contributes to the development of more sustainable and efficient synthetic routes, highlighting the potential of photocatalysis in continuous systems for pharmaceutical industry applications. The initial results indicate that photocatalysis constitutes a promising approach for this system, being applied through a continuous flow process. These results demonstrate that optimizing the photocatalytic conditions significantly increases the efficiency of oxidative dehydrogenation, highlighting the feasibility of this new process.



Scheme: Reaction for the synthesis of midazolam base (I) via photocatalysis.

Acknowledgements: We thank CAPES, CNPq, UFRJ and collaborating institutions for financial support.

References:

1. Taghizadeh, M.; Chardolie, E.; Malekpoori, G. R. *Iran. J. Chem. Chem.l Eng.* **2021**, *40*, 1–12.
2. Wang, Q.; Zhang, X.; Han, F.; Liu, J.; Xu, Q. *Chem.Sus.Chem*, **2021**, *14*, 2866–2871.
3. Wang, Z; Fei, G; Shi, S; Liu, M; Li, P; Xie, P. *Mol. Catal.* **2024**, *564*, 114334.
4. Ivanova, M.; Poisson, T.; Jubault, P.; Legros, J. *J. Flow Chem.* **2022**, *12*, 45–56.

Synthesis of Benzoxazoles from Acid Chlorides and o-Aminophenol using Microwave Irradiation

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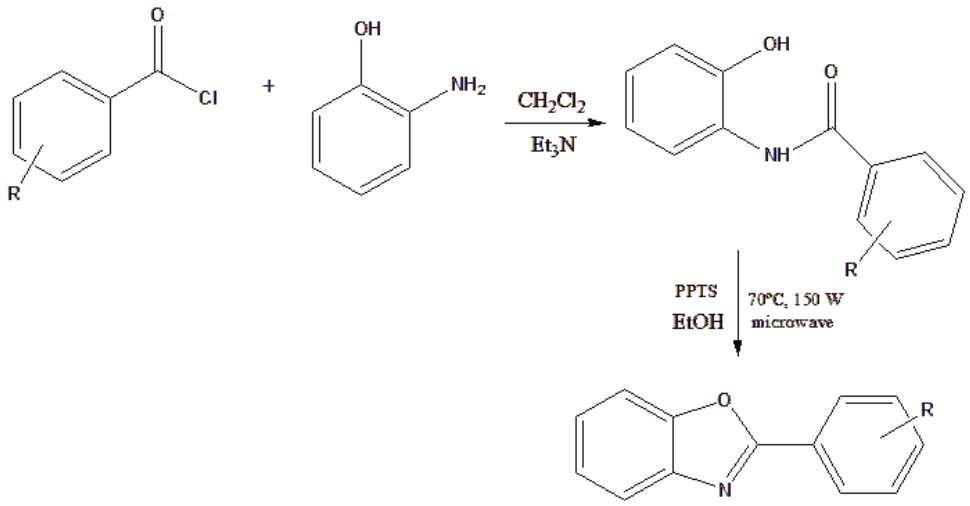
Oxazoles are heterocycles characterized by the presence of oxygen and nitrogen atoms at the 1 and 3 positions of their structure, respectively. The efficient synthesis of oxazoles has been of significant interest, as the oxazole core finds applications in medicine, chemistry, and agriculture.[1] According to Ramos (2024)[2], its presence in various drugs is associated with a wide range of biological responses, including antibiotic, antiviral, antitumoral, and antifungal activities. In this context, benzoxazoles formed by the fusion of an oxazole ring to a benzene ring also stand out, being widely used in biochemical and pharmaceutical derivatives, as well as in several industrial applications.[3]
Therefore, investigating new and efficient synthetic routes is an ongoing target for preparing of such heterocycles.In this sense, the present work describes a study of synthetic pathways for obtaining benzoxazole derivatives from the reaction between acid chlorides and *o*-aminophenol, followed by cycling the benzamide pyridinium *p*-toluenesulfonate (PPTS) as an acid catalyst under microwave irradiation, as illustrated in **Scheme 1**. According to Santos (2021)[4], microwave irradiation technology surpasses conventional heating by offering superior heating rates and the capacity for selective heating, in which energy is absorbed directly by the reagents or solvents without contact with the heat source. Such characteristics result in significant benefits, including increased yields and selectivity, as well as a reduction in thermal decomposition.The synthesized structures were duly confirmed by ^{1}H and ^{13}C NMR spectroscopic techniques.



Scheme 1:Formation of 2-substituted-benzoxazole

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References:

1. BECHE, Ricardo Ismael et al. Synthesis of functionalized 2-methyloxazoles as building blocks for obtaining heterocycles. **2022**.
2. RAMOS, Giovana da Silva et al. One-pot synthesis of functionalized 2-hydrazono-3-thiazolines from multicomponent reaction followed by rearrangement of 2-substituted oxazoles. **2024**.
3. BANSAL, Shivani. Recent advances in the synthesis of benzoxazole. Mini-Reviews in Organic Chemistry, v. 18, n. 3, p. 383-397, **2021**.
4. SANTOS, Jayne Maria Sabino dos et al. Synthesis of 2-arylquinoline-4-carboxylic acids via Pfitzinger reaction under microwave irradiation. **2021**.

Cu(II)-Mediated Oxidative Cyclization of Azocoumarins to New N^2-1,2,3-Chromenotriazoles

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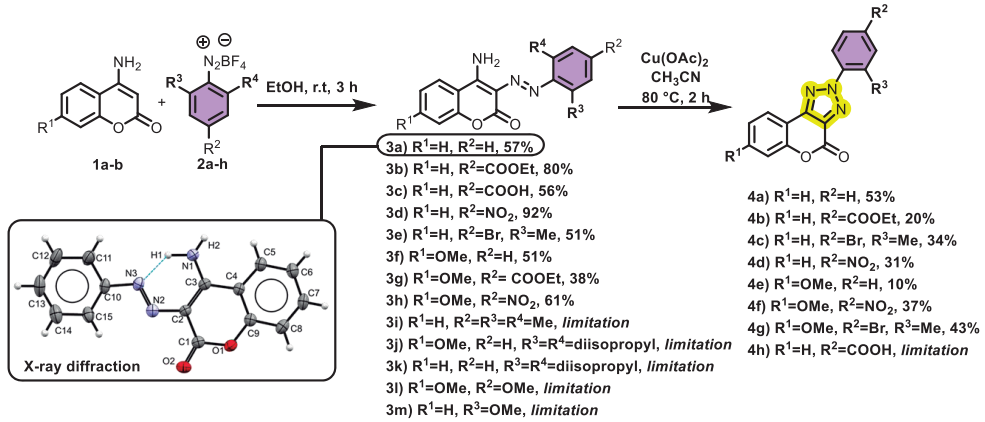
Triazoles are an important class of five-membered aromatic heterocyclic compounds containing three nitrogen atoms, widely explored in medicinal chemistry and materials science.[1] Among their isomers, N^2-1,2,3-triazoles are considerably less common than N^1-1,2,3-triazoles and N^4-1,2,4-triazoles. In parallel, coumarins have been extensively investigated, both in the formation of azo compounds[2a] and in the construction of triazole cores[2b]. However, studies involving N^2-1,2,3-triazole-containing coumarins remain scarce[3], revealing a significant gap in understanding their potential applications. The present work describes the synthesis of azocoumarins (**3a–m**) via diazotization reactions between 4-aminocoumarins (**1a–b**) and diazonium salts (**2a–h**) in ethanol at room temperature for 3 h, followed by Cu(II)-mediated oxidation using $Cu(OAc)_2$ in CH_3CN at 80 °C for 2 h to afford new N^2-1,2,3-chromenotriazoles (**4a–h**). The compounds were characterized by spectroscopic techniques (^1H, ^{13}C, and 2D NMR, FTIR, and HRMS), and structural elucidation was further confirmed by X-ray crystallography of intermediate **3a**, which demonstrated a preference for the enamine tautomer stabilized by hydrogen bonding (Scheme 1).



Scheme 1: Synthesis of chromenonetriazole **4a-h**.

Acknowledgments: We thank CAPES, CNPq, and FAPERJ.

References:

1 a) Gouault, N., Cupif, J. F., Sauleau, A., David, M. *Tetrahedron Lett.*, **2000**, *41*, 7293-7297. b) Oliveira-Campos, A. M., Rodrigues, L. M., Esteves, A. P., Silva, M. E., Sivasubramanian, A., Hrdina, R., Machalicky, O. *Dyes Pigments*, **2010**, *87*, 188-193. c) Mondal, S., Dey, S. *ACS omega*, **2021**, *6*, 27936-27945. d) Kumar, S., Khokra, S. L., Yadav, A. *Future J. Pharm. Sci.*, **2021**, *7*, 106. e) Olomola, T. O., Klein, R., Lobb, K. A., Sayed, Y., Kaye, P. T., *Tetrahedron Lett.*, **2010**, *51*, 6325-6328.

2 a) Evangelista, E., de Carvalho, Y. P., de Jesus, I. S., Rodrigues, M. E. S., Hayashi, E. P., de Andrade, K. N., da SM Forezi, L. *J. Org. Chem.*, **2024**, *90*, 300-308. b) Huang, Y., Zhang, Y., Yuan, Y., Cao, W. *Tetrahedron*, **2015**, *71*, 2124-2133.

3 BAYER AG, HARNISCH HORST DR, VIC-TRIAZOLVERBINDUNGEN, Federal Republic of Germany, DE2300488A1, Publication Jul. 11,**1974**.

Light-Mediated Synthesis of Chalcogen-Decorated 2,3-Dihydrobenzofurans

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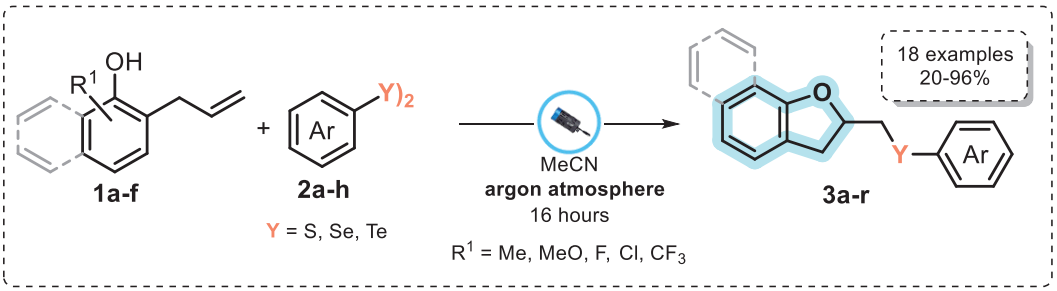
Since the introduction of the 12 Principles of Green Chemistry by Anastas and Warner, the development of sustainable synthetic methodologies has expanded considerably, particularly through the search for alternative energy sources that minimize the need for catalysts and stoichiometric redox agents. In line with Principle #6 (design for energy efficiency), visible-light-mediated reactions have emerged as a powerful and sustainable tool for organic transformations under mild conditions.[1] In parallel, 2,3-dihydrobenzofurans constitute an important class of heterocycles, serving as building blocks for the synthesis of complex molecules and exhibiting great potential for biological application.[2] In this context, we report hereina new methodology for the synthesis of chalcogen-decorated 2,3-dihydrobenzofurans **3** under blue-light irradiation, without the need for photocatalysts, oxidants, or additives.

The methodology developed in this work consists of the visible-light-mediated reaction between 2-allylphenols **1** and diaryl dichalcogenides **2**. To establish the best reaction conditions, a series of optimization experiments was performed, evaluating the influence of stoichiometry, solvent, reaction time, and light wavelength. The best results were obtained using 0.3 mmol of substrate **1**, 1.3 equivalents of dichalcogenide **2**, and acetonitrile (2.0 mL) as the solvent, under argon atmosphereand blue light irradiation (Kessil PR160L, λ max = 440 nm) for 16 h, affording **3a** in 96% yield (Scheme 1). With the optimized reaction condition in hands, the reaction scope was then explored with substrates bearing electron-donating and electron-withdrawing groups, furnishing a library of 18 derivatives **3a-r**, in yields ranging from 20% to 96%. Control experiments (TEMPO, DPE) and UV–Vis analysis support a radical pathway initiated by direct photolysis of the Se–Se bond, consistent with the lower yields observed for electron-deficient diselenides. The protocol was also scaled up to 3.0 mmol, delivering 3a in 76% yield.

In summary, the protocol reported herein represents an efficient and sustainable alternative for the synthesis of chalcogen-functionalized 2,3-dihydrobenzofurans, aligning with the principles of green chemistry through the use of visible light as the energy source and the complete absence of external oxidants, additives, and metal-based photocatalysts. Instead, the diorganyl dichalcogenide itself acts as the light-absorbing species that initiates the radical pathway. Overall, this work expands the toolkit of light-mediated organochalcogen chemistry and offers a simple, operationally friendly route to bioactive heterocyclic scaffolds.



Scheme 1: Into a reaction vial was added the 2-allylphenol derivative **1a-f** (0.3 mmol), **2a-h** (1.3 equiv, 0.2 mmol), and MeCN (2.0 mL). The resulting mixture was stirred under blue light irradiation (Kessil PR160L, λmax = 440 nm) for 16h.

References:

1. Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. Chemical Reviews 2013, 113 (7), 5322–5363.
2. Chand, K.; Rajeshwari; Hiremathad, A.; Singh, M.; Maria José Santos; Keri, R. S. A Review on Antioxidant Potential of Bioactive Heterocycle Benzofuran: Natural and Synthetic Derivatives. Pharmacological Reports 2017, 69 (2), 281–295.

Photocatalyzed Synthesis of Benzothiazoles Under Continuous-Flow Process Optimization

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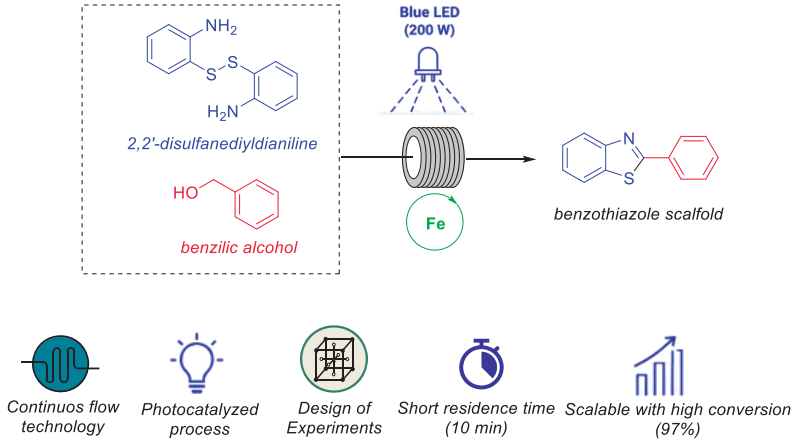
Benzothiazoles are privileged sulfur-containing heterocycles widely present in pharmaceuticals, bioactive compounds, and functional materials. Conventional synthetic approaches to prepare this class of compounds generally rely on oxidative cyclization under harsh conditions and long reaction times in the presence of stoichiometric oxidants. Therefore, the development of sustainable and efficient synthetic routes remains highly desirable.[1,2]

The merger of photochemistry and continuous-flow processing represents an attractive strategy due to improved photon transfer, enhanced safety, precise control of reaction parameters, and facile scalability.[3,4] Herein, we report a photocatalyzed continuous-flow methodology for the synthesis of benzothiazoles from 2-amino(disulfides) and alcohols under blue LEDs irradiation.

Initial transfer of the optimized batch conditions to flow mode revealed a strong influence of lamp power and residence time. Moderate conversions were obtained at 50–100 W (53–58%), while 200 W increased conversion to 70%; higher irradiation (300 W) led to substrate/product degradation. A residence time of 10 min was identified as the best compromise between high conversion and productivity.

To systematically optimize the process, two sequential Design of Experiments (DoE) studies were conducted. The first design delivered 87% conversion using 4 equiv of benzyl alcohol, 20 mol% photocatalyst, and 200 W irradiation. A second expanded DoE identified light intensity as the most influential factor and enabled conversions up to 97% under 8 equiv benzyl alcohol, 30 mol% photocatalyst, and 300 W. Response-surface analysis confirmed a broad high-performance operational region.

These findings demonstrate the potential of integrating photochemistry, continuous-flow technology, and statistical optimization for efficient benzothiazole synthesis, opening perspectives for broader scope and future scale-up studies.



Scheme. Photocatalyzed synthesis of Benzothiazoles.

Acknowledgements: We thank CAPES, CNPq, FAPERJ, FAPERGS, UFRJ, and collaborating institutions for financial support.

References:

(1) Gao, X.; Liu, J.; Zuo, X.; Feng, X.; Gao, Y.. *Molecules* **2020**, *25*, 1675.
(2) Keri, R. S.; Patil, M. R.; Patil, S. A.; Budagumpi, S. *Eur. J. Med. Chem.* **2015**, *89*, 207–251.
(3) Capaldo, L.; Wen, Z.; Noël, T.. *Chem. Sci.* **2023**, *14*, 4230–4247.
(4) Williams, J. D.; Kappe, C. O. *Curr. Opin. Green Sustain. Chem.* **2020**, 25, 100351.

Toward a Scalable Manufacturing Route for Thiamethoxam: Reaction and Crystallization Optimization

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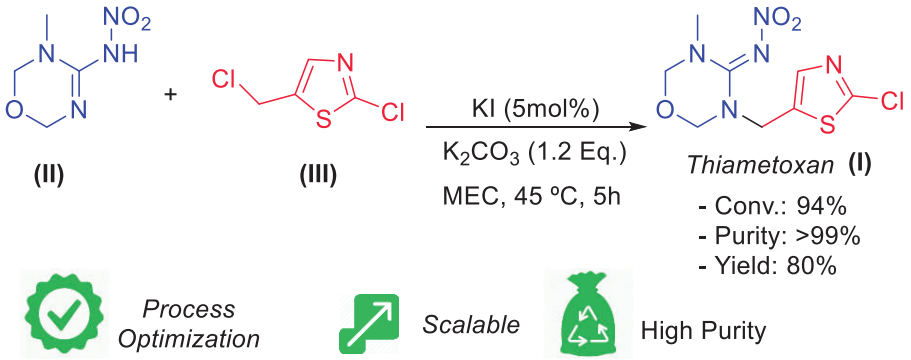
Thiamethoxam (I) is one of the most widely used insecticides in the world, belonging to the neonicotinoid chemical class.[1,2] Introduced to the market in the late 1990s, it revolutionized pest control due to its high efficiency at low doses and its versatility of application. Thiamethoxam is characterized as a synthetic organic compound with a specific molecular formula. It features an oxadiazine ring, which chemically distinguishes it from the first generation of neonicotinoids.Thiamethoxam can be synthesized through an SN2 nucleophilic substitution reaction between the oxadiazine (II) intermediate and thiazole (III) under basic conditions using K_2CO_3, catalyzed by KI.[3] Among the variables investigated, potassium iodide loading proved to be the most critical parameter: increasing the catalyst amount to 5 mol% raised conversion to 94% after 5 h at 45 °C. Kinetic studies also showed that prolonged reaction times reduce selectivity and promote by-product formation, defining an optimal reaction window between 5 and 7 h Product isolation and crystallization were identified as the most critical downstream stages due to significant mass losses during purification. These steps were optimized through solvent screening and crystallization studies. Dichloromethane showed the best performance during filtration and product recovery, while selective washing/crystallization with ethyl acetate provided isolated yields of 78–80 % and final purity of 97–99 %, demonstrating a robust and scalable route to Thiamethoxam. The next stage of development will focus on expanded crystallization screening with alternative solvents to reduce solvent consumption during purification, as well as reaction calorimetry and exothermicity studies to evaluate how temperature deviations influence impurity and by-product formation.



Scheme: Synthesis of thiamethoxam between the oxadiazinic intermediate and the thiazolic derivative, in a basic medium (K_2CO_3) via potassium iodide (KI) catalysis.

Acknowledgements: We thank CAPES, CNPq, UFRJ, and collaborating institutions for financial support.

References:

(1) Maienfisch, P. *Z. Naturforsch. B* **2006**, *61*, 353–359.
(2) Taillebois, E. et al. *Bioorganic & Medicinal Chemistry Letters* **2014**, *24*, 3552–3555.
(3) Ihang, X. et al. CN 106496215 A, March 15, **2017**.

Fluorogenic 7-azidocoumarin and 3/4-azidophthalimide derivatives as indicators of reductase activity in microorganisms

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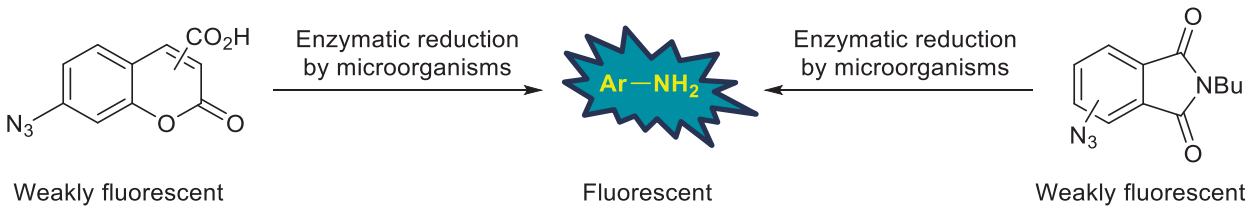
A series of fluorogenic heterocyclic azides were prepared and assessed as reductase substrates across a selection of Gram-negative and Gram-positive microorganisms. The majority of these azides showed similar activity profiles to nitroreductase substrates. Microorganisms that do not produce hydrogen sulfide reduced the azides, indicating reductase activity was not linked to hydrogen sulfide production.



Scheme 1. Detection of reductase activity via azide reduction.

Acknowledgements: We thank bioMérieux SA for generous funding and the EPSRC UK National Mass Spectrometry Facility at Swansea University, UK, for high resolution mass spectra. We also thank Samantha Bowerbank for the HPLC work.

References:

1. V. Chalansonnet, J. Lowe, S. Orenga, J. D. Perry, S. N. Robinson, S. P. Stanforth, H. E. Sykes and T. V. Truong, Bioorg Med Chem Lett, 2019, 29, 2354-2357.
2. M. Cellier, O. J. Fabrega, E. Fazackerley, A. L. James, S. Orenga, J. D. Perry, V. L. Salwatura and S. P. Stanforth, Bioorg Med Chem, 2011, 19, 2903-2910.
3. M. Cellier, A. Gignoux, A. L. James, S. Orenga, J. D. Perry, S. N. Robinson, S. P. Stanforth and G. Turnbull, Bioorg Med Chem Lett, 2015, 25, 5694-5698.
4. N. Velusamy, A. Binoy, K. N. Bobba, D. Nedungadi, N. Mishra and S. Bhuniya, Chem Commun (Camb), 2017, 53, 8802-8805.
5. Y. Kanaoka, A. Kobayashi, E. Sato, H. Nakayama, T. Ueno, D. Muno and T. Sekine, Chem Pharm Bull (Tokyo), 1984, 32, 3926-3933.
6. N. U. Hofsløkken and L. Skattebøl, Acta Chem Scand, 1999, 53, 258-262.
7. L. J. O'Connor, I. N. Mistry, S. L. Collins, L. K. Folkes, G. Brown, S. J. Conway and E. M. Hammond, ACS Cent Sci, 2017, 3, 20-30.
8. RSC Analytical Division Horizon Prize 2022, http://www.rsc.org/prizes-funding/prizes/2022-winners/the-northumbria-sunderland-freeman-biomerieux-collaboration/, (accessed March 2026)
9. CHROMID® Culture Media, https://www.biomerieux.com/us/en/our-offer/clinical-products/chromid-culture-media.html, (accessed March 2026)

Dual-Target Nitroheterocyclic Carbamates as Novel Antileishmanial Agents

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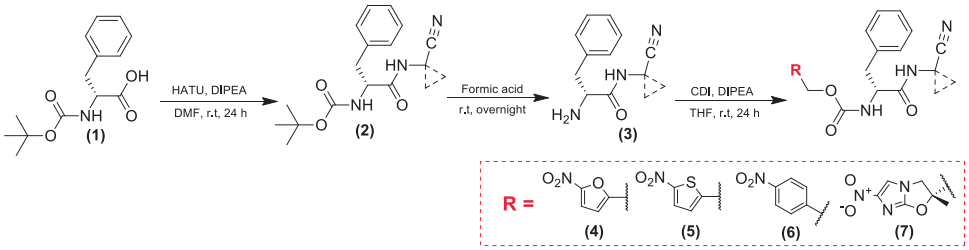
Introduction: Nitroheterocycles comprise a class of compounds with broad application in the treatment of parasitic diseases [1]. Two representative examples of this class are the drugs nifurtimox, a nitrofuran derivative, and benznidazole, a nitroimidazole derivative. The mechanism of action of these molecules involves the bioactivation by nitroreductase enzymes (NTR), which during reduction process of nitro groups yields toxic metabolites that cause parasite death [2,3]. In this work, compounds containing a nitroheterocyclic moiety were designed to achieve a dual mechanism of action targeting nitroreductase (NTR) and the *Leishmania* cysteine protease CPB. Cysteine proteases of *Leishmania* have diverse functions, ranging from macrophage infection to cellular differentiation and the progression of lesions caused by the parasite [4]. In addition, they are involved in the parasite's growth, viability, and pathogenicity [5,6]. To this end, the NTR recognition portion of the molecules were combined with an amino acid substituted with a *warhead* moiety, capable of covalently binding to cysteine residue in CPB. **Methods:** A series of carbamates bearing nitrofuran, nitrothiophene, nitrobenzene, or nitroimidazooxazole moieties, an *L*-phenylalanine portion, and nitrile warheads targeting cysteine residues was designed. Scheme 1 outlines the synthetic route. The first step involved the reaction of Boc-L-phenylalanine (1) with the warhead moiety (2-aminoacetonitrile or 1-aminocyclopropanecarbonitrile) using HATU as a coupling agent and DIPEA as a base, affording intermediate (2) in yields ranging from 37 to 40 %. Subsequently, Boc deprotection was carried out with acetic acid, yielding compound (3), which was neutralized with sodium bicarbonate during liquid–liquid extraction to provide the free amine. This intermediate was then reacted with nitroheterocyclic reagents using carbonyldiimidazole (CDI) and DIPEA, affording the desired carbamate derivatives (4-7). **Results:** Six carbamates were obtained and characterized by NMR and HRMS, with average yields of 20%. These compounds were evaluated against CPB enzyme, with IC_{50} values ranging from 1.38 to 0.39 µM. Cytotoxicity was assessed in murine peritoneal macrophages and all compounds showed CC_{50} values higher than 240 µM. Two compounds were evaluated against *Leishmania amazonensis*, with EC_{50} values of 3.096 µM (SI ~96.89), and 10.247 µM (SI ~ 23.83). **Conclusions:** Results indicate that dual-targeting sign yielded potent in vitro leishmanicidal compounds. Evaluation of the full series will provide valuable insights into the structure–activity relationships of these carbamates.



Scheme 1: Synthetic route for carbamate series.

Acknowledgements: We thank support of FAPESP (financial code: 2024/20579-8), FAPESP (financial code: 2025/17976-8).

References:

1. Santos-Júnior P. F. S.; Silva L. R.; Quintans-Júnior L. J.; Silva-Júnior E. F. Nitro compounds against trypanosomatidae parasites: Heroes or villains? Bioorg. Med. Chem. Lett. ***2022***, *75*, 128930.
2. Wyllie S.; Patterson S.; Fairlamb A. H. Assessing the Essentiality of *Leishmania donovani* Nitroreductase and Its Role in Nitro Drug Activation. Antimicrob. Agents Chemother. ***2013***, *57*, 901–906.
3. Patterson S.; Wyllie S. Nitro drugs for the treatment of trypanosomatid diseases: past, present, and future prospects. Curr. Opin. Chem. Biol. ***2014***, *19*, 1–8.
4. Otto H.; Schirmeister T. Cysteine Proteases and Their Inhibitors. *Chem. Rev.* ***1997***, 97, 133–172.
5. McKerrow J. H.; Engel J. C.; Caffrey C. R. Cysteine protease inhibitors as chemotherapy for parasitic infections. *Bioorg. Med. Chem.* ***1999***, 7, 639–644.
6. Williams R. A.; Tetley L.; Mottram J. C.; Coombs G. H. Cysteine peptidases CPA and CPB are vital for autophagy and differentiation in *Leishmania mexicana*. *Mol. Microbiol.* ***2006***, 61, 655–674.

Design, synthesis, and prodrug optimization of quinolone-based acyclonucleosides: a heterocyclic platform for antiviral drug development

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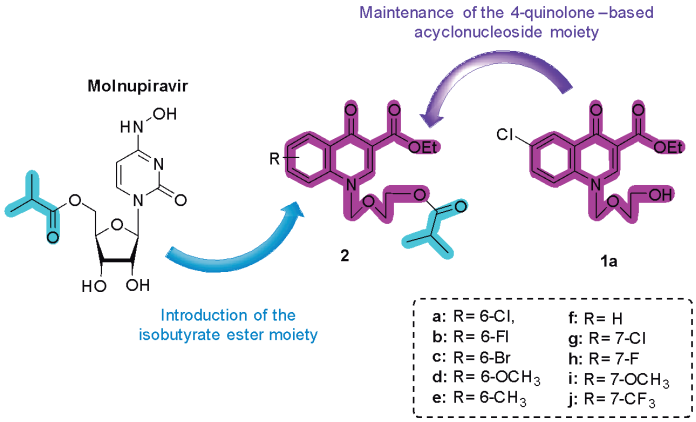
The 4-quinolone nucleus is a privileged scaffold widely explored in medicinal chemistry due to its structural and biological versatility. In this context, the introduction of nucleoside-mimetic motifs into the 4-quinolone framework represents a promising strategy for the development of novel antiviral agents. Herein, we report the design and synthesis of a new series of 4-quinolone-based acyclonucleosides (**1a-j**) and their corresponding isobutyrate prodrugs (**2a-j**), aiming to investigate the impact of esterification on antiviral activity and physicochemical properties (Scheme 1). The synthetic approach involved a one-pot procedure starting from substituted 4-quinolones, including an initial silylation step followed by nucleophilic addition of 1,3-dioxolane to afford the acyclonucleoside derivatives. Subsequent functionalization with isobutyric anhydride afforded the efficient preparation of the corresponding prodrugs in satisfactory yields.



Scheme 1: Synthetic design for the preparation of quinolone-based acyclonucleoside isobutyrates **2**.

All compounds were fully characterized by spectroscopic methods. Their antiviral activity was evaluated against SARS-CoV-2 in HuH-7 and Calu-3 cell lines. Several derivatives exhibited significant inhibition of viral replication, with selected compounds showing ≥ 80% inhibition in both cellular models. Notably, the incorporation of the isobutyrate moiety consistently enhanced antiviral activity, highlighting the relevance of the prodrug strategy in modulating antiviral performance.

Acknowledgements: We thank PPGQ-UFF, CAPES (Finance code 001), FAPERJ and CNPq.

References:

1- Xu, H.; Li, B. e*t al.* Privileged scaffold repurposed: the evolving role of quinolone derivatives in antiviral therapy. *Bioorg Med Chem Lett.*, 2026, 130, 130427
2-Mahajan, S.; Choudhary, S. *et al.* Antiviral strategies targeting host factors and mechanisms obliging +ssRNA viral pathogens. *Bioorg Med Chem*, 2021, 46, 116356.
3-Lucero BD *et al*. Quinolonic acyclovir analogues. *Bioorg Med Chem Lett.*, 2006, 16, 1010-1013.

Synthesis of 1,2,3,4-Tetrahydroquinolines through *N*-Arylation of Adducts of the Ugi 5-Center-4-Components Reaction

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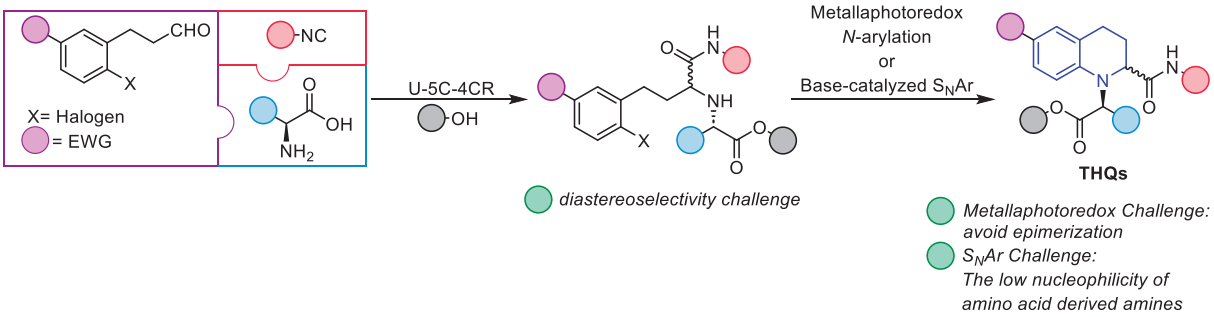
The modular synthesis of 1,2,3,4-tetrahydroquinolines (THQs), alkaloid compounds of significant structural relevance, is highlighted by their presence in bioactive compounds, pharmaceuticals, and natural products, and can be achieved through various synthetic routes with different degrees of substitution.[1] Therefore, the approach described in this project is based on the combination of the Ugi five-center four-component multicomponent reaction, using amino acids as bifunctional reagents, followed by an N-arylation cyclization step. Appropriate selection of multicomponent reaction substrates will provide access to functionalized intermediates suitable for efficient cyclization.
Two distinct methodologies are currently being investigated for the cyclization step. The first approach involves exploring base-catalyzed nucleophilic aromatic substitution (S_NAr) reactions,[2] which have already enabled the synthesis of a glycine-decorated tetrahydroquinoline. The second approach focuses on metallaphotoredox C-N couplings, aiming to expand the scope of THQs obtained from Ugi adducts and to circumvent epimerization issues commonly observed in related transition-metal cross-couplings.[3] Additionally, improvements in the diastereoselectivity of the central Ugi reaction are currently being pursued.



Scheme 1: Exploring the Ugi 5C-4CR *en route* to asymmetric synthesis of Tetrahydroquinolines from amino acids.

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References:

1) Goli, N.; Ummanni, R.; Chandrasekhar, S.; K, T.; Ummanni, R.; Chandrasekhar, S. Expanding the Tetrahydroquinoline Pharmacophore. *Bioorg. Med. Chem. Lett.* **2017**, *27* (8), 1714.
2) Osinubi, A. D.; Izunobi, J. U.; Asekun, O. T.; Familoni, O. B.; Bao, X. Transition Metal-Free, Base-Induced Arylation of Amino Acids: Synthesis of *N* -(Para -Substituted Phenyl)Amino-2-carboxylic Acids. *ChemistrySelect* **2020**, *5* (28), 8644.
3) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116* (19), 12564.

Synthesis of Heterocyclic Unnatural Amino Acids as Building Blocks for Peptidomimetic Inhibitors of Cysteine Proteases

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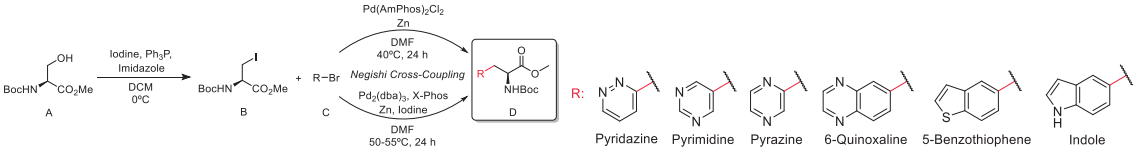
Amino acids are the fundamental monomers of peptides and proteins, featuring a basic structure composed of a central (α) carbon bonded to amino and carboxyl groups, as well as a variable side chain that defines their chemical properties.[1] Although nature predominantly utilizes a set of 20 canonical amino acids, advances in synthetic and medicinal chemistry have expanded the interest in unnatural amino acids (UAAs) due to their ability to modulate metabolic stability, solubility, and lipophilicity.[2] In parallel, compounds containing nitrogen- or sulfur- heterocycles stand out in medicinal chemistry, making them valuable building blocks in the development of UAAs and peptidomimetics with high affinity and selectivity. In this context, cysteine proteases, nucleophilic enzymes essential in various pathological processes, emerge as strategic therapeutic targets, driving the design of new inhibitors based on structurally optimized UAAs.[3]

Therefore, this work aims at the synthesis and development of unnatural amino acids (UAAs) containing different heterocyclic cores, targeting their application as building blocks in peptidomimetic inhibitors of cysteine proteases, such as SARS-CoV-2 M^{pro}, cruzain (Cz), and human cathepsin L (hCatL). The proposed methodology comprises three steps: (i) the synthesis of the precursor *N*-(Boc)-3-iodo-L-alanine methyl ester following a protocol adapted from Atmuri and Lubell (2015)[4]; (ii) the obtainment of UAAs through Negishi cross-coupling based on the protocols of Dachwitz (2021)[5] and Nimje *et al.* (2020)[6]; and (iii) structural characterization. In total, six UAAs containing the heterocycles pyridazine, pyrimidine, pyrazine, quinoxaline, benzothiophene, and indole were synthesized (Scheme 1).



Scheme 1: Synthetic route for the obtainment of heterocyclic unnatural amino acids (UAAs) via Negishi cross-coupling. Synthesis of the iodinated precursor (B) from the L-serine derivative (A), followed by Negishi cross-coupling with different aryl bromides (C) to obtain structurally diversified UAAs (D).

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References:

1. Nelson D. L.; Cox M. M.; Hoskins A. A. *Lehninger Principles of Biochemistry*. 8th ed.; W. H. Freeman and Company: New York, 2021.
2. a) Feng R.-r.; Wang M.; Zhang W.; Gai F. *Chem. Rev.* **2024**, *124*, 6501. b) Sharma K. K.; *et al. Med. Chem.* **2024**, *67*, 19932.
3. Cianni L.; *et al. J. Med. Chem.* **2019**, *62*, 10497.
4. Atmuri N. D. P.; Lubell W. D. *Org. Synth.* **2015**, *92*, 103.
5. Nimje R.; *et al. J. Org. Chem.* **2020**, *85*, 11519.
6. Dachwitz S.; Scharkowski B.; Sewald N. *Chem. Eur. J.* **2021**, *27*, 18043.

Phosphoramide-Linked 4-Quinolone-3-carboxamides: Synthesis and Evaluation as Antitumor Agents

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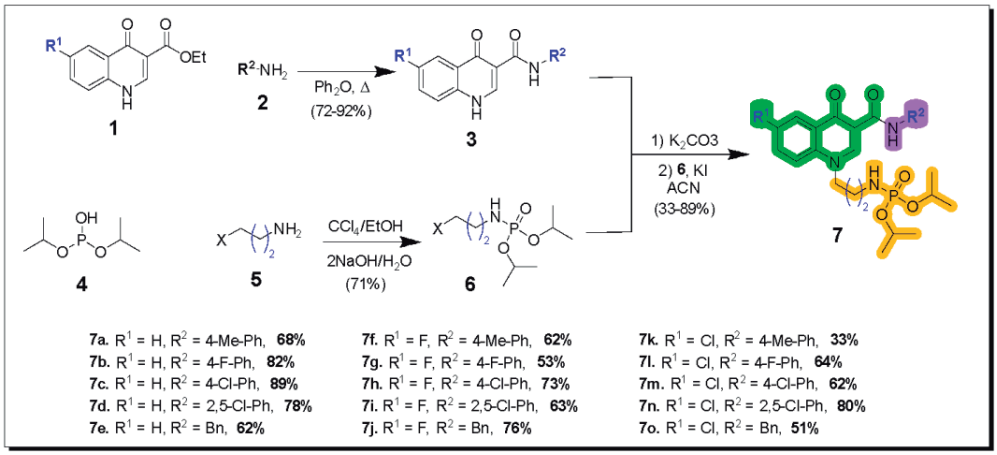
The 4-quinolone scaffold represents a versatile heterocyclic framework that can be readily modified at different positions, particularly at the nitrogen atom and the C-3 position, including a carboxamide moiety. Such structural modifications enable access to a wide range of derivatives with distinct functional and biological properties. In addition to the classical antimicrobial potential, 4-quinolone derivatives may act as antitumoral agents[1], standing out as a promising molecular platform. Structural derivatization of this system has generated derivatives with antitumor activity both *in vitro* and *in vivo*.[2] In this work, we report the synthesis and characterization of a novel series of phosphoramide-linked 4-quinolone-3-carboxamides (**7**). Different derivatization strategies were explored, aiming to expand the structural diversity off the system and to support future structure–activity relationships (SAR) studies. To date, 15 derivatives have been obtained in yields ranging from 33% to 89% through the reaction of 4-quinolone-3-carboxamides (**3**) with diisopropyl *N*-(3-chloropropyl)phosphoramidate (**6**) under optimized conditions. In addition, precursor 4-quinolone-3-carboxamides not previously reported in the literature were also synthesized. All compounds and intermediates were characterized by IR spectroscopy and ^{1}H, ^{13}C and ^{31}P NMR. The synthesized phosphoramide-containing derivatives, along with their corresponding precursors, are currently under *in vitro* evaluation against melanoma cell lines (A375 and SK-MEL). These results highlight the synthetic flexibility of the 4-quinolone core and demonstrate the feasibility of introducing phosphorus-containing functionalities into this heterocyclic system, contributing to the development of structurally diverse quinolone-based derivatives.



Scheme 1: Reaction conditions and yields for the synthesis of the target molecules **7**.

Acknowledgements: We thank PPGQ-UFF, CAPES (Finance code 001), FAPERJ and CNPq.

References:

1. Dine, I.; Mulugeta, E.; Melaku, Y.; Belete, M. *RSC Adv.* **2023**, 13*(13)*, 8657-8682.
2. Forezi, L. S. M.; Tolentino, N. M. C.;. Souza, A. M. T.; Castro, H. C.; Montenegro, R. C.; Dantas, R. F.; Oliveira, M. E. I. M.; Silva Jr, F. P.; Barreto, L. H.; Burbano, R. M. R.; Oliveira, R.; Cunha, A. C.; Ferreira, V. F.; Boechat, F. C. S.; Souza, M. C. B. V. *Molecules.* **2014**, *19(5)*, 6651-6670.

Development of functionalized pyrimido[6,1-*a*]isoindole derivatives as novel heterocyclic scaffolds for medicinal chemistry applications.

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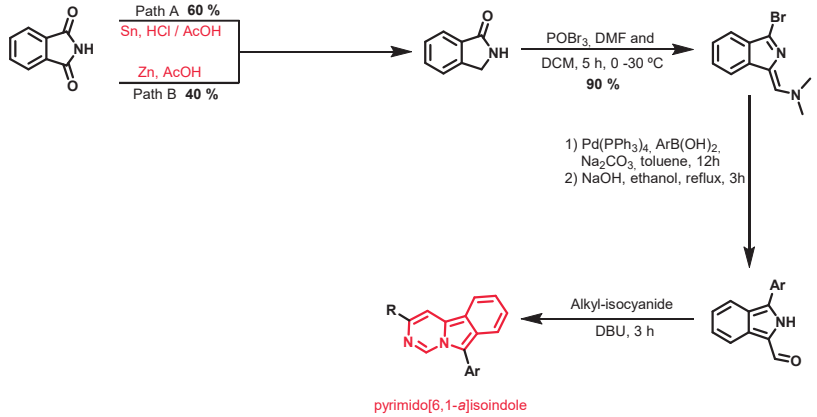
Fused *N*-heterocyclic systems serve as key scaffolds in medicinal chemistry due to structural diversity, established reactivity and druglike molecular properties. The pyrimido[6,1-*a*]isoindole ring system remains underexplored in synthetic and medicinal chemistry studies, despite its potential application in drug design. This work describes the synthesis of functionalized pyrimido[6,1-*a*]isoindole derivatives through a four-step sequence involving phthalimide reduction (Sn/HCl/AcOH, or Zn/AcOH), Vilsmeier-Haack transformation, and a Suzuki cross-coupling reaction. Final annulation with alkyl isocyanides yields the fused core[1,2] **(Scheme 1)**. These standard procedures enable efficient assembly of the fused core from readily available precursors, and substitutions at multiple positions to explore steric and electronic effects on the molecular scaffold. The synthesis of substituted pyrimido[6,1-*a*]isoindoles is expected to proceed under mild conditions and afford the target compounds in moderate to good yields. The synthetic approach accommodates late-stage functionalization, making it amenable for expanding chemical space and structure-activity relationship studies. This scaffold was selected in view of the potential compatibility with fragment-based drug discovery approaches[3] to find innovative ligands for biologically relevant protein targets. Ongoing studies focus on developing a library of substituted pyrimido[6,1-*a*]isoindoles, and on the biological evaluation and physicochemical characterization of selected derivatives. Overall, this work expands the accessible chemical space around pyrimido-fused *N*-heterocycles and supports their further exploration in a medicinal chemistry context.



Scheme 1: Synthetic route to pyrimido[6,1-*a*]isoindole derivatives. Reduction of phthalimide via Path A (Sn/HCl/AcOH) or Path B (Zn/AcOH) is followed by Vilsmeier–Haack reaction, Suzuki coupling, and annulation with alkyl isocyanides.

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References:

1. Diana, P.; Martorana, A.; Barraja, P.; et al. *Tetrahedron* 2011, 67, 2072–2080.
2. Vera, G.; Diethelm, B.; Terraza, C. A.; et al. *Molecules* 2018, 23, 2051.
3. Xu, W. J.; Kang, C. B. *J. Med. Chem.* 2025, 68, 5000–5004.

Metal-free route toward the synthesis of 1,2,3-triazole derivatives inspired in Hsp90 inhibitors: synthesis of potential new antifungal agents

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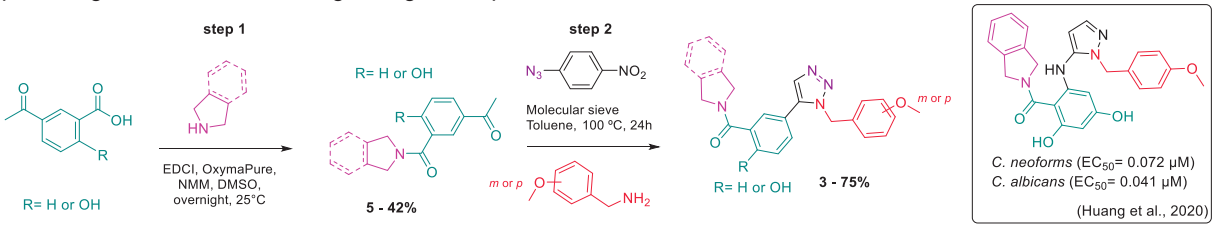
INTRODUCTION: Fungal diseases affect more than 6.55 million people annually, resulting in approximately 3.75 million deaths worldwide[1]. Despite the availability of four major classes of antifungal agents like polyenes, triazoles, echinocandins, and pyrimidine analogues, the prolonged use of these drugs has promoted the emergence of resistance among opportunistic pathogens, representing a major public health concern[2,3]. In this context, the development of new antifungal agents, particularly against *Cryptococcus* spp., is urgently needed. Medicinal chemistry strategies such as scaffold hopping and molecular simplification have proven valuable in generating novel bioactive compounds[4,5]. Here, these approaches were applied to obtain triazole derivatives inspired in inhibitors of chaperone Hsp90, a key protein involved in fungal survival, virulence, and drug resistance[6,7]. **OBJECTIVE:** Synthesize novel potential antifungal agents based on resorcinol aminopyrazole scaffolds using a metal-free route to obtain 1,2,3-triazole derivatives. **METHODS:** Target compounds were synthesized through a two-step protocol. First, amide bonds were formed via coupling reactions between amines and carboxylic acids using EDCI and OxymaPure® as activating agents[8]. Subsequently, a triazole moiety was introduced via a triazolization reaction[9] involving an amine, a ketone, and 1-azido-4-nitrobenzene in toluene (Scheme 1). **RESULTS:** In the amide coupling step, 3-acetylbenzoic acid and 5-acetylsalicylic acid were reacted with isoindoline hydrochloride (yields of 42% and 14%, respectively) and pyrrolidine (33% and 5%, respectively) to obtain the first ketone derivatives to use in step 2. In the triazolization reaction, the free hydroxyl group did not interfere with triazole formation; however, yields varied widely across the different scaffolds, making it impossible to establish a relationship between structure and yield, which ranged from 3% to 75%. **CONCLUSION:** A total of four compounds bearing the isoindoline moiety were obtained, including analogues with and without a hydroxyl substituent on the aromatic ring and incorporating either *m*- or *p*-methoxybenzylamine fragments. For the pyrrolidine derivatives, so far only the *p*-methoxybenzylamine analogue was successfully obtained under the evaluated conditions. The proposed synthetic strategy proved effective for generating Hsp90 inhibitor-inspired compounds, which represent promising candidates for antifungal drug development.



Scheme 1. General synthetic route for the preparation of the target compounds.

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References:

1. Denning, D. W. *The Lancet Infectious Diseases* **2024**, 24 (7), e428–e438.
2. Revie, N. M.; Iyer, K. R.; Robbins, N.; Cowen, L. E. *Current Opinion in Microbiology* **2018**, 45, 70–76.
3. World Health Organization. WHO Fungal Priority Pathogens List to Guide Research, Development and Public Health Action. **2022**.
4. Böhm, H.-J.; Flohr, A.; Stahl, M. *Drug Discovery Today: Technologies* **2004**, 1 (3), 217–224.
5. Barreiro, E. J. *Quím. Nova* **2002**, 25 (6b), 1172–1180.
6. Cowen, L. E.; Singh, S. D.; Köhler, J. R.; Collins, C.; Zaas, A. K.; Schell, W. A.; Aziz, H.; Mylonakis, E.; Perfect, J. R.; Whitesell, L.; Lindquist, S. *Proc. Natl. Acad. Sci.* U.S.A. **2009**, 106 (8), 2818–2823.
7. Huang, D. S.; LeBlanc, E. V.; Shekhar-Guturja, T.; Robbins, N.; Krysan, D. J.; Pizarro, J.; Whitesell, L.; Cowen, L. E.; Brown, L. E. *J. Med. Chem.* **2020**, 63 (5), 2139–2180.
8. Caporale, A.; Doti, N.; Monti, A.; Sandomenico, A.; Ruvo, M. *Peptides* **2018**, 102, 38–46.
9. Thomas, J.; Jana, S.; John, J.; Liekens, S.; Dehaen, W. *Chem. Commun.* **2016**, 52 (14), 2885–2888.

C–H annulation strategy to obtain furo[2,3-*d*]pyrimidines

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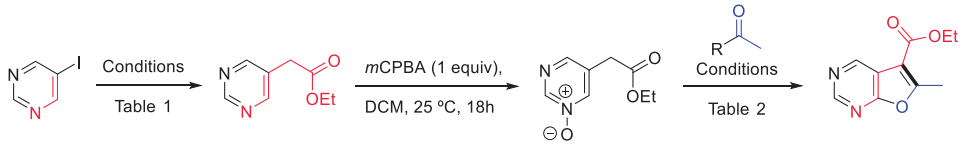
5,6-Fused bicyclic heteroaromatic cores containing azine moieties are widely present in drugs and other biologically active compounds[1–3]. However, due to the electron-deficient nature of azines, the C–H functionalization of this ring to synthesize these fused compounds can be challenging[4]. In this way, we expanded the application of a C–H annulation strategy already used for pyridine analogues[5] to synthesize furo[2,3-*d*]pyrimidines. Using a three-step route (Scheme 1), we first synthesized the α-aryl ester from 5-iodopyrimidine. The conditions of the Ullmann-type reaction[6,7] were optimized (Table 1), and the conditions in entry 1 were selected. In the sequence, *N*-oxidation was achieved in 55% yield. For the heterocyclization, we started with the optimized condition for the furo[2,3-*b*]pyridine core[5] (entry 1, Table 2). But using anhydride, the higher yield (81%) was achieved in entry 2 (Table 2), and when acetyl chloride was used as the acyl source, the higher yield (43%) was obtained under the conditions in entry 10 (Table 2). The results so far have demonstrated the feasibility of this synthetic route for obtaining the furo[2,3-*d*]pyrimidine core via C–H annulation.



Scheme 1. Synthetic route for furo[2,3-*d*]pyrimidines.

Table 1. Optimization of reaction conditions for the synthesis of α-aryl-esters. 1 mmol scale. *Starting material recovery.

Entry	Copper source (0.1 equiv)	Ligand (0.2 equiv)	Additive (3 equiv)	Solvent (2 mL)	Temperature/ time	Yield (*)
1	CuI	5-F-picolinic acid	-	DMF	80 °C, 24h	40% (55%)
2	CuI	L-proline	-	DMF	80 °C, 24h	23% (60%)
3	CuI	5-F-picolinic acid	EtOH	DMF	80 °C, 24h	24% (40%)
4	CuBr	5-F-picolinic acid	-	DMF	80 °C, 24h	12% (60%)
5	CuI	5-F-picolinic acid	-	DMF	80 °C, 48h	40% (30%)
6	CuI (0.2 equiv)	5-F-picolinic acid (0.4 equiv)	-	DMF	80 °C, 24h	40% (21%)
7	CuI	Picolinic acid	-	DMF	80 °C, 24h	27% (10%)

Table 2. Optimization of reaction conditions for the synthesis of furo[2,3-*d*]pyrimidines. 0.5 mmol scale. Reaction time: 18h.

Entry	Base (1.2 equiv)	Acyl source (equiv)	Additive (equiv)	Solvent (3 mL)	Temperature	Yield
1	DBU	Acetic anhydride (6)	DMAP (2)	DCM	25 °C	73%
2	DBU	Acetic anhydride (6)	DMAP (2)	MeCN	25 °C	81%
3	DBU	Acetic anhydride (6)	DMAP (2)	MeCN	80 °C	81%
4	DBU	Acetic anhydride (3)	DMAP (1)	MeCN	25 °C	52%
5	*t*-BuONa	Acetic anhydride (6)	DMAP (2)	MeCN	25 °C	40%
6	LiHMDS	Acetic anhydride (6)	DMAP (2)	MeCN	25 °C	42%
7	DBU	Acetic anhydride (6)	DMAP (1)	MeCN	25 °C	71%
8	DBU	Acetyl chloride (6)	DMAP (2)	MeCN	25 °C	14%
9	DBU	Acetyl chloride (6)	DMAP (3)	MeCN	25 °C	22%
10	DBU	Acetyl chloride (6)	DMAP (6)	MeCN	25 °C	43%
11	DBU	Acetyl chloride (3)	DMAP (3)	MeCN	25 °C	33%
12	DBU	Acetyl chloride (12)	DMAP (12)	MeCN	25 °C	35%

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References:

1. Pradeep Kumar, M.; Annie, A. S.; Kumar Bind, V.; Adithya, R.; Amaladass, P.; Dhayalan, V. *Chem. Asian J.* **2024**, *19* (22), e202400455.
2. Luo, W.; Liu, Y.; Qin, H.; Zhao, Z.; Wang, S.; He, W.; Tang, S.; Peng, J. *Eur. J. Med. Chem.* **2024**, *279*, 116838.
3. Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57* (24), 10257–10274.
4. Theisen, M. C.; de Borba, I. A. S.; Joaquim, A. R.; Fumagalli, F. Reactions **2025**, *6* (4), 72.
5. Fumagalli, F.; da Silva Emery, F. *J. Org. Chem.* **2016**, *81* (21), 10339–10347.
6. Ke, J.; He, C.; Liu, H.; Xu, H.; Lei, A. *Chem. Commun.* **2013**, *49* (60), 6767.
7. Cheng, F.; Chen, T.; Huang, Y.-Q.; Li, J.-W.; Zhou, C.; Xiao, X.; Chen, F.-E. *Org. Lett.* **2022**, *24* (1), 115–120.

Enantioselective Synthesis of γ-Butyrolactones Bearing a Quaternary Stereocenter from Allylic Alcohols via a Palladium-Catalyzed Carbonylative Heck–Matsuda Reaction

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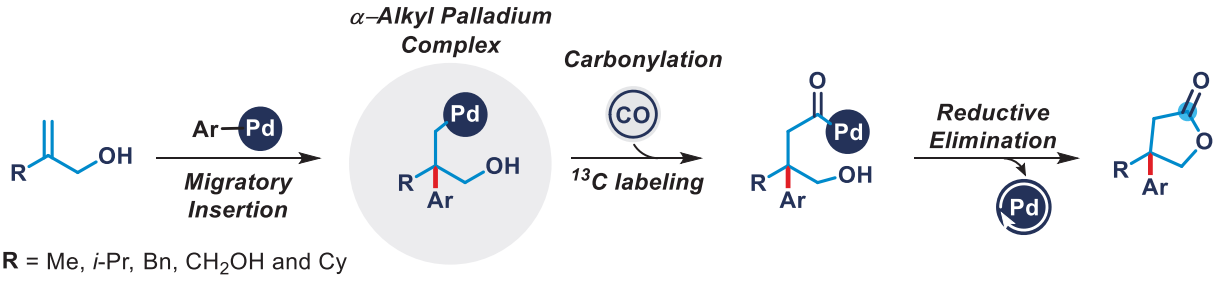
A practical and efficient palladium-catalyzed carbonylative Heck–Matsuda reaction has been developed for the synthesis of aryl γ-butyrolactones and δ-valerolactones bearing quaternary stereocenters directly from readily available allylic alcohols. Using *ex situ* carbon monoxide generation *via* a two-chamber COware® system, the protocol enables rapid access to structurally diverse lactones in excellent yields of up to 99% under operationally simple conditions. The methodology displays broad substrate scope and high tolerance toward electronically diverse arenediazonium salts as well as sterically differentiated allylic alcohols.

The asymmetric variant of the transformation was also investigated using chiral *N,N*-ligands, providing enantioenriched γ-butyrolactones with enantiomeric ratios of up to 80:20. Additionally, the method enables straightforward and cost-effective incorporation of ^{13}C isotopic labels at the lactone carbonyl through the use of ^{13}C-formic acid as the carbon monoxide precursor.

This strategy provides a valuable synthetic platform for the preparation of isotopically labeled and enantioenriched γ-butyrolactone scaffolds of significant interest in medicinal chemistry, mechanistic studies, and synthetic methodology development.



Scheme 1: Strategy for the synthesis of γ-butyrolactones adopted in this work.

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References:

1. J. Hur, J. Jang, and J. Sim. Int. J. Mol. Sci., 22 (2021) 2769.
2. L. P. M. de O. Leão, O. D. Köster, L. J. Duarte, A. A. C. Braga, and C. R. D. Correia, *J. Org. Chem.*, **2025**, *90*, 8835–8845.

Synthesis, Antibacterial and Antifungal Activity Evaluation of N-(4,6-Diaryl-pyrimidin-2-yl)-1*H*-benzo[*d*]1,3-thiazol-2-ylamines

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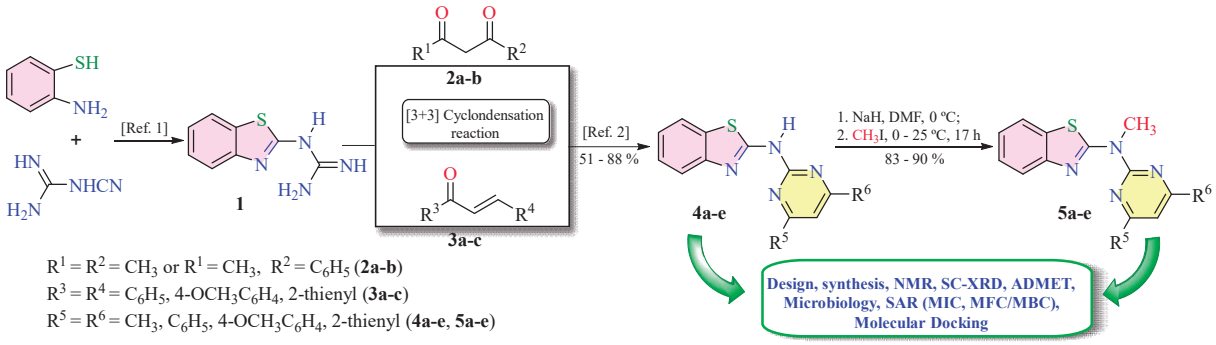
In this study, we report the design, synthesis, structural characterization (^{1}H- and ^{13}C-NMR, HRMS, and single-crystal X-ray diffraction analysis), and microbiological evaluation of two novel series of *N*-(4,6-dialkyl(aryl/heteroaryl)-pyrimidinyl)-1*H*-(benzo[*d*]thiazolyl)-2-amines (**4a-e**) and their *N*-methylated derivatives (**5a-e**) as dual antibacterial and antifungal agents. Compounds **1** and **4** were obtained according to similar procedures already described in the literature[1,2] and the reaction conditions for obtaining series **5** are shown in **Scheme 1**.



Scheme 1. Design, synthesis, structure and microbiological study overview for compounds **4** and **5**.

A structure–activity relationship (SAR) analysis indicated that N-methylation at the exocyclic nitrogen significantly enhances the anti-staphylococcal activity.[3] In silico ADME profiling and molecular docking simulations were conducted to correlate structural features with biological performance.[4]The results revealed favorable binding energies and increased hydrophobic and π-interactions for the N-methylated derivative **5d** (R^5 = R^6 = 4-OMeC$_6$H$_4$), supporting a relationship between structural modification and enhanced activity. Compound **5d** showed potent inhibition of S. aureus (MIC = 0.25 µg/mL) and fungistatic activity against Candida spp. (MIC = 4 µg/mL), while maintaining acceptable drug-likeness based on ADME predictions.[5] These findings provide mechanistic insight and identify N-methyl-N-(pyrimidin-2-yl)-1*H*-benzo[*d*]thiazolyl-2-amine scaffolds **5** as promising candidates for further antimicrobial optimization.

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References:

1. Takahashi, T.; Niino, A. Yakugaku Zasshi **1943**, 63, 249-252.
2. Cassol, R. R. C.; Luz, F. M.; Machado, É. T. O.; Pereira, V. S.; Frizzo, C. P. et al. Dyes Pigm. **2024**, 231, 112435.
3. Mahapatra, A.; Prasad, T.; Sharma, T. Futur. J. Pharm. Sci. **2021**, 7, 123.
4. Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Adv. Drug Deliv. Rev. **1997**, 23, 3–25.
5. Keri, R. S.; Patil, M. R.; Patil, S. A.; Budagumpi, S. Eur. J. Med. Chem. **2015**, 89, 207–251.

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From privileged scaffolds to heterocyclic hybrids: Design and antibacterial evaluation of chromene–pyrimidine derivatives

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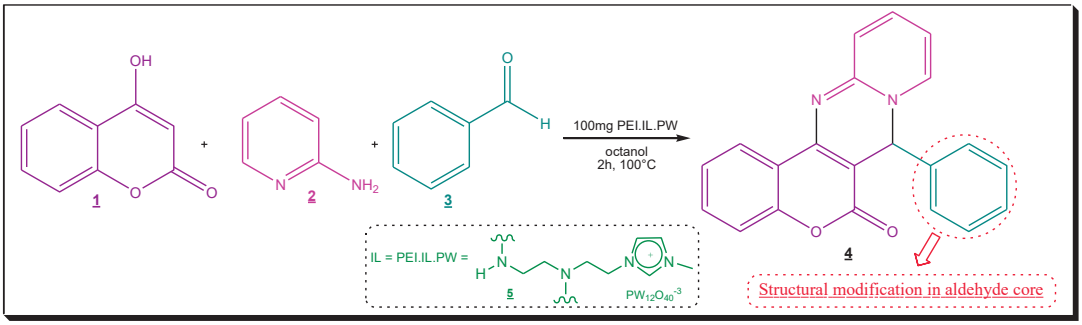
Keywords: *Chromenes derivatives, One-pot synthesis, Ionic liquid..*

Pyrimidine and coumarin-based scaffolds occupy a prominent place in medicinal chemistry due to their well-documented and several biological activities, including antitumor[1], anticoagulant[2], and antibacterial[3] effects. Building on this pharmacological relevance, the strategic combination of these two privileged structures through molecular hybridization represents a promising approach for the development of new antibacterial heterocyclics agents. Since both coumarin and pyrimidine nucleus individually exhibit antibacterial properties, their fusion into a single molecular framework may enhance biological performance and broaden therapeutic potential. In this context, a straightforward and environmentally benign synthetic strategy was developed, aligned with green chemistry principles. A one-pot multicomponent reaction was employed to access a chromene-based hybrid, using equimolar amounts of 4-hydroxycoumarin **1**, 2-aminopyridine **2**, and benzaldehyde **3**. This efficient approach led to the formation of 7-phenyl-6*H*,7*H*-chromene[4,3-*d*]pyrido[1,2-*a*]pyrimidin-6-one **4** in excellent yield. Reaction kinetics were systematically investigated by evaluating the influence of catalyst type, solvent, temperature, reaction time, and reagent proportions. These studies enabled the establishment of optimized conditions, resulting in a fast, robust, and highly reproducible protocol (**Scheme 1**). A key feature of this methodology is the combination of a one-pot procedure, without the isolation of intermediates, with a recyclable ionic liquid catalyst **5**, synthesized from a polymeric matrix (polyethyleneimine) combined with a heteropolyacid (phosphotungstic acid).



Scheme 1: Synthesis of the hybrid obtained by combination of pyrimidine and coumarin nucleus.

Under these optimized conditions, the target hybrid was obtained in 91% yield, highlighting the efficiency and sustainability of the process. To explore structural diversity, the aldehyde core was systematically modified, leading to the obtainment of sixteen additional derivatives. All compounds were isolated and fully characterized by NMR and infrared spectroscopy, with yields ranging from 22% to 99%.

The antibacterial potential of the synthesized hybrids was evaluated through minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) assays against *Staphylococcus aureus* and *Escherichia coli*. The biological results were encouraging, revealing strong inhibitory activity for four derivatives and moderate antibacterial effects for eight others. Overall, the results demonstrated that the developed one-pot strategy is highly effective for molecular hybridization, providing access to a relevant class of chromene–pyrimidine hybrids with significant potential as antibacterial drug candidates.

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References:

1. Chiacchio, M. A.; Ianazzo, D.; Romeo, R.; Giofrè, S. V.; Legnani, L. Current Medicinal Chemistry, **2020**, 26, 7166.
2. Mustafa, Y. F.; Mohammed, E.T.; Khalil, R. R. Egyptian Journal of Chemistry, **2021**, 64, 4461.
3. Jebir, R.M.; Mustafa, Y. F. Eurasian Chemical Comunication, **2022**, 4, 692.

Detection of L-Alanylaminopeptidase activity in microorganisms using fluorogenic self–immolative enzyme substrates.[1]

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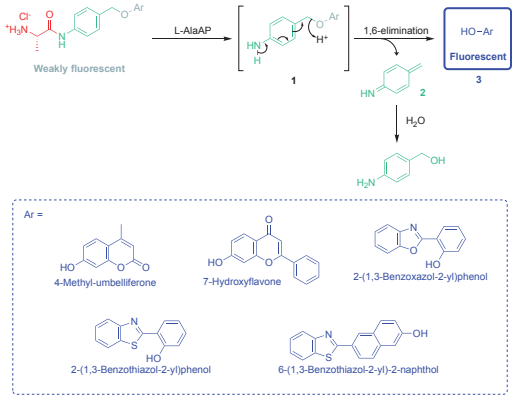
Antimicrobial resistance poses a significant global health threat. An approach to this global issue is the development of cost-effective diagnostic methods for use in clinical settings and quality control. bioMérieux develop products for identification of pathogens by discriminating the unique enzymatic profile of each microorganism. Fluorogenic enzyme substrates for L-Alanylaminopeptidase (L-AlaAP) activity serve as a valuable tool for distinguishing between Gram-negative and Gram-po sitive bacteria in clinical settings. In this study, a series of phenolic fluorophores were derivatised with a distal L-alanyl residue through a p-aminobenzyl alcohol (PABA) linker to provide a variety of substrates for L-AlaAP (Scheme 1). Hydrolysis of the scissile L-alanyl peptide bond by L-AlaAP unmasks the O-arylated-4-aminobenzyl alcohol intermediate **1**, which readily undergoes a 1,6-elimination to liberate the corresponding imine fragment **2** concomitantly with the phenolic fluorophore **3** (as displayed in **Scheme 1**). A benefit of the self-immolative PABA linker is that a vast pool of known phenolic fluorophores could be derivatised into L-AlaAP substrates without the requirement of an aromatic amine handle, essentially broadening the potential of phenolic fluorophores as substrates for aminopeptidase activity. The substrates described released highly fluorescent phenolic derivatives upon enzymatic hydrolysis, allowing for rapid and selective bacterial identification. Evaluation of substrates in agar media demonstrated bright fluorescence in Gram-negative colonies, whilst showing limited activity in Gram-positive colonies due to lack of L-AlaAP expression. These probes offer promising potential as substrates for microbial diagnostics in clinical settings.



Scheme 1: L-AlaAP mediated hydrolysis of substrates through a self-immolative PABA linker to liberate the phenolic fluorophore.

References:

1. M. Cellier, A. L. James, J. Lowe, S. Orenga, J. D. Perry, A. K. Rasul and S. P. Stanforth, *Bioorg. Med. Chem.*, 2016, **24**, 4066-4074.

Metal-Free and Visible-Light-Driven Multicomponent Synthesis of Chalcogenated Pyrazoles

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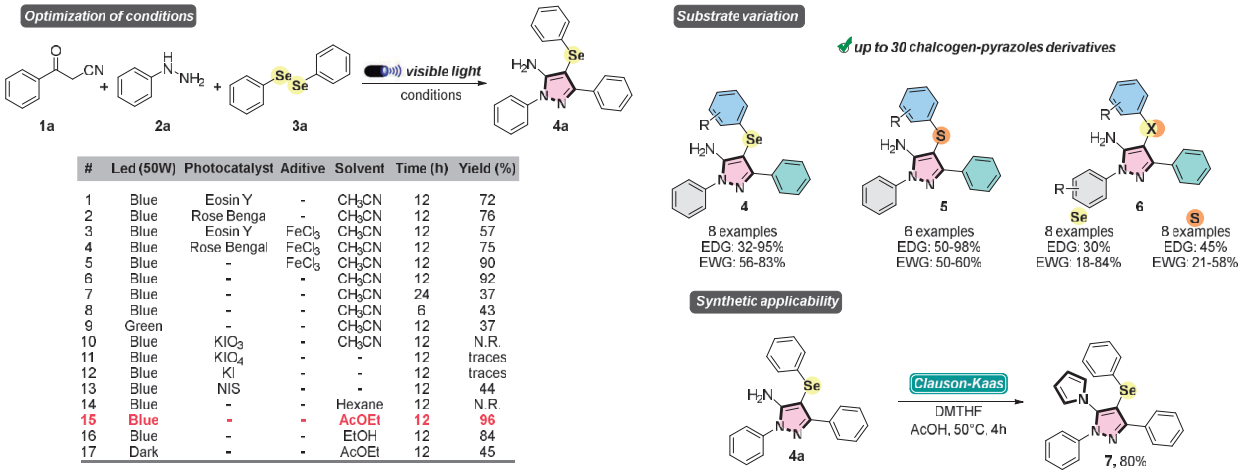
Pyrazole derivatives are an important class of heterocycles with broad applications in medicinal chemistry, materials science, and catalysis due to their unique electronic structure and versatile functionalization.[1] The introduction of chalcogen elements into heterocyclic frameworks is an efficient strategy to modulate molecular properties, benefiting from the high polarizability and directional noncovalent interactions of sulfur and selenium. In this work, we report a mild, multicomponent, visible-light-driven and photocatalyst-free approach or the synthesis of an unprecedented class of chalcogen-containing pyrazoles.[2] Initially, the reaction conditions were carefully optimized by systematically varying the light source, irradiation power, photocatalyst, additives, reaction time, temperature, solvent, and iodine source. This study revealed that the best performance was achieved under additive- and photocatalyst-free conditions using catalytic iodine under blue LED irradiation (50 W) for 12 h in ethyl acetate as a greener solvent. The substrate scope was expanded to a broad range of diselenides and, for our delight, disulfides, as well as diverse hydrazines, enabling the synthesis of more than 30 structurally diverse chalcogenated pyrazole derivatives. Finally, the synthetic utility of the method was demonstrated through derivatization of the main product via a Clauson-Kaas reaction, providing access to more complex molecular architectures (Figure 1). This operationally simple, metal-free, and visible-light-promoted methodology provides an unprecedented and efficient platform for the synthesis of structurally diverse chalcogenated pyrazoles containing both selenium and tellurium motifs, a transformation not previously described for these two chalcogen classes under unified conditions.



#	Led (50W)	Photocatalyst	Aditive	Solvent	Time (h)	Yield (%)
1	Blue	Eosin Y	-	CH_3CN	12	72
2	Blue	Rose Benga	-	CH_3CN	12	76
3	Blue	Eosin Y	$FeCl_3$	CH_3CN	12	57
4	Blue	Rose Bengal	$FeCl_3$	CH_3CN	12	75
5	Blue	-	$FeCl_3$	CH_3CN	12	90
6	Blue	-	-	CH_3CN	12	92
7	Blue	-	-	CH_3CN	24	37
8	Blue	-	-	CH_3CN	6	43
9	Green	-	-	CH_3CN	12	37
10	Blue	KIO_3	-	CH_3CN	12	N.R.
11	Blue	KIO_4	-	-	12	traces
12	Blue	KI	-	-	12	traces
13	Blue	NIS	-	-	12	44
14	Blue	-	-	Hexane	12	N.R.
15	Blue	-	-	AcOEt	12	96
16	Blue	-	-	EtOH	12	84
17	Dark	-	-	AcOEt	12	45

Figure 1: Synthesis of 4-arylchacogenyl-1*H*-pyrazoles.

Acknowledgements: UFSC, UFF, CNPq, FAPERJ

References:

1. Moussa Z.; Ramanathan M.; Alharmoozi S. M.; Alkaabi S. A. S.; Al Aryani S. H. M.; Ahmed S. A.; Al-Masri H. T. Heliyon **2024**, 10, e38894.
2. Ángel A. Y. B.; Campos P. R. O.; Alberto E. E. Molecules **2023**, 28, 3056.

OPTIMIZATION OF THE SYNTHESIS OF BENZOTHIAZOLE HETEROCYCLIC NUCLEUS DERIVATIVES UNDER GREEN CHEMISTRY CONDITIONS

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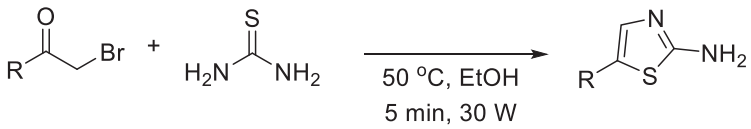
The benzothiazole nucleus is part of a class of bioactive molecules, featuring a benzene ring followed by a thiazole ring. According to Bandock *et al*., (2010), this nucleus is the basis of many drugs, as it has interesting biological properties such as antitumor agent, neurotransmitter blocker, among others. Other types of biological activity include: antifungal, antiviral, antibacterial, antitumor, antimalarial, antidiabetic, antischizophrenic, and anti-inflammatory.

Gawali *et al*., (2018) studied the obtaining of benzothiazole nuclei using 2-bromomethylacetophenone derivatives, thiourea, reflux, 8-12 hours, and ethanol, with yields of 89-96%. These compounds were used as reaction intermediates for the synthesis of dihydro-2-(4-(4-methoxyphenyl)thiazol-2-yl)-1H-naphtho[1,2-e][1,3]oxazine compounds that exhibited significant HIV-1 RT activity inhibition compared to commercial drugs such as Zidovudine and Efavirenz.

In the works of SHEN *et al*., (2010); WAN, (2010) several modifications to the original procedure are proposed, since the reaction requires heating at high temperatures, requires prolonged time and results in low yield at the end of the reaction. Some of these changes include the use of Lewis acids for catalysis, the absence of solvents, and the application of microwave energy.

Considering that the benzothiazole nucleus is important for the synthesis of new drugs and bioactive compounds, the methodologies of synthetic routes for obtaining products derived from these compounds are continuously studied so that new routes can be optimized in order to improve yield, cost and reaction time. Thus, the present study aims to optimize the synthetic route for obtaining benzothiazole nucleus derivatives through a multicomponent reaction, in order to improve time and yield, reducing the use of toxic solvents (**Scheme 1**).



R= C_6H_5, 4-BrC_6H_5, 4-O$CH_3C_6H_5$, 4-FC_6H_5, 4-$CH_3C_6H_5$, 4-ClC_6H_5

Scheme 1: Reaction scheme for the synthesis of benzothiazole compound derivatives with thiourea.

Benzothiazole nuclei showed relevant antimicrobial and antifungal activities against the tested bacteria (*Staphylococcus Epidermidis* -ATCC 12228, *Staphylococcus Aureus* -ATCC 6538P, *Escherichia Coli* -ATCC 25922, and *Pseudonomas Aeruginosa* -ATCC 9027), and yeasts (*Candida krusei* -ATCC 6258 and *Candida albicans* -ATCC 10231) with moderately low minimum inhibitory concentrations (62.5-250 µg/mL). Furthermore, these same compounds exhibited low toxicity with HC_{50} between 1.59-4 mg/mL. The study confirms that the heterocyclic nuclei studied stood out, presenting moderately low minimum inhibitory concentrations.

Acknowledgements: We thank the Postgraduate Program in Pharmaceutical Sciences and the Laboratory of Bioacatalysis and Applied Organic Synthesis at the Federal University of Amapá for their support and infrastructure.

References:

1. Bondock, S.; Fadaly, W.; Metwally, M. A. *Eur. J. Med. Chem*. **2010**, 45, 3692.
2.Gawali, R. *Eur. J. Med. Chem*. **2018**, 157, 310.
3. Shen, Z.; Xu, X,; Ji, S. *J. Org. Chem*. **2010**, 4, 1162.
4. Wan, J.; Liu, Y. *Synth*. **2010**, 23, 3943.

Unveiling Heterocycles Containing Exo-Allenes from Sulfoxonium Ylides

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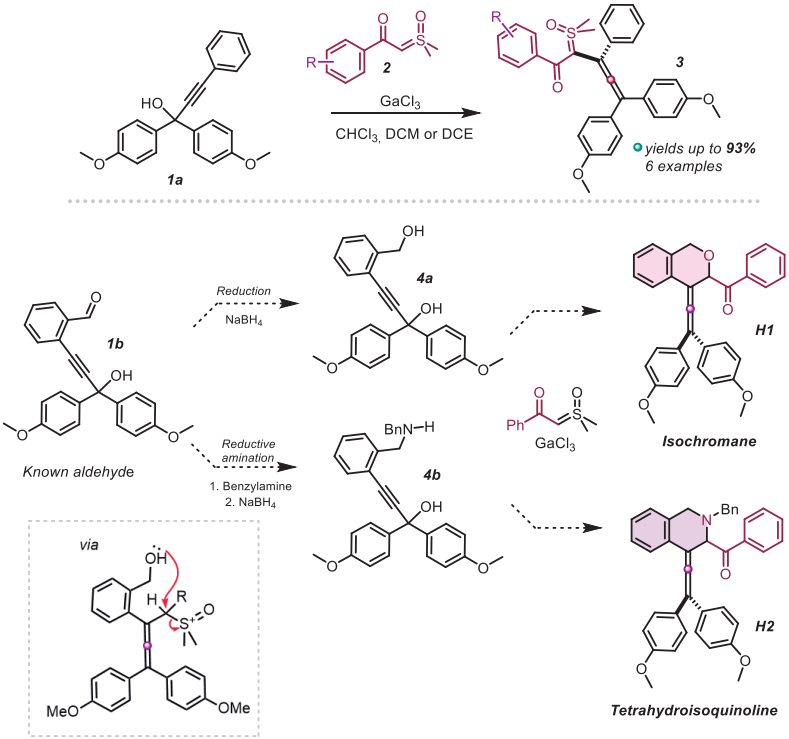
In this work, we describe the synthesis of tetrasubstituted allenes (**3**) from keto-sulfoxonium ylides (**2**) and propargylic alcohols (**1a**) under mild reaction conditions. Sulfoxonium ylides act as carbene precursors and display high functional group tolerance, making them versatile tools for the development of new synthetic methodologies.

Allenes, in turn, constitute a unique class of compounds featuring orthogonal π-systems, which impart distinct structural and electronic properties. The synthesis and derivatizations of highly substituted allenes can be challenging, particularly due to issues of regioselectivity. Therefore, the molecules synthesized in this study exhibit significant synthetic potential, as they incorporate two important functional motifs in organic chemistry.

Finally, we propose a synthetic route toward heterocycles containing allenes using the methodology developed herein. In this synthetic route, we proposed the formation of the heterocycles isochromane (**H1**) and tetrahydroisoquinoline (**H2**) via intramolecular cyclization.



Scheme 1: Possible heterocycles obtained using our developed metodology

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References:

1. a) Qian, D.; Wu, L.; Lin, Z.; Sun, J. *Nat. Commun.* **2017**, 8, 567 b) Shen, C.-P.; Zhu, H.-T.; Li, G.-H.; Chang, X.; Xi, J.-J.; Zhou, N.-N.; Zhou, A.-X. *Org. Biomol. Chem.*, **2025**, 23, 3870.

Silver-Mediated Electrosynthesis of Substituted Isoquinolines via Cyclization of 2-Ethynylbenzaldehydes

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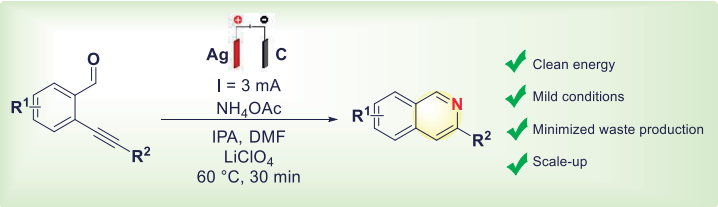
Isoquinoline derivatives constitute an important class of nitrogen-containing heterocycles widely found in natural products and biologically active compounds, displaying relevant antitumor, anti-inflammatory, and analgesic properties. However, traditional synthetic approaches generally rely on transition-metal catalysis under harsh conditions, involving expensive catalysts, oxidants, and environmentally unfavorable reagents. In this context, electrosynthesis has emerged as an attractive alternative, offering improved atom economy, reduced waste generation, and milder reaction conditions. Herein, we report an efficient silver-mediated electrochemical methodology for the synthesis of substituted isoquinolines through intramolecular cyclization of 2-ethynylbenzaldehydes using ammonium acetate as a nitrogen source. The reactions were carried out in an undivided electrochemical cell employing a sacrificial silver anode and a graphite cathode under constant current conditions. Optimization studies demonstrated that the best results were obtained using a DMF/isopropanol mixture at 60 °C in the presence of $LiClO_4$ as supporting electrolyte, affording the desired isoquinoline derivatives in yields up to 76%.



Scheme 1: Silver-Mediated Cyclization via Electrosynthesis.

Mechanistic investigations involving control experiments, cyclic voltammetry, ON/OFF electrolysis experiments, and density functional theory (DFT) calculations supported a non-radical anodic pathway involving *in situ* generation of Ag^+ species from the sacrificial silver anode, followed by silver-mediated alkyne activation and selective 6-*endo-dig* cyclization. Overall, this work demonstrates that sacrificial silver electrodes can efficiently mediate electrochemical annulation reactions for the preparation of isoquinoline derivatives under mild and sustainable conditions. The developed protocol represents a valuable contribution to modern organic electrosynthesis and sustainable heterocycle construction.[1–3]

The authors acknowledge the financial support provided by the São Paulo Research Foundation - FAPESP (grant numbers 2023/04020-8 and 2025/14388-8), FAPEMIG (APQ 01259/24), and FAPESC (S.R.M., T.O. No.: 2023TR000502). Additional support from CNPq (G.M.M, grant number 446457/2024-8, F.R.X grant number 306851/2022-9 and K.T.O. grant number 303333/2022-7) and CAPES code 001 (E.S.B) is also gratefully acknowledged.

References:

(1) De Borba, E. S.; Amélio, D. C. A.; Gomes, K. P.; De Castro, P. P.; Xavier, F. R.; Martins, G. M.; De Oliveira, K. T.; Mendes, S. R. *ACS Omega* **2025**, *10* (49), 60744–60751.
(2) Martins, G. M.; Simoso, G. B.; De Castro, P. P.; De Lucca, F.; Mendes, S. R.; Brocksom, T. J.; De Oliveira, K. T. *J. Org. Chem.* **2025**, *90* (27), 9532–9540.
(3) Santos, W. A. B.; De Castro, P. P.; Xavier, F. R.; Braga, A. L.; Martins, G. M.; Mendes, S. R. *Synthesis (Germany)* **2022**.

Catalyst-Free Synthesis of Trifluoromethylated Tetrahydrofurans via EDA-Mediated Cyclization

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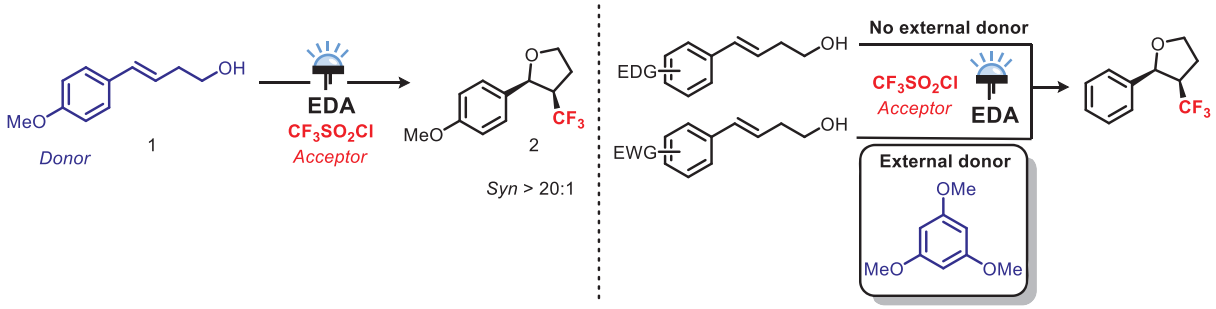
The incorporation of trifluoromethyl groups into organic frameworks is often employed in medicinal chemistry, especially to improve lipophilicity, hydrophobicity, metabolic stability, and overall physicochemical properties.[1] In particular, trifluoromethylated heterocycles are highly valuable motifs due to their frequent presence in bioactive molecules. Among the approaches for C-CF_3 bond formation, photochemical methods have attracted increasing attention, including transition-metal photocatalysis, organophotocatalysis, and electron donor–acceptor (EDA) activation. However, many of these methods rely on costly or hazardous trifluoromethylating reagents, such as Togni reagent, Umemoto reagent, or CF_3I. In this context, trifluoromethanesulfonyl chloride (CF_3SO_2Cl) represents an attractive alternative due to its commercial availability, operational simplicity, and especially an efficient radical fragmentation profile, releasing CF_3 radicals with extrusion of SO_2 and chloride as byproducts. Although broadly employed in traditional radical chemistry and photocatalysis for the trifluoromethylation of arenes, alkenes, and difunctionalization processes, its application in EDA reactivity remains scarcely explored.[2,3] Herein, we report one of the few examples employing CF_3SO_2Cl as an acceptor in EDA complex activation, for the synthesis of trifluoromethylated tetrahydrofurans through visible-light-induced cyclization of homoallylic alcohols (Scheme 1). The transformation proceeds in a highly diastereoselective fashion and was developed through two complementary protocols to accommodate substrates with distinct electronic profiles. In this sense, electron-rich aryl-substituted homoallylic alcohols undergo productive cyclization, affording the desired tetrahydrofurans in 40–76% yield, without the need of an additive, such as an external donor. In contrast, electron-poor substrates that showed low reactivity under this first condition were subjected to donor-assisted conditions, using 1,3,5-trimethoxybenzene as an external donor, providing the cyclized products in 30–50% yield. Current efforts are focused on expanding the substrate scope, replacing the hydroxyl nucleophile with carboxylic acids and amines to access trifluoromethylated lactones and pyrrolidines, respectively. In parallel, mechanistic studies involving photophysical techniques and computational investigations are underway to elucidate the activation modes operating in both protocols.



Scheme 1 – synthesis of trifluoromethylated tetrahydrofurans through visible-light-induced cyclization of homoallylic alcohols

Acknowledgements: We thank FAPESP (grants 2024/00752-7, 2026/00341-2)

References:

(1) Shah, P.; and Westwell, A. D. The Role of Fluorine in Medicinal Chemistry: Review Article. *Journal of Enzyme Inhibition and Medicinal Chemistry* **2007**, *22* (5), 527–540. https://doi.org/10.1080/14756360701425014.
(2) Maiti, R.; Nath, A.; Guimarães, A. B. R.; Bagnich, S.; Köhler, A.; Maseras, F.; Das, S. Mechanistic Insights into the Light-Driven Difunctionalization of Alkenes with a Sulfonyl-Based Reagent: A Catalyst-Free Approach. *J. Am. Chem. Soc.* **2025**, *147* (42), 38021–38032. https://doi.org/10.1021/jacs.5c08562.
(3) Zhan, R.; Zou, X.; Han, X.; Jiang, Y.; Zeng, H. Visible-Light-Induced Trifluoromethyloximation of Alkenes with Sodium Nitrite as Oxime Source. *J. Org. Chem.* **2025**, *90* (50), 17860–17868. https://doi.org/10.1021/acs.joc.5c02372.

Synthesis of Novel Quinazoline–Pyridine Derivatives with Activity Against *Trypanosoma cruzi*

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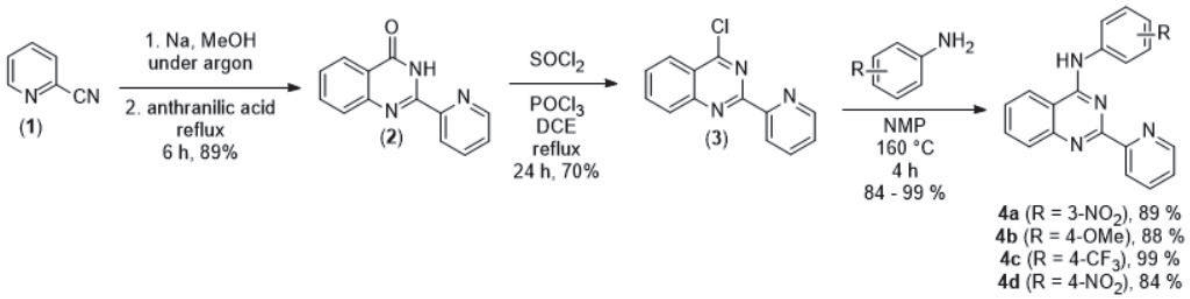
Chagas disease is a neglected tropical disease caused by the flagellated protozoan *Trypanosoma cruzi*. The two clinically available drugs, benznidazole and nifurtimox, both nitro-heterocyclic compounds discovered empirically in the 1970s, present limited efficacy, particularly in the chronic phase of the disease, and are often associated with significant side effects[1]. In this context, the search for new heterocyclic prototypes with antiparasitic activity remains highly relevant. Thus, the present study focuses on the synthesis and antiparasitic evaluation of novel quinazoline–pyridine derivatives. Derivatives were obtained via a three-step linear synthetic route, as depicted in Scheme 1. In the first step, 2-cyanopyridine (**1**) was treated with sodium methoxide at room temperature under an inert atmosphere, leading to the formation of the corresponding methyl benzimidate intermediate. Subsequently, anthranilic acid was introduced, and the reaction mixture was heated under reflux for 6 h, affording 2-(pyridin-2-yl)quinazolin-4(3*H*)-one (**2**) in 89% yield[2]. In the following step, (**2**) was converted into the chlorinated intermediate through treatment with thionyl chloride ($SOCl_2$) and phosphorus oxychloride ($POCl_3$) in 1,2-dichloroethane (DCE) under reflux for 24 h, yielding 4-chloro-2-(pyridin-2-yl)quinazoline (**2**) in 70% yield[3]. Finally, the key intermediate (**2**) underwent nucleophilic aromatic substitution with substituted anilines in *N*-methyl-2-pyrrolidone (NMP) at 160 °C, providing the desired 4-amino-2-(pyridin-2-yl)quinazoline derivatives (**4a-d**) in excellent yields[4].



Scheme 1: Synthetic route for the preparation of quinazoline–pyridine derivatives (**4a-d**).

Before the *in vitro* antiparasitic evaluation, the synthesized derivatives (**4a-d**) were screened for cytotoxicity in mammalian LLC-MK2 cells after 96 h of treatment. Since these compounds exhibited low cytotoxicity, with CC_{50} values ranging from 20 to 28 μM, they were selected for subsequent biological assays against Chagas disease. The compounds were evaluated against the three developmental forms of Chagas disease and exhibited pronounced trypanocidal activity against the trypomastigote form, with LD_{50} values below 0.5 μM, as well as relevant activity against the epimastigote form, with IC_{50} values ranging from 1.5 to 10 μM. However, the molecules showed low activity against the intracellular amastigote form, possibly due to limited cellular permeation, which may be associated with their low aqueous solubility. Among the evaluated compounds, **4d** emerged as the most promising derivative, exhibiting the best selectivity index, with an IC_{50} value of 3 μM against the epimastigote form and an LD_{50} value below 0.5 μM against the trypomastigote form of Chagas disease.

Acknowledgements: FAPERJ, CAPES and CNPq.

References:

1. a) Pérez-Molina J. A., Molina I. *The Lancet* **2018**, *391*, 82. b) Hahn F. E. *Angew. Chem. Int. Ed.* **2006**, *45*, 1348. 2. Zhang, F. *et al. J. Med. Chem.*, **2013**, *56*, 3996. 3. Krapf, J. G. and Wiese M. *J. Med. Chem.*, **2017**, 60, 4474. 4. Gellibert, F. *et al. Bioorg. Med. Chem. Lett.*, **2009**, *19*, 2277.

In silico evaluation of the *Trypanosoma cruzi* proteasome inhibitory potential of the heterocyclic compounds LASSBio-458 and LASSBio-2030

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Key words: Molecular modeling, pyridine, pyrazole

Chagas disease, caused by the protozoan *Trypanosoma cruzi*, affects approximately 6–7 million people worldwide and leads to more than 10,000 deaths annually[1]. The *T. cruzi* proteasome, a key multisubunit complex of the ubiquitin–proteasome system, represents a promising target for antiparasitic drug development[2]. Initially, two heterocyclic compounds from the LASSBio® synthetic chemical library, LASSBio-458 (4-(((3-(benzyloxy)-8-methyl-6-phenyl-6*H*-pyrazolo[3,4-*b*]thieno[2,3-*d*]pyridin-2-yl)methoxy)methyl)benzoic acid) and LASSBio-2030 (*N*-(4-fluorobenzyl)-5-(pyridin-3-yl)-1,3,4-thiadiazol-2-amine)[3], were evaluated through *in silico* studies against the *T. cruzi* proteasome (PDB ID: 9F9T). LASSBio-458 showed a binding free energy (ΔG) of −12.016 kcal/mol, whereas LASSBio-2030, previously identified as a hit with anti-*T. cruzi* activity (IC_{50}/24 h = 16.6 ± 0.9 μM), exhibited a ΔG value of −7.829 kcal/mol. Although LASSBio-2030 showed a less favorable docking score, its reported antiparasitic activity supported its selection as a structural component in the molecular design strategy. Based on these findings, a molecular hybridization approach was employed to design novel heterocyclic analogues combining structural features of both compounds. Four new 6*H*-pyrazolo[3,4-*b*]thieno[2,3-*d*]pyridine hybrid molecules were proposed and evaluated using the same molecular docking protocol implemented in Flare Software[4]. The results demonstrated that all new analogues exhibited improved theoretical affinity for the target compared with LASSBio-2030. Notably, compound 4 (C4) showed the most favorable binding energy (ΔG = −12.335 kcal/mol), surpassing both LASSBio-458 and LASSBio-2030. The remaining compounds also displayed enhanced affinity relative to LASSBio-2030: C1 (ΔG = −11.547 kcal/mol), C2 (ΔG = −11.714 kcal/mol), and C3 (ΔG = −11.691 kcal/mol). Analysis of the ΔG/mass ratio (Table 1) further highlighted the performance of C4, which presented a value of −0.10, compared with −0.09 for LASSBio-458. These findings indicate that molecular hybridization was effective in generating novel compounds with improved predicted affinity for the *T. cruzi* proteasome, highlighting its potential as a rational strategy for the development of new antichagasic agents.

Table 1: Correlation between ΔG and the molecular mass of the synthesized compounds (LASSBio-458; LASSBio-2030) and the planned ones (C1, C2, C3, and C4)

Compound	ΔG (kJ/Mol)	Molecular mass	ΔG/Mass
LASSBio-458	-50,27	549,64	-0,09
LASSBio-2030	-32,76	286,33	-0,11
C1	-48,31	552,62	-0,09
C2	-49,01	569,07	-0,08
C3	-48,91	613,52	-0,08
C4	-51,61	525,61	-0,10

Acknowledgements: We thank to: CAPES – CNPq – FAPERJ – INCT-INOFAR – LASSBio®

References: [1]WHO. *Global Chagas Report***(2024).**[2]KHARE *et al*., *Nature***(2016)**, 537, 229. [3]FREITAS *et al*., *Biomedicine & Pharmacotherapy***(2020)**, 127, 110162. [4]FLARE. User Manual versão 10.0.0. Cambridge Cresset, **(2023)**. 108049

Data science applied to the design of redox-active phthalimides

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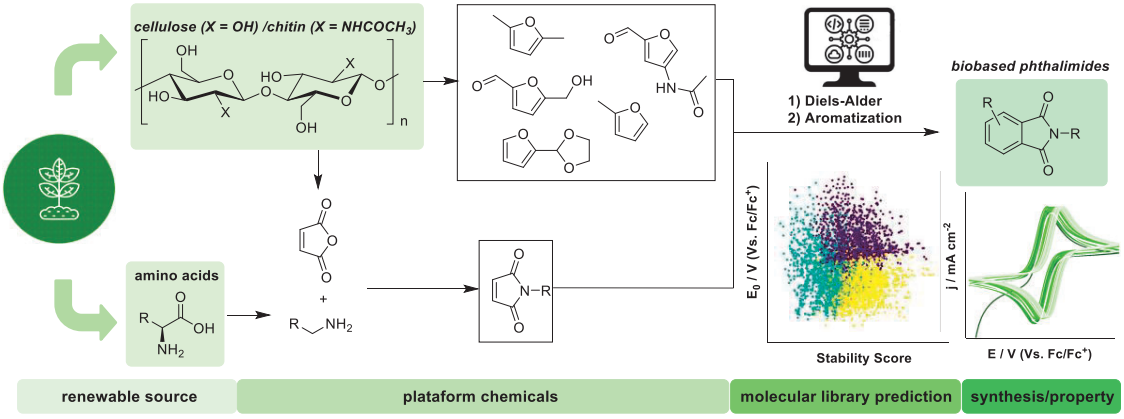
Phthalimides have emerged as promising scaffolds for the development of sustainable redox-active materials for energy storage applications, particularly as anolytes in redox flow batteries (RFBs). Beyond their favorable electrochemical properties, this class of heterocycles can be synthesized through a sustainable route based on renewable feedstocks. Biobased phthalimides can be accessed through Diels–Alder cycloaddition followed by aromatization, employing maleimides and furan derivatives obtained from biomass-derived sources such as amino acids, cellulose, and chitin[1] (Scheme 1). This strategy provides an atom-economical and structurally modular pathway for constructing functional phthalimide frameworks aligned with green chemistry principles. In this work, a combined design and synthesis approach was employed to explore the chemical space of phthalimide derivatives. A virtual library comprising 5,705 compounds was constructed to guide the selection of synthetically accessible targets. Structure–property relationships[2] were investigated using principles of physical organic chemistry to identify key properties relevant to the development of redox-active molecules, such as redox potential and radical stability. Statistical modeling and clustering analyses further enabled the identification of promising candidates for application as anolytes in fully organic RFBs. Guided by these computational insights, four phthalimide derivatives displaying distinct structural and physicochemical features were synthesized through a sustainable route involving Diels–Alder and aromatization reactions, as well as complementary classical synthetic methodologies. Electrochemical characterization of phthalimide 8′ revealed excellent cycling stability over 2,000 redox cycles without detectable degradation. Overall, these findings show that combining computational screening with sustainable synthesis speeds up the discovery of tunable, renewable, high-performance organic materials for next- generation energy storage.



Scheme 1: Design of biobased redox-active phthalimides from renewable feedstocks, integrating physical organic principles and high-throughput screening to guide synthesis.

Acknowledgements: We thank CNPq (405733/2022-4, 381789/2024-1, 350252/2024-6 and 181511/2024-0) and FAPESP (2013/07296-2, 2017/11986-5, 2020/10246-0, 2021/12394-0, 2022/11314-5, 2020/04796-8 e 2024/00752-7).

References:

1. a) Kucherov, F. A.; Romashov, L. V.; Averochkin, G. M.; Ananikov, V. P. *ACS Sustainable Chem. Eng.* **2021**, 9, 3011. b) Settle, A. E.; Berstis, L.; Rorrer, N. A.; Roman-Leshkóv, Y.; Beckham, G. T.; Richards, R. M.; Vardon, D. R. *Green Chem.* **2017**, 19, 3468.
2. a) Er, S.; Suh, C.; Marshak, M. P.; Aspuru-Guzik, A. *Chem. Sci.* **2015**, 6, 885. b) Sevov, C. S.; Hickey, D. P.; Cook, M. E.; Robinson, S. G.; Barnett, S.; Minteer, S. D.; Sigman, M. S.; Sanford, M. S. *J. Am. Chem. Soc.* **2017**, 139, 2924. c) V, S. S. S.; John, P. C. S.; Paton, R. S. *Chem. Sci.* **2021**, 12, 13158.

Synthesis of Furalaxyl and Benalaxyl under Batch and Continuous-Flow Electrochemical Conditions

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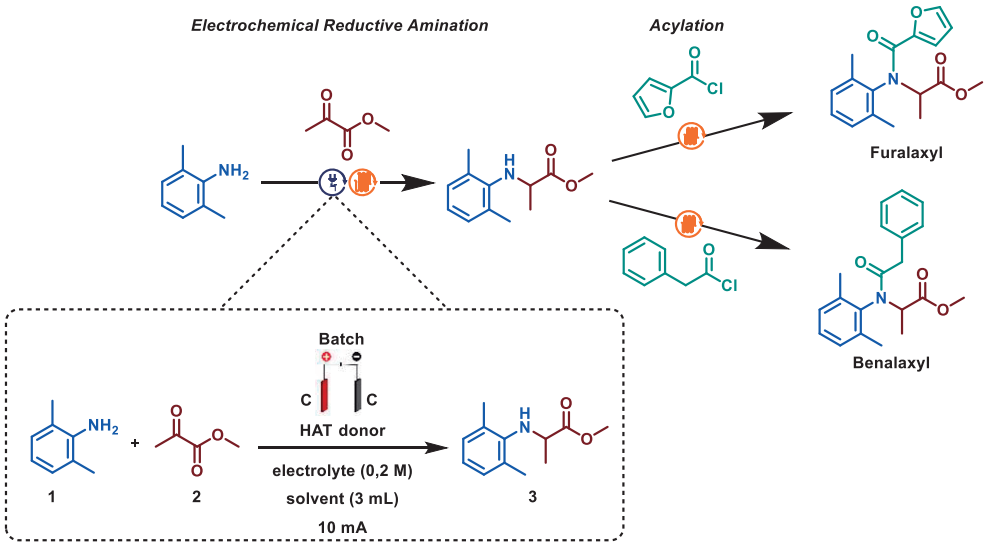
We present a synthetic route to the agrochemicals Furalaxyl and Benalaxyl,[1] emphasizing the use of enabling technologies to improve the production of these compounds. The key step involves an electrochemical reductive amination of 2,6-dimethylaniline (**1**) with methyl pyruvate (**2**), affording the key intermediate **3**. This transformation is being investigated in both batch and continuous-flow electrochemical conditions to evaluate efficiency and scalability.The key intermediate **3** will then be submitted to an acylation reaction, leading to the target molecules Furalaxyl and Benalaxyl (Scheme 1). This approach aims to improve the process chemistry of these relevant agrochemicals by replacing the use of conventional stoichiometric reducing agents.[2] Preliminary results in batch indicate the formation of **3** in up to 53% yield, and further studies are ongoing.



Entry	Electrolyte (0.2 M)	HAT (MPA:AsCH$_2$)	GC-FID Yield (%)
1	$TBAPF_6$	3 eqv : 1 eqv	42%
2	NH_4Cl	3 eqv : 1 eqv	34%
3	NH_4Cl	1.5 eqv : 0.5 eqv	39%

[a]Reaction conditions: 0.5 mmol of (1), 0.75 mmol of (2), MeOH as solvent, 2.5F (2 h)

Scheme 1: General scheme and Table of the reductive amination.

Acknowledgements: We thank the São Paulo Research Foundation FAPESP (grant number 2023/04020-8, 2025/ 14388-8 (K.T.O), 2024/11868-6 (G.H.S.R), 2024/07235-8 (T.O.R)) as well as the 'Conselho Nacional de Pesquisa – CNPq (K.T.O research fellowship 303333/2022-7) and CAPES – Financial Code 001

References:

1. *Pesticide residues in food – 2005.* https://www.fao.org/4/a0209e/a0209e09 (accessed 2026-04-22).
2. Horn, E. J.; Rosen, B. R.; Baran, P. S. *ACS Cent. Sci.* **2016**, *2* (5), 302–308.

Photoinduced three-component alkylazolylation of alkenes enabled by halogen-atom transfer (XAT)

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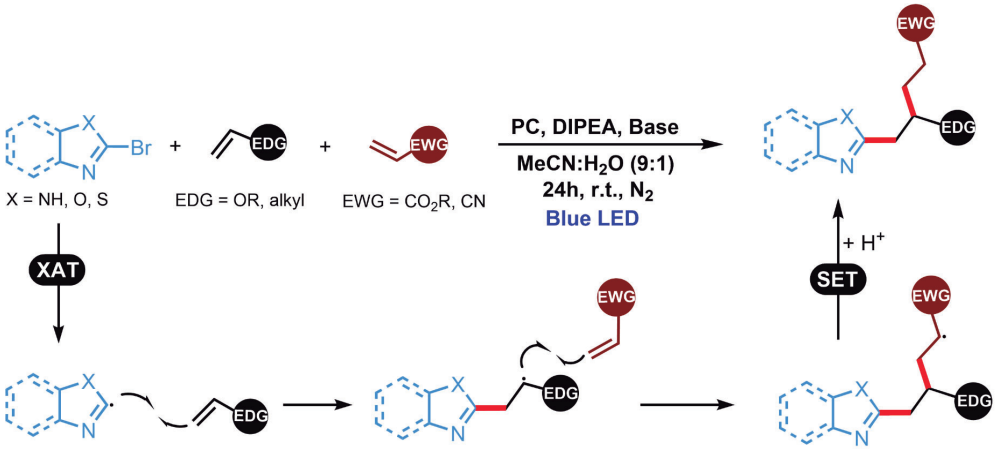
Azole compounds, such as (benzo)imidazoles, (benzo)thiazoles, and (benzo)oxazoles, are ubiquitous in biologically active molecules.[1] However, the synthesis of 2-substituted azoles often requires transition-metal catalysis, elevated temperatures, or costly additives, limiting functional-group tolerance and operational simplicity.[2] As part of our ongoing efforts to develop synthetically useful methodologies based on photoinduced radical processes, we herein report a visible-light-catalyzed three-component radical cascade involving a C2-haloazole, an electron-rich alkene, and an electron-deficient alkene, providing straightforward access to structurally complex 2-alkylazole derivatives. This approach relies on halogen-atom transfer (XAT) to generate electrophilic azolyl radicals, species that have so far been largely neglected in azole functionalization.[3] Despite the growing prominence of alkene difunctionalization methodologies in recent years, only a few protocols have been reported for the synthesis of 2-alkylazoles through this strategy. In these cases, the azole-containing component typically behaves as a radical acceptor, leading to Markovnikov-type incorporation of the azolyl unit across the alkene.[4] In contrast, our strategy exploits azolyl radicals as radical donors, reversing the conventional regioselectivity and enabling the preparation of a new family of azole compounds with potential biological activity.



Scheme 1: Multicomponent synthesis of 2-substituted azoles enabled by photoredox catalysis.

Acknowledgements: We thank FAPESP and CAPES for their financial support.

References:

1. Lee A.-L.; Mooney D. T.; McKee H. *Org. Biomol. Chem.* **2024**, 22, 9145.
2. a) Aljaar, N.; Ibrahim, M. M.; Younes, E. A.; Al-Noaimi, M.; Abu-Safieh, K. A.; Ali, B. F.; Kant, K.; Al-Zaqri, N.; Sengupta, R.; Malakar, C. C. *Asian J. Org. Chem.* **2023**, 12, e202300036. b) Punji, B.; Pradhan, C. *Synlett* **2022**, 34, 683.
3. a) Arora, A.; Teegardin, K. A.; Weaver, J. D. *Org. Lett.* **2015**, 17, 3722. b) Arora, A.; Weaver, J. D. *Acc. Chem. Res.* **2016**, 49, 2273.
4. a) Bao, Y.; Wu, C.; Li, F.; Gao, C.; Wei, Y.; Yuan, Q.; Wang, S. *J. Org. Chem.* **2026**, 91, 1767. b) Ma, X.; Zhang, G. *ACS Catal.* **2021**, 11, 5108.

Iodine-Promoted Mechanochemical Synthesis of Functionalized *N*-Arylpyrazoles from Aza-Michael Adducts

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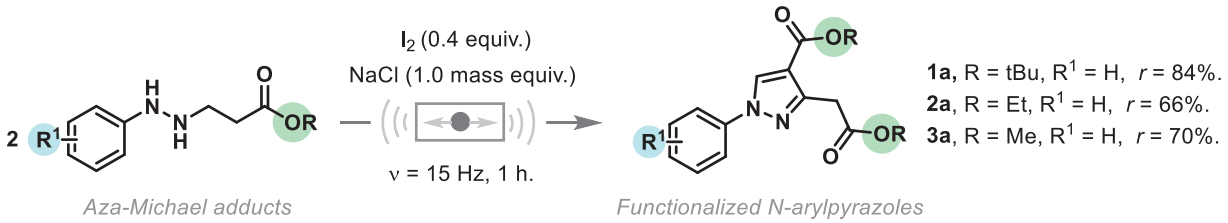
Pyrazoles are heterocyclic compounds of high biological relevance, widely present in FDA-approved drugs and agrochemicals, exhibiting anticancer, anti-inflammatory, and antibacterial activities.[1] Their synthesis is commonly performed via condensation between hydrazines and 1,3-dicarbonyl compounds or enones.[2] More recent approaches include dual indium/silver catalysis for [2+2+1] oxidative *N*-annulation and cascade reactions catalyzed by montmorillonite K10 under solvent-free conditions.[3] In this scenario, the development of sustainable methodologies for the synthesis of these compounds has attracted increasing interest. In this context, mechanochemistry emerges as a promising strategy, aligned with green chemistry principles, allowing access to new reactivity under solvent-free conditions.[4] Therefore, this work reports a new methodology for the synthesis of pyrazole derivatives via mechanochemistry, employing aza-Michael adducts between phenylhydrazine and acrylates, activated by iodine. Under the optimized conditions, using of aza-Michael adduct (0.3 mmol), iodine (0.05 mmol, 0.4 equiv.), and 1 mass equivalent of sodium chloride as a grinding auxiliary, the reactions were carried out in a 5 mL jar containing one 7 mm ball, at a frequency of 15 Hz for 1 h in a ball mill, affording the desired product (**1a**) in 84% yield (**Scheme 1**). The reaction scope is currently under investigation. Nevertheless, the methodology demonstrated an efficient approach for the synthesis of pyrazole derivatives under solvent- and metal-free conditions, with short reaction times, highlighting its potential as a promising alternative to conventional synthetic strategies.



Scheme 1: Mechanochemical synthesis of functionalized *N*-arylpyrazoles under ball-milling conditions.

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References:

1. a) Wang, Y.; Shao, X.; Wang, M.; Li, Z.; Sun, Y.; Meng, X. *Bioorg. Chem*. **2026**, *171*, 109573. b) Kulu, I, *et al*. *Bioorg. Chem*. **2026**, *173*, 109633.c) Habeeb, A. G.; Rao, P. N. P.; Knaus, E. E. *J. Med. Chem.* **2001**, *44*, 3039. d) Liu, J.-J.; Sun, J.; Fang, Y.-B.; Yang, Y.-A.; Jiao, R.-H.; Zhu, H.-L. *Org. Biomol. Chem*. **2014**, *12*, 998. e) Luo, W., Liu, Y., Qin, H., Zhao, Z., Wang, S., He, W., Tang, S., Peng, J. *Eur. J. Med. Chem.* **2024**, *279*, 116838.
2. a) Ruang, Y. R.; Katzenellenbogen, J. A. *Org. Lett.* **2000**, *2*, 2833. b) Katritzky, A. R.; Wang M.; Zhang, S.; Voronkov, M. V.; Steel, P. *J. Org. Chem.* **2001**, *66*, 6787.
3. a) Thombal, R. S.; Lee, Y. R. *Org. Lett.* **2018**, *20*, 4681−4685. b) Annes, S. B.; Saritha, R.; Subramanian, S.; Shankar, B.; Ramesh, S. *Green Chem*. **2020**, *22*, 2388.
4. Emmerling, F. *et al*. Chem **2026**, *12*, 102880.

30th ISHC Congress Brazil - 2026
INTERNATIONAL SOCIETY OF HETEROCYCLIC CHEMISTRY

Design and Synthesis of new Chalcogenbenzimidazolone-Triazole Hybrids with Biological Potential

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Benzimidazolone is a heterocyclic scaffold of considerable relevance in medicinal chemistry due to its structural versatility and ability to interact with multiple biological targets[1], as observed in Bendamustine, an antineoplastic agent containing the benzimidazole nucleus.[2] Thus, our research group is dedicated to combining biologically active scaffolds with organochalcogen compounds, which exhibit important pharmacological properties, using 1,2,3-triazoles as molecular linkers.[3] In this work, we aimed to develop a library of compounds combining benzimidazolone and selenium azides and evaluate their biological potential.Initially, *o*-phenylenediamine reacted with ethyl chloroformate, affording benzimidazolone in **74%** yield.[4] Subsequently, this intermediate was subjected to propargylation, yielding the corresponding propargylated derivative in **64%** yield. The formation of the 1,2,3-triazole core was achieved through a 1,3-dipolar cycloaddition between the terminal alkyne and selenium azide, synthesized from sodium azide and diselenide, using the CuAAC methodology in a DMF/water solvent system,[3] leading to the regioselective formation of triazoles in 35% yield after purification. Based on the analysis of the ^{1}H NMR spectra, it was possible to confirm the formation of the desired product through the presence of characteristic signals attributed to hydrogen **(A)** from the triazole ring and hydrogen **(C)** corresponding to the azide CH_2 group. Ongoing studies are focused on applying this strategy to obtain new benzimidazolone–triazole hybrids, as well as optimizing key reaction parameters, such as temperature, reaction time, solvent, and copper source, in order to improve yields and expand the synthetic scope.

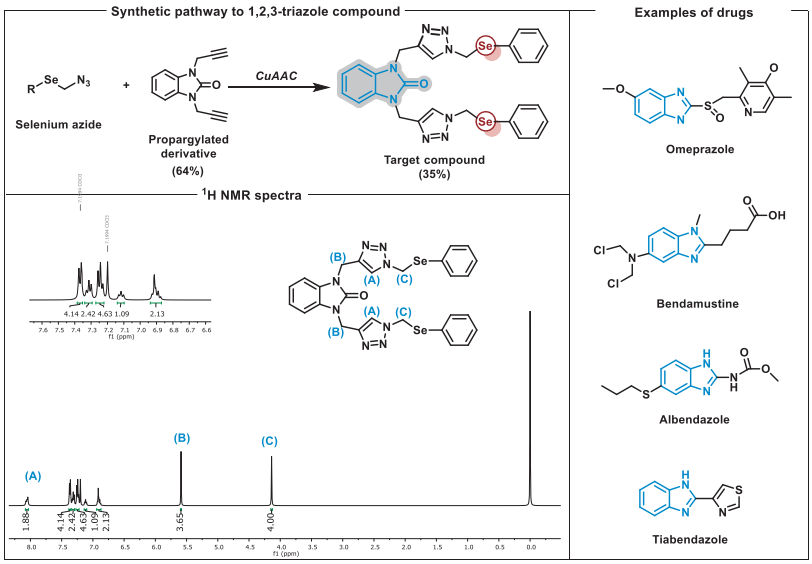

Figure 1: Synthetic pathway to 1,2,3-triazole compound; ^{1}H NMR spectra; Examples of drugs

Acknowledgements: UFF, CAPES, FAPERJ, CNPq

References:

1. Marinescu, m.; zălaru, c. pharmaceuticals, basel, v. 18, art. 1225, 2025.
2. Santa catarina. Secretaria de estado da saúde. Bendamustina. Infosus, [s.d.].
3. Gomes, l. S.; costa, é. O.; duarte, t. G. Et al. Rsc advances, v. 13, p. 34852–34865, 2023.
4. Patil, u. K.; vaidya, s. R.; madje, b. R. Oriental journal of chemistry, v. 39, n. 1, p. 212–215, 2023.

3-(Aryl-1*H*-1,2,3-triazo-4-yl)-1,1-difluoro-1*H*-1λ⁴,10λ⁴-benzo[4,5]thiazolo[3,2-*c*][1,3,5,2]oxadiazaborinines: Design, Synthesis and Photophysics of Rufinamide Luminescent Hybrids

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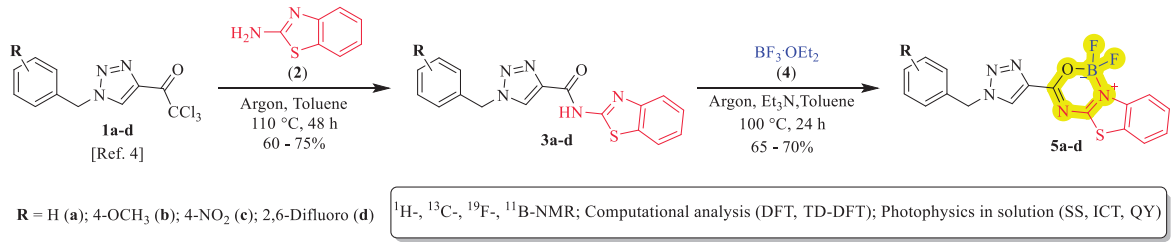
Rufinamide is a drug that was granted orphan drug status for the adjunctive treatment of Lennox-Gastaut syndrome. Being a drug leader, analogues have been developed and studied to achieve greater effectiveness, and also, to add new physical chemistry properties [1]. A recent study reported an innovative series of *Rufinamide* analogs that exhibited luminescent properties, including good fluorescence emission. However, the quantum yields were low and the Stokes shifts were short [2]. In order to increase these values, the system benzo[4,5]thiazolo[3,2-*c*][1,3,5,2]oxadiazaborinine was designed and synthesized by us. This heterocyclic core is a well-known fluorophore and exhibits high quantum yields and large Stokes shifts, consequently, compounds containing this system have been used as molecular probes in photodynamic therapies [3]. Molecular probes are important for investigating and elucidating a drug's mechanism of action and could helps to understand the action mechanism of *Rufinamide*. Based on data from the literature [2] and in order to obtain the benzo[4,5]thiazolo[3,2-*c*][1,3,5,2]oxadiazaborinine derivatives **5**, a new series of amides of *Rufinamide* analogs **3** were synthesized by us from ketone precursosrs **1** [2,4] and cyclized with $BF_3{\cdot}OEt_2$ to furnish the novel series of *Rufinamide* luminescent hybrids **5**, (Scheme 1). As predicted, the new products **5** showed an improvement of quantum yields from 8 to 26% and larger Stokes shifts from 56 to 128 nm compared with literature data [2]. TD-DFT computational calculations corroborate with the photophysical behavior showing significant low values of band gap and revealing the ICT phenomenon for chemical scaffolds like **5a-d**.



Scheme 1: General view and scope of the present study.

Acknowledgements: The author H. G. Bonacorso would like to thank the following entities: National Council for Scientific and Technological Development – CNPq (Grants 305.379/2020-8) and the Research Support Foundation of the State of Rio Grande do Sul – FAPERGS Prog. AFJDB 23/2551-00018667-7) for the fellowships and financial support.

References:

1. Bezençon O.; Heidmann B.; Siegrist R.; Stamm S.; Richard S.; Pozzi D.; Corminbouef O.; Roch C.; Kessler M.; Ertel E. A.; Reymond I.; Pfeifer T.; de Kanter R.; Toeroek-Schafroth M.; Moccia L. G.; Mawet J.; Moon R.; Rey M.; Capeleto B.; Fournier E. *J. Med. Chem.* **2017**, *60*, 9769.
2. Luz F. M.; Cassol R. R. C.; Meinerz M.; Martins N. A. P.; Zanatta N.; Iglesias B. A.; Bonacorso H G. *J. Mol. Struct.* **2025**, *1348*, 143477.
3. Potopnyk M. A.; Volyniuk D.; Cebroska M.; Cmoch P.; Hladka I.; Danyliv Y.; Gražulevičius J. V. *J. Org. Chem.* **2018**, *83*, 12129.
4. Bonacorso H. G.; Moraes M. C.; Luz F. M.; Quintana P. S.; Zanatta, N.; Martins M. A. P. *Tetrahedron Let.* **2015**, *56*, 441.

Design, synthesis, and inhibitory potential of *tert*-butyl based Ugi products towards butyrylcholinesterase

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By condensing an aldehyde, an amine, a carboxylic acid, and an isocyanide, the Ugi multicomponent reaction provides efficient access to structurally complex molecules, peptidomimetics, with high atom economy in one-step synthesis.[1] This reaction plays an important role in drug discovery, as it represents a tool for exploring chemical space and identifying molecules with activity against various biological targets. Recently, some compounds prepared by the Ugi reaction were identified as potent inhibitors of butyrylcholinesterase, which is important for the treatment of progressive neurodegenerative disorders such as Alzheimer's and Parkinson's disease.[2]

In this work, we have designed and synthesized a library of structurally related peptidomimetics by employing the Ugi multicomponent reaction using an carbocyclic acid (*N*-(*tert*-butoxycarbonyl)-glycine or tryptophan, benzoic acid), heterocyclic amine (4-(aminomethyl)pyridine, quinuclidin-3-amine or benzylamine), *tert*-butyl isocyanide, and a paraformaldehyde or acetone (Figure 1). The Ugi reaction was performed using microwave irradiation or conventional methods. The structures of the prepared compounds were determined by 1D and 2D ^{1}H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry. The purity of the compounds was checked by HPLC. The inhibitory potential of the synthesized Ugi products against equine butyrylcholinesterase was evaluated using the spectroscopic Ellman method.[3]

The prepared compounds exhibited potent activity against equine butyrylcholinesterase (with IC_{50} values in the low to mid-micromolar range), indicating their potential as promising scaffolds for the further development of butyrylcholinesterase inhibitors.

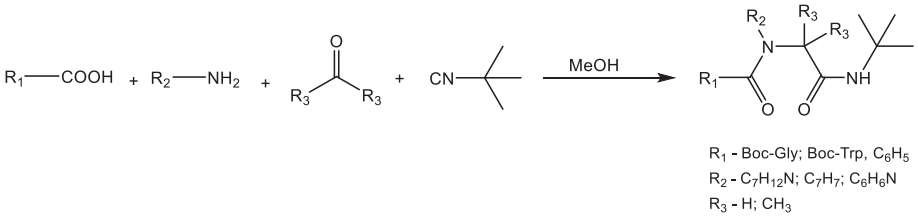

Figure 1. Scheme of Ugi reaction

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References:

1. Ugi I.; Werner B.; Dömling A. *Molecules* **2003**, *8*, 53–66.
2. a) Heise N. V.; Schmidt A.; Schüler J.-A.; Csuk R. *Eur. J. Med. Chem. Rep.* **2024**, *10*, 100124. b) Camargo-Ayala L.; Polo-Cuadrado E.; Osorio E.; Soto-Delgado J.; Duarte Y.; Prent-Peñaloza L.; Gutiérrez M. *J. Mol. Struct.* **2022**, *1264*, 133307.
3. Ellman G.L.; Courtney K.D.; Andres V. Jr.; Featherstone R.H. *Biochem. Pharmacol.* **1961**, *7*, 88–95.

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Anisole as a Strategic Green Solvent in the Synthesis of Furoic Esters

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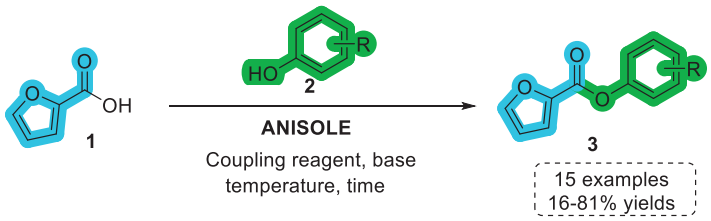
The replacement of conventional organic solvents with sustainable alternatives is a fundamental pillar of Green Chemistry, especially given the urgent need to increase crop yields to meet global population growth (Tavares & Neto, 2020). Traditionally, ester synthesis via Steglich esterification relies on solvents such as dichloromethane (DCM) or toluene. DCM, while efficient, exhibits high toxicity and volatility, being classified as a potential carcinogen (Sousa et al., 2020). In this context, anisole (methoxybenzene) emerges as a high-performance "eco-friendly" alternative, capable of reconciling reaction efficiency with operational safety. Anisole is an aromatic ether that stands out for being biodegradable and possessing a significantly lower toxicological profile compared to halogenated solvents. Its relevance in the bioeconomy is reinforced by its renewable origin, as it can be obtained from the valorization of lignin, an abundant natural polymer derived from biomass that is frequently underutilized. Transitioning to bio-based solvents is essential to mitigate environmental impacts caused by reliance on fossil resources (Maja & Ayano, 2021). Technically, anisole offers advantageous physicochemical properties for the synthesis of furoic esters. Its moderate boiling point (154 °C) allows reactions to be conducted under heating, whether conventional or microwave-assisted, in a much safer manner than in volatile solvents. Furthermore, its solvation capacity enables the effective dissolution of aryl carboxylic acids and coupling agents, ensuring satisfactory yields and aligning with the urgency for new methodologies to synthesize value-added compounds (Rother *et al*., 2022). The application of anisole in this synthetic route is positively reflected in sustainability metrics, such as the E-factor and the Green Star. By eliminating halogenated compounds and reducing the process mass intensity (PMI), this methodology responds to global challenges regarding biodiversity preservation and food security (Kubiak *et al*., 2022). The result is a cleaner process for obtaining furoic esters, whose final products serve as essential building blocks for the development of new agrochemicals, bridging methodological innovation with ecosystem protection.



Scheme 1: General synthetic route towards furoic esters.

Acknowledgements: The authors gratefully acknowledge FAPERJ, CNPq and CAPES for funding, as well as PPGQ-UFF

References:

[1] TAVARES, J. M. DA S.; NETO, C. P. Aspectos Do Crescimento Populacional: Estimativas E Uso De Indicadores Sócio Demográficos. Formação (Online), v. 27, n. 50, p. 3–36, 2020.

[2] SOUSA, S. et al. Chemistry and toxicology behind insecticides and herbicides. In: Controlled Release of Pesticides for Sustainable Agriculture. Cham: Springer, 2020. cap. 3.

[3] MAJA, M. M.; AYANO, S. F. The Impact of Population Growth on Natural Resources and Farmers' Capacity to Adapt to Climate Change in Low-Income Countries. Earth Systems and Environment, v. 5, n. 2, p. 271–283, 2021.

[4] ROTHER, B. et al. Tackling the Global Food Crisis: Impact, Policy Response, and the Role of the IMF. IMF Notes, v. 2022, n. 004, 2022.

[5] KUBIAK, A. et al. The Problem of Weed Infestation of Agricultural Plantations vs. the Assumptions of the European Biodiversity Strategy. Agronomy, v. 12, n. 8, 2022.

Enantioseletive Synthesis of Artemisinin Inspired Tetracyclic Compounds

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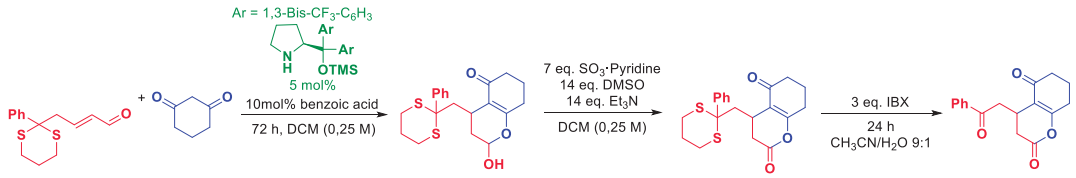
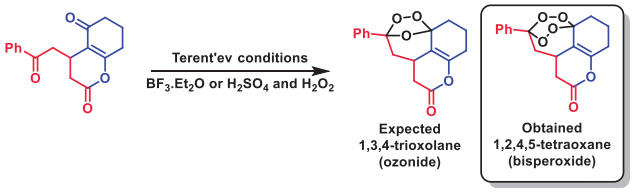
Artemisinin (ART) is one of the most used drug against malaria. However, numerous strains of *Plasmodium falciparum* resistant to various drugs, including ART itself, were observed. This highlights the need for the discovery and development of new antimalarial drugs. In this context, there is precedent that the 1,2,4-trioxolane (ozonide) endoperoxide system exhibits good anti-malarial activity, as seen with arterolane and artefenomel, which have already been approved for clinical trials in some countries.

In this context, the present work aimed to obtain an ART inspiredmolecules that contain an ozonide group, a bridged peroxide moiety different from the present in ART itself that has a 1,2,4-trioxane (endoperoxide). To achieve this, we build the desired 1,5-dicarbonyl system using a previously described asymmetric Michael addition with Jørgensen-Hayashi catalyst, followed by a cyclic hemiacetal formation[1,2]. The 1,3-cyclohexadione and a α,β-unsaturated aldehyde bearing a strategically placed dithiane moiety were used as substrates in the enantioselective organocatalytc step. From that, a sequence of oxidations take part, the first aimed at obtaining the lactone using the Parikh-Doering oxidation. This is followed by an oxidative deprotection of the 1,3-dithiane group revealing the 1,5-dicarbonyl compound for which, based on Terent'ev's work[3], we expected to find the ozonide product. Unexpectedly, we detected the bisperoxide that usually forms only when 1,3- and 1,4-dicarbonyl systems are subjected to these reaction conditions.



Scheme 1: Preparation of the desired 1,5-Dicarbonyl compound

With these results at hand, we tried to optimize the experimental conditions but the major product observed was mostly the outcome of a Baeyer-Villiger oxidation (BV) (phenol detect on GC-MS). We are currently working on the influence of eletronics effects on the aromatic substituent of the molecule, which we expect will reverse the product ratio observed between the BV and the desired bis-peroxide formation.



Scheme 2: Expected ozonide and bis-peroxide obtained from the 1,5-Dicarbonyl compound

Acknowledgements: We would like to acknowledge the financial support granted by the São Paulo State Research Foundation (FAPESP Grant 2022/14310-0; FAPESP Scholarships 2024/09649-4) and the University of São Paulo (USP Grant 2022.1.9345.1.2).

References:

[1] Franke, P. T.; Richter, B.; Jørgensen, K. A. *Chem. Eur. J.* **2008**, *14*, 6317.
[2] Rueping, M.; Sugiono, E.; Merino, E. *Chem. Eur. J.* **2008**, *14*, 6329.
[3] Yaremenko, I. A.; Gomes, G. P.; Radulov, P. S.; Belyakova, Y. Y.; Vilikotskiy, A. E.; Vil, V. A.; Korlyukov, A. A.; Nikishin, G. I.; Alabugin, I. V.; Terent'ev, A. O. *J. Org. Chem.* **2018**, *83*, 4402.

Tetracyclic Alkaloidal-Like Pseudonatural Products

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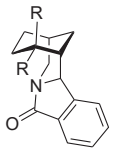
The chemical merging of isoindoline and indolizidine structural frameworks may qualify as an entry into a unique set of pseudo-natural products with therapeutic potential. Benzylic acyliminium ions derived from isoindolinones have proven to be effective in generating polycyclic structures which are of interest in both the natural products and synthetic medicinal arenas. In the present work, the utilization of an intramolecular acyliminium ion reaction in conjunction with a substrate bearing a suitably-disposed unsaturated cyclic appendage gives rise to a tetracyclic carbon framework **1** which is hitherto unknown in the natural product realm. The overall process has the potential to accommodate substituents at several positions of the tetracycle once formed. The conditions for the generation of the tetracyclic framework and the routes and reactions for the preparation of its functional derivatives such as ester, hydroxyl, mesylate, azide and amine. The synthetic sequences used to arrive at tetracyclic 1 and its analogues will be presented.



1

R=Various Substituents

Figure 1: Tetracycle formed through acyliminium cyclization

Acknowledgements: We thank the University of Louisville Dissertation Completion Program for Generous Support

References:

1. Gally, J.-M.; Pahl, A.; Czrodowski, P. Waldmann, H. Pseudonatural Products Occur Frequently in Biologically Relevant Compounds *J. Chem. Inf. Model.* **2021**, *61*, 5458-5468. https://doi.org/10.1021/acs.jcim.1c01084
2. Greiner, L. C.; Pahl, A.; Heinzke, A. L.; Zdrazil, B.; Leach, A. R. Young, R. J.; Leeson, P. D.; Waldmann, H. Pseudonatural Products for Chemical Biology and Drug Discovery *J. Med. Chem.* **2025**, *68*, 14137-14170. https://doi.org/10.1021/acs.jmedchem.5c00643
3. Dijkink, J.; Schoemaker, H. E.; Speckamp, W. N. Biomimetic Heterocyclizations Reactivity of Rigid Unsaturated Systems *Tetrahedron Lett.* **1975**, *46*, 4043-4046. https://doi.org/10.1016/S0040-4039(00)91231-0

Novel Epigenetic Regulators for Cancer Therapy through Dual CDK9/HDAC Inhibition

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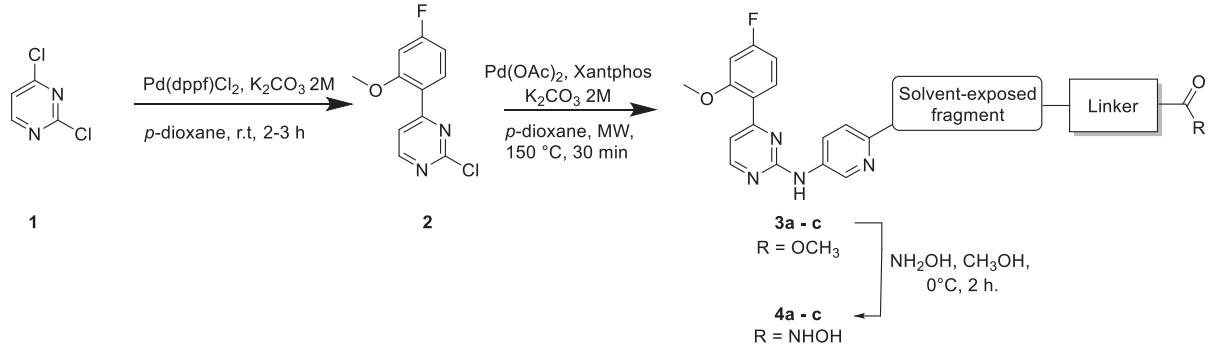
Cyclin-dependent kinase 9 (CDK9) plays a fundamental role in transcriptional regulation by phosphorylating RNA polymerase II, thereby sustaining short-lived oncogenic drivers such as MYC and MCL-1. Although selective CDK9 inhibition represents a powerful therapeutic strategy for transcription-addicted cancers, first-generation candidates often trigger adaptive compensatory mechanisms—such as epigenetic remodeling—leading to transcriptional recovery and drug resistance[1]. To overcome these limitations, the simultaneous dual inhibition of CDK9 and HDACs emerges as a highly promising synergistic strategy. By concurrently disrupting RNA polymerase II elongation and blocking chromatin-mediated adaptive reprogramming, this dual-targeting approach aims to thoroughly dismantle oncogenic survival networks and prevent resistance[2,3].

Driven by this compelling therapeutic rationale, as shown in Scheme 1, we developed a synthetic route to access the target pyrimidine derivatives starting from the versatile 2,4-dichloropyrimidine scaffold **1**. First, a Suzuki–Miyaura cross-coupling reaction, catalyzed by $Pd(dppf)Cl_2$, was employed to introduce the desired aryl substituent, affording compound **2**. Subsequently, C–N bond formation was achieved through a $Pd(OAc)_2$-catalyzed Buchwald–Hartwig amination, furnishing intermediates **3a–c**. Finally, treatment with hydroxylamine promoted a carbonyl addition–elimination reaction, providing the target compounds **4a–c**.



Scheme 1: Synthesis of pyrimidine-based dual CDK9-HDAC inhibitors.

Acknowledgements: The authors gratefully acknowledge the financial support provided by ANID (PROYECTO FONDECYT POSTDOCTORADO N°3240522)

References:

1. E. Thieme *et al.*, "CDK9 inhibition induces epigenetic reprogramming revealing strategies to circumvent resistance in lymphoma," *Mol. Cancer*, vol. 22, no. 1, p. 64, 2023, doi: 10.1186/s12943-023-01762-6.
2. X. Chen *et al.*, "Design, synthesis, and biological evaluation of N-(2-amino-phenyl)-5-(4-aryl- pyrimidin-2-yl) amino)-1H-indole-2-carboxamide derivatives as novel inhibitors of CDK9 and class I HDACs for cancer treatment," *Bioorg. Chem.*, vol. 162, Jul. 2025, doi: 10.1016/j.bioorg.2025.108577.
3. A. Saidahmatov *et al.*, "Discovery of Novel 2-Aminopyridine-Based and 2-Aminopyrimidine-Based Derivatives as Potent CDK/HDAC Dual Inhibitors for the Treatment of Refractory Solid Tumors and Hematological Malignancies," *J. Med. Chem.*, vol. 67, no. 17, pp. 15220–15245, Sep. 2024, doi: 10.1021/acs.jmedchem.4c00837.

Condition-Controlled Synthesis of Functionalized Selenophenes via Cyclization of 1,4-Diyn-3-ones

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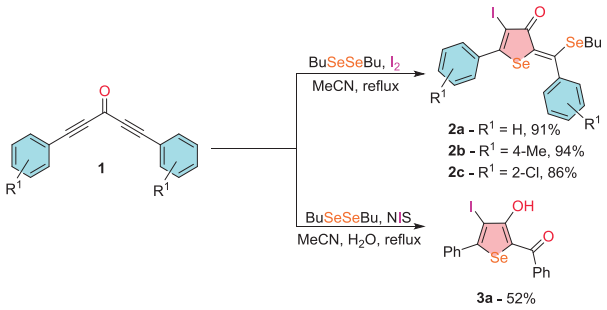
Selenophenes are a prominent class of organoselenium heterocycles whose unique electronic properties arise from the high polarizability of selenium. Recent advances in their synthesis include transition-metal-catalyzed cyclizations, electrophilic selenylation of alkynes, and multicomponent strategies that enable efficient access to structurally diverse selenophene derivatives.[1] These methodologies have expanded the scope of functionalized selenophenes with precise control over substitution patterns. Owing to their narrow band gaps and strong intermolecular interactions, selenophenes are widely applied in organic electronics, including OLEDs, OFETs, and photovoltaic devices.[1] In addition, they exhibit promising biological activities, such as antioxidant and anticancer properties.[2] Consequently, the development of new synthetic approaches to selenophenes remains of significant importance for both materials science and medicinal chemistry. In this context, we herein describe the synthesis of iodine- and methylene-functionalized selenophen-3-ones **2** via the cyclization of 1,4-diyn-3-ones under BuSeSeBu/I_2 conditions, affording the desired products in yields up to 94% (**Scheme 1**). A key outcome of this study is the strong dependence of product formation on the reaction conditions. While the BuSeSeBu/I_2 system promotes the incorporation of the SeBu moiety, switching the halogen source to NIS, in the presence of water, completely alters the reaction pathway, leading instead to hydroxylated selenophene derivatives **3** without selenium incorporation (Scheme 1). Thus, by simply modulating the reaction conditions, it is possible to selectively access distinct classes of selenophenes. The obtained scaffolds are highly versatile, bearing multiple reactive sites, including iodine, selenium, and carbonyl functionalities, which enable diverse post-functionalization strategies and expand their potential applications in synthesis.



Scheme 1

In conclusion, this work highlights the continued relevance of developing versatile synthetic strategies for selenophenes, given their importance in materials science and medicinal chemistry. The proposed methodology provides access to functionalized selenophen-3-ones with good yields. The ability to control the reaction outcome by simple variation of the halogen source, in the presence or absence of water, enables the selective synthesis of distinct classes of selenophenes. The resulting scaffolds, endowed with multiple reactive sites, represent valuable platforms for further functionalization and broaden the synthetic and application potential of organoselenium compounds.

***Acknowledgements**:* We thank CAPES, CNPq (INCT SiPu21 No 409156/2024-8) and FAPERGS for financial support of this work.

References:

1. a) Ye, S.; Lotocki, V.; Xu, H.; Seferos, D. S. *Chem. Soc. Rev*. **2022**, *51*, 6442. b) X. Liu, X. Jiang, K. Wang, C. Miao, S. Zhang, *Materials* **2022**, *15*, 7883.
2. Y. Chen, C. Li, J. Chen, T. Shih, *Arch. Pharm.* **2023**, 356, 2200486.

Study of Spirocyclopropanation of α,β-unsaturated Isoxazol-5(4*H*)-ones Using Sulfoxonium Ylides

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The α,β-unsaturated isoxazol-5(4H)-ones are five-membered heterocycles widely applied in the synthesis of natural products and medicinal compounds, and their scaffolds are also found in nature. Methodologies aimed at introducing structural modifications to these compounds have been extensively investigated due to their broad applicability. Examples include flash vacuum pyrolysis and intramolecular hetero-Diels-Alder cycloaddition reactions. Spirocyclization reactions can afford a wide variety of spiro-isoxazole-5-one structures through approaches such as multicomponent reactions, asymmetric catalysis, and synthesis of compounds exhibiting antitubercular, cytotoxic, and antibacterial activities.[1]

Sulfur ylides are versatile reagents capable of generating cyclic structures through cyclopropanation of α,β-unsaturated compounds.[2] In 1976, Croce described a reaction involving α,β-unsaturated isoxazol-5(4*H*)-ones with sulfonium ylides and speculated on the reaction mechanism based on the stereochemistry of the obtained products.[3] However, neither experimental nor computational methods were employed to propose mechanistic pathways at that time.

In this work, we describe a spirocyclopropanation reaction between α,β-unsaturated isoxazol-5(4*H*)-ones and sulfoxonium ylides that afforded 12 examples of spiro-isoxazole-5-one in yields ranging from 93 to 99% and a diastereomeric ratio from 6:1 to >19:1 (**Figure 1**). In contrast to the cis product reported in Croce's work, the major product was characterized as the trans isomer by X-ray diffraction, despite the large NMR coupling constant in the doublet signals corresponding to the hydrogen in the cyclopropyl moiety. A Michael-type addition pathway was proposed as the mechanism governing the reaction system based on Density Functional Theory calculations performed at the SMD/ωB97M-V/def2-TZVP//SMD/X3LYP/def2-SVP level. Furthermore, the microkinetic analysis model employing the calculated energy barriers at this level successfully reproduced the experimentally observed reaction time for the complete consumption of the starting material and correctly predicted the trans isomer as the major product.

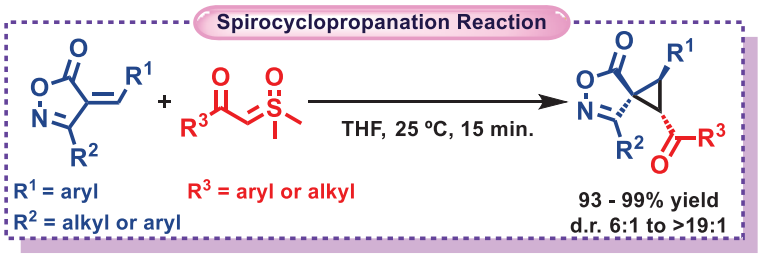

Figure 1: Spirocyclopropanation reaction of α,β-unsaturated isoxazol-5(4H)-ones using sulfoxonium ylides.

Acknowledgements: The authors are grateful for financial support from CAPES (Finance Code 001), CNPq, UFJF, and FAPEMIG.

References:

1. da Silva, A. F.; Fernandes, A. A.; Thurow, S.; Stivanin, M. L.; Jurberg, I. D. *Synthesis.* **2018**, *50, 13*, 2473-2489.
2. Caiuby, C. A.; Furniel, L. G.; Burtoloso, A. C. *Chemical science.* **2022**, *13, 5*, 1192-1209.
3. Croce, P. D. *Journal of Heterocyclic Chemistry.* **1976**, *13, 5*, 1109-1110.

Michael additions to ketosulfoxonium ylides to obtain heterocycles

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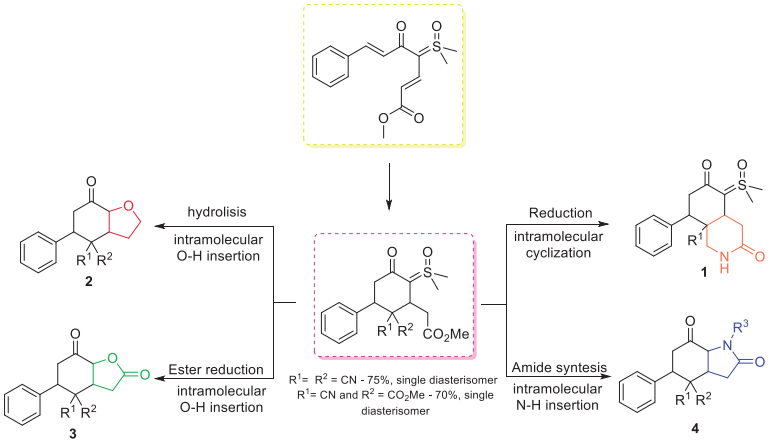
In this work, a new method for the synthesis of cyclic ketosulfoxonium ylides, containing a tetra-substituted cyclohexanone moiety, is described. These new cyclic ylides were obtained in an one-pot reaction through two sequential Michael additions from α,β-unsaturated ketosulfoxonium ylides, employing various carbon nucleophiles containing electron-withdrawing groups. Products were obtained in yields up to 90% and as single diastereomers. The main results are presented in **Scheme 1**.

The cyclic ylides structure will be further functionalized through reduction, substitution, or insertion reactions, enabling access to a variety of substituted heterocycles. Reduction of the nitrile group to the corresponding alkyl amine can promote the formation of the six-membered lactone **1** after an intramolecular cyclization involving the ester functionality. Alternatively, reduction of the methyl ester group to the corresponding alcohol or its hydrolisis to the corresponding carboxylic acid can yield furan **2** or the substituted lactone **3,** through intramolecular O–H insertion reactions with the ylide functionality. Furthermore, nucleophilic addition of an amine on the methyl ester group can afford the corresponding amide intermediate, which may subsequently undergo intramolecular N–H insertion to furnish the five-membered lactam **4**.

Given the significance of this class of compounds and the synthetic versatility of the obtained scaffold, ongoing efforts are focused on accessing and expanding this family of derivatives.



Scheme 1: Possible heterocycles obtained by the derivatization of the cyclic ylides obtained.

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References:

1. a) Kabir, E.; Uzzaman, M. *Results in Chemistry*, **2022** v. 4, p. 100606. b) Jayalakshmi J. et al. *ACS Omega*, **2023** v. 8, n. 41, p. 37731–37751. C) Scott, K.; Njardarson,T. *Topics in Current Chemistry*, **2018**. v. 376, n. 1. 2018.

Asymmetric Synthesis of 1,4-Oxachalcogenanes

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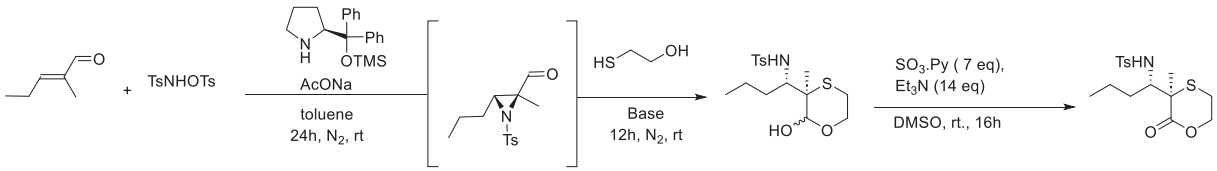
Morpholines and piperazines are heterocycles found in numerous drugs, including those targeting the central nervous system and bearing antitumoral acitivity.[1,2] Their presence is associated to several different contribution on the drug's mechanism of action, including potential increases of *in vivo* stability, affinity, potency and bioavailability.[1] Given their strong pharmacological potential, we are particularly interested in exploring their bioisosteres by synthesizing novel variations. Introducing heteroatoms such as sulfur allows for the formation of 1,4-oxathianes and thiomorpholine rings, which may alter and even enhance drug effectiveness and bioavailability.[3] Despite that, 1,4-Oxathiane is a heterocyclic system still underexplored in medicinal chemistry. Due to the limited literature on the enantioselective synthesis of these structures, we are developing a methodology that could also enable similar modifications with Se and Te variations.

Based on the methodologies previously described for the formation of α-substituted α,β-*N*-Tosyl aziridines,[4,5] we are utilizing these species as electrophiles in reactions with 2-mercaptoethanol acting as a bis-nucleophile, leading to a cyclic hemiacetal. A subsequent oxidation allowed the isolation of the desired heterocycle as described on Scheme 1. The reported enantioselective cyclization, followed by the stereospecific aziridine ring-opening, is expected to ensure the enantiopurity of the product.



Scheme 1: Enatiosselective cyclization and formation of the 1,4-Oxathiane.

Acknowledgments: We thank to São Paulo Research Foundation (FAPESP) Brasil (2022/14310-0) for the financial support and CAPES (88887.150453/2025-00) for the scholarship.

References:

(1) Kourounakis, A. P.; Xanthopoulos, D.; Tzara, A. *Med. Res. Rev.* **2019**, *40*, 709.
(2) Shaquiquzzaman, M.; Verma, G.; Marella, A.; Akhter, M.; Akhtar, W.; Khan, M. F.; Tasneem, S.; Alam, M. M. *Eur. J. Med. Chem.* **2015**, *102*, 487.
(3) Kozlova, A.; Thabault, L.; Dauguet, N.; Deskeuvre, M.; Stroobant, V.; Pilotte, L.; Liberelle, M.; Van den Eynde, B.; Frédérick, R. *Eur. J. Med.* Chem. **2022**, *227*, 113892.
(4) Albrecht, Ł.; Jiang, H.; Dickmeiss, G.; Gschwend, B.; Grann Hansen, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 26, 9188.
(5) Deiana, L.; Dziedzic, P.; Zhao, G.-L.; Vesely, J.; Ibrahem, I.; Rios, R.; Sun, J.; Córdova, *A. Chem. Eur. J.* **2011**, *17*, 7904.

Fluorogenic 2-(Nitroaryl)benzothiazole & Benzoxazole Derivatives for the Detection of Nitroreductase Activity

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Due to the continual evolution of mutations within bacteria, the risk of antimicrobial resistance is becoming an ever-increasing threat towards public health. By 2050 it is predicted that antimicrobial resistance will pose a greater threat to life than cancer and will prove to be an enormous economic burden.[1] The development of novel and rapid microbial diagnostic methods is therefore a priority within clinical research, but additionally within the food industry and the environmental sector.[2] Having the ability to detect which pathogenic bacteria are the cause of an infection allows the correct prescription of antibiotics, reduces the likelihood of resistance developing, maintains efficacy of antibiotics currently in use and provides a more effective form of treatment.

Incorporation of fluorogenic enzyme substrates into bacterial growth media is an attractive diagnostic method. This particular research details the synthesis of weakly-fluorogenic benzothiozole (**1,4** and **7, scheme 1**) and benzoxazole (**2, 5, 6** and **8, scheme 1**) derivatives containing nitro functionality, for use as nitro-reductase substrates.[3] These nitro-aromatic substrates undergo reduction to their corresponding, fluorescent, hydroxylamines in the prescence of nitroreductase enzymes within the bacteria. Hence, allowing for rapid detection of such bacteria on biological media.

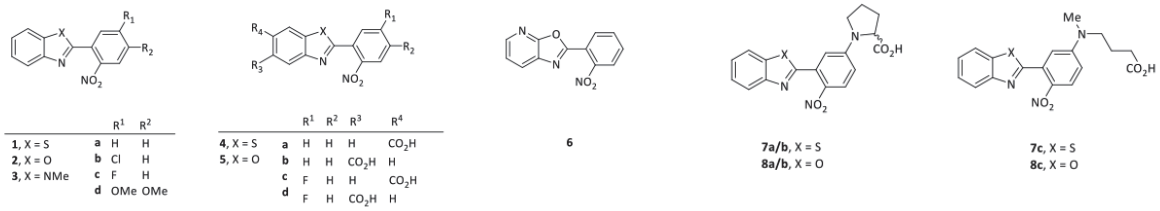

Figure 1. Library of benzothiazole and benzoxazole derived compounds synthesised as part of this project.

This presentation compares the effects of inclusion of a thiol moiety in contrast to an oxazole moiety, in addition to how the addition of carboxyl functionality impacts the solubility, and therefore efficacy, of these substrates within culture media. Several of these compounds were successful in producing coloured colonies in the presence of the majority of Gram-negative bacteria used within this study, as well as with 2 of the 8 Gram-positive bacteria they were tested against,[3] allowing for their use in the detection of a wide range of clinically important microorganisms.

Acknowledgements: We thank bioMérieux SA, La-Balme-les-Grottes France for their funding of this project. We would also like to thank the Freeman Hospital Newcastle for allowing the use of their microbiology facilities and expertise, allowing for the testing of synthesised compounds.

References:

1. Varadi, L.; Luo, J. L.; Hibbs, D. E.; Perry, J. D.; Anderson, R. J.; Orenga, S.; Groundwater, P. W. Methods for the detection and identification of pathogenic bacteria: past, present, and future. *Chem Soc Rev,* **2017**, 46, 4818-4832.
2. Orenga, S.; James, A. L.; Manafi, M.; Perry, J. D.; Pincus, D. H., Enzymatic substrates in microbiology, *J. Microbiol. Methods.*, 2009, 2, 139-155
3. Cellier, M; Gignoux, A; James, A. L..; Orenga, S.; Perry, J. D.; Robinson, S. N.; Stanforth, S. P.; Turnbull, G., 2-(nitroaryl)benzothiazole and benzoxazole derivatives as fluorogenic substrates for the detection of nitroreductase activity in clinically important microorganisms, *Bioorg. Med. Chem. Lett*, **2015**, 25, 5694-5698.

EVALUATING DIFFERENT NITROGEN-CONTAINING HETEROCYCLES AS POTENTIAL NEW SCAFFOLDS FOR ALKYNE-BASED *Hs*DHODH INHIBITORS

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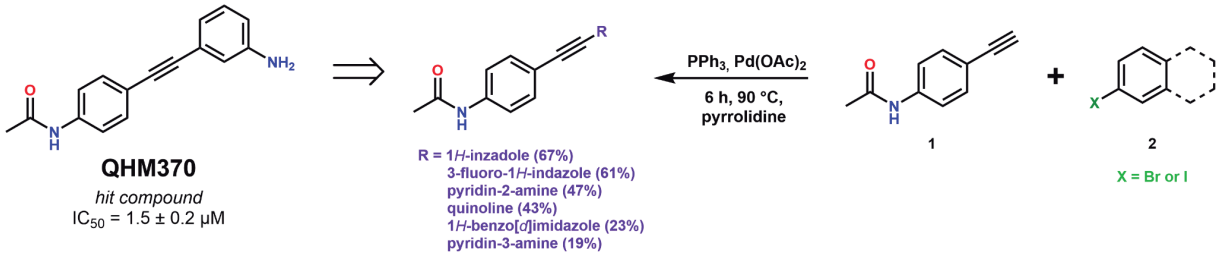
Introduction: Building upon the previous 1,2-diarylethine fragment[(1)], a human dihydroorotate dehydrogenase (*Hs*DHODH) inhibitor with favorable inhibitory (IC_{50} = 1.5 ± 0.2 μM) and antiviral activity (EC_{50} = 1.7 ± 0.5 μM), but insufficient water solubility, this work employs Sonogashira coupling reactions to synthesize a new series of fragments bearing different nitrogen-containing heterocycles. Through the capacity of these scaffolds to modulate physicochemical properties relevant to aqueous solubility and intermolecular interactions with biological targets[,(2)] we are introducing heterocycles to the 1,2-diarylethines as a strategy to obtain structurally diverse alkyne fragments with improved physicochemical properties and potency. **Methods:** Using a copper-free Sonogashira coupling with pyrrolidine[(1,3)] exemplified in **Scheme 01**, it was possible to obtain the coupling products with **1**, where the *p*-acetamide functional group is essential for the activity, and **2,** with diverse homo and bicyclic nitrogenated heterocycles.



Scheme 01 - The hit compound of the alkyne series and the methodology to obtain the diarylalkyne fragments. The heterocycles coupled with N-*p*-ethynylphenylacetamide are described in R, along with their respective reaction yields.

Results: To date, the successfully synthesized alkyne fragments present commonly explored nitrogen-containing heterocycles in medicinal chemistry: benzimidazole (IC_{50} = 200 μM), indazole (C3 = H: IC_{50} = 9.0 ± 1.0 μM; C3 = F: IC_{50} = 18.0 ± 1.0 μM), quinoline, and different substituted pyridines with isolated yields of 19–67%. **Conclusions:** As only two of the heterocyclic 1,2-diarylethine fragments have been evaluated in enzymatic assays so far, both displaying intermediate potency, it is essential to continue exploring additional heterocyclic scaffolds and assess the inhibitory activity of the remaining fragments to elucidate the structure-activity relationships of this series and guide the optimization of antiviral compounds.

Acknowledgements: The authors acknowledge the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) for the funding of the project (n° 2024/23733-8).

References:

1. Vaidergorn *et al. E. J. Med. Chem.* **2025**, *297*, 117876.
2. Barbosa *et al. Tetrahedron*. **2026**, *195*, 135240.
3. Lara-Ochoa, F., Espinosa-Pérez, G. *Tetrahedron Lett.* **2007**, *48*, 39.

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Study focusing on the synthesis of pseudopeptides with a 1,4-dihydropyridine nucleus through combined multicomponent reactions.

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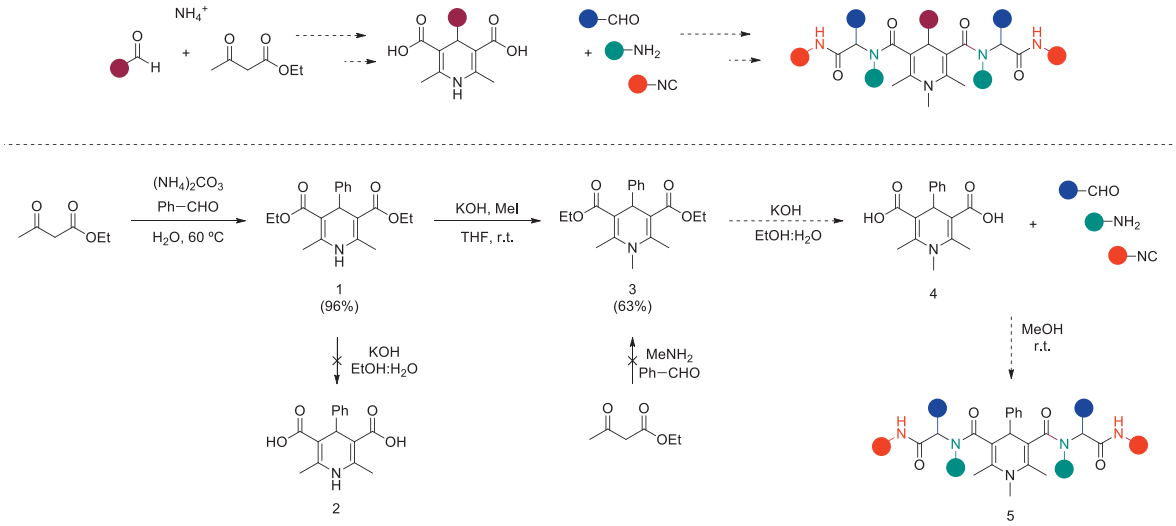
Multicomponent reactions are one of the synthetic strategies employed in the preparation of bioactive compounds, and the combination of these reactions has already led to the production of molecules with broad biological activity, as well as compounds with high diversity and structural complexity.[1] Among the structural and reactional frameworks that remain unexplored, the Hantzsch reaction and the Ugi-4CR stand out. The combination of the 1,4-dihydropyridine nucleus with pseudopeptides may result in molecules with high biological potential. The present study aims to integrate these reactions to obtain a series of novel compounds.

The synthetic route shown in **Scheme 1** is currently in the validation and optimization phase. Using benzaldehyde as a prototype, the Hantzsch reaction produced the 1,4-dihydropyridine nucleus **1** with a 96% yield. Initially, the compound was subjected to a hydrolysis reaction to obtain compound **2**; however, due to the rigidity and resonance effects of the structure, the reaction did not proceed. Alkylation of the nitrogen atom of the 1,4-dihydropyridine nucleus is essential to increase the susceptibility of the structure to reactions in its side substituents.[2] Therefore, attempts were made to obtain compound **3** through a modified Hantzsch reaction, in which methylamine replaced the ammonium salt. However, the reaction produced a complex mixture of product and by-products. Compound **3** was then obtained in 63% yield by *N*-alkylation with iodomethane. The subsequent steps of the study consist obtaining compound **4** through hydrolysis reaction and using it in the Ugi-4CR to obtain the desired type **5** compound series.



Scheme 1: Synthetic scheme under study for obtaining peptides with a 1,4-dihydropyridine nucleus.

Acknowledgements: We thank the CAPES (0001) grant.

References:

1. a) Zhang, W.; Zhi, S.; Ma, X. *Org Biomol Chem*, **2019,** 17, 7632–7650. b) Ghashghaei, O.; Seghetti, F.; Lavilla, R. *Beilstein Journal of Organic Chemistry*, **2019**, 15, 521–534.
2. Sobolev, A.; Franssen, M. C. R.; Duburs, G.;Groot, Ae. D. *Biocatalysis and Biotransformation*,**2004**, *22*(4), 231–252.

Visible-Light-Driven Synthesis of Heterocyclic Vinyl Aryl Sulfides from Diphenylacetylene derivatives with Photophysical Potencial

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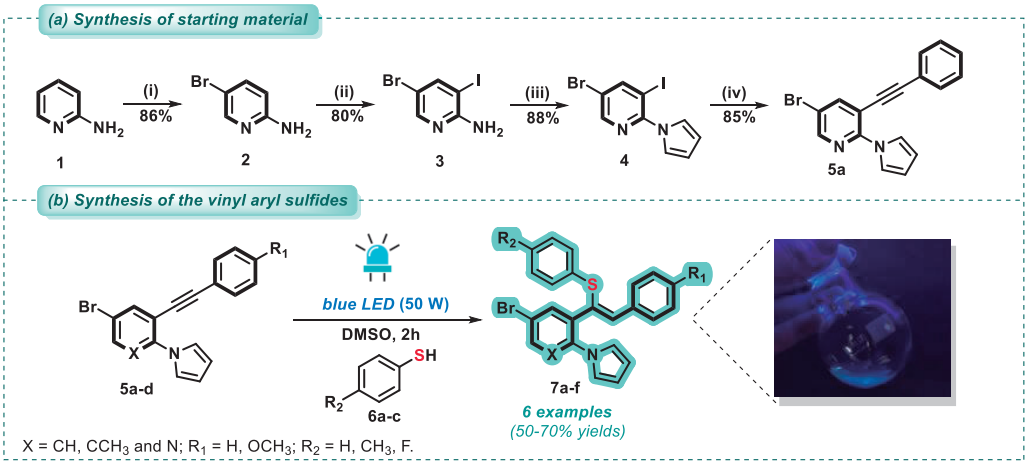
Diarylacetylene derivatives are important scaffolds in organic chemistry due to their extended π-conjugation and photophysicial properties, enabling applications in luminescent and optoelectronic materials.[1] Furthermore, sulfur-functionalized vinyl systems, in particular, exhibit light-sensitive fluorescence with red-shift effects, making them promising for sensors and organic emitters.[2] However, any approaches for the preparation of vinylaryl sulfides and related π-conjugated systems still rely on expensive metals or non-sustainable conditions, reinforcing the importance of more sustainable approaches. In this context, this work presents a visible-light-driven methodology for the synthesis of vinylaryl sulfides from diphenylacetylene derivatives and explores their tunable optical properties, contributing to the development of sustainable methods for next-generation functional materials.

The synthesis started with the preparation of 5a from 2-aminopyridine, which underwent a bromination-addition reaction (i), followed by iodination (ii), then pyrrole functionalization (iii) and finally a Sonogashira cross-coupling reaction (iv) (Scheme 1a). For the synthesis of the vinylaryl sulfide derivatives **7a-f**, an optimization study was carried out. The best condition was achieved using blue LED light (50 W) as the energy source, DMSO as solvent during 2 hours of reaction in the presence of thiophenol **6a**. Through this condition, the desired product **7a** was obtained with a 70% yield (Scheme 1b). After optimization, the protocol was applied to three *p*-substituted thiols **6a-c** and four diphenylacetylene derivatives **5a-d**, affording six new products in 50-70% yields, demonstrating good efficiency.

The compounds are currently under photophysical evaluation by Professor Fabiano Rodembusch's group, and preliminary observations suggest that structural modifications may influence their photophysical behavior, highlighting their potential as promising building blocks for the development of functional materials. Thus, the developed protocol provides an efficient and practical approach to access vinylaryl sulfides under mild visible-light conditions while enabling the exploration of their structure-property relationships.



Scheme 1. (a) Synthesis of starting material and (b) synthesis of the vinyl aryl sulfides.

Acknowledgements: We thank UFF, CAPES, FAPERJ and CNPq.

References:

1. Kobayashi K. *et al. Beilstein J. Org. Chem.* **2024,** *20*, 2682-2690.
2. Yasabu, B.; Gashaw F. *IJANS.* **2021**, *14*, 16-24.

Design and Synthesis of Chalcogen-Containing Coumarin Hybrids as Potential Bioactive Scaffolds

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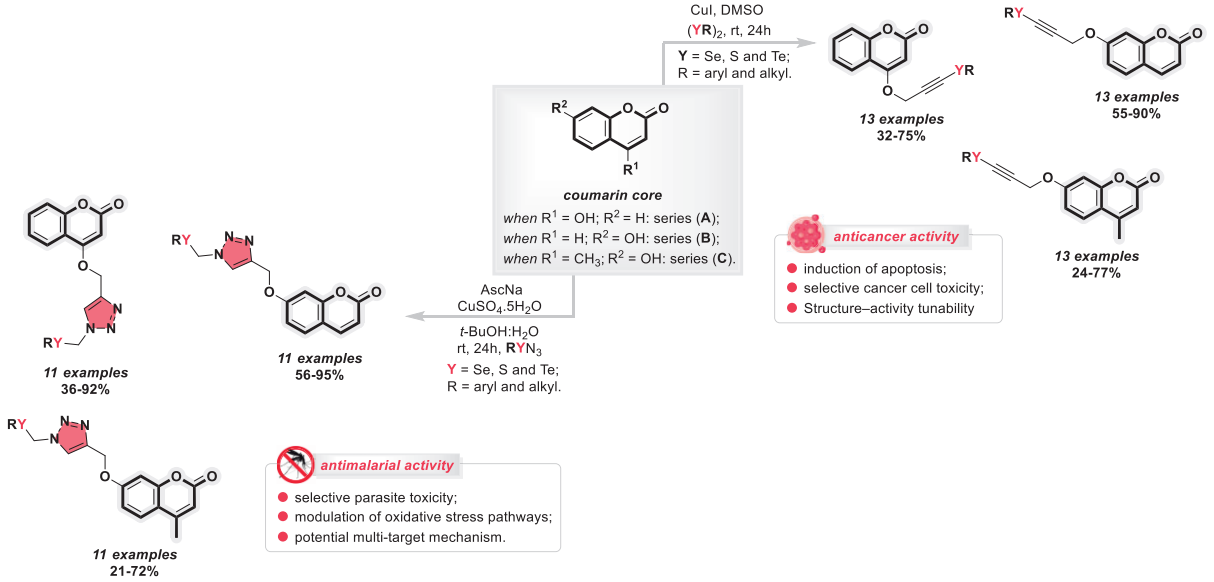
Coumarins are heterocyclic compounds widely distributed in plants and well known for their diverse biological activities, particularly their anticancer and antimalarial potential.[1a] In parallel, compounds containing chalcogens have attracted significant attention due to their pharmacological properties.[1b,2a] Our research group has stood out in the combination of chalcogen-containing moieties with important bioactive scaffolds.[2b,2c] In this context, in the present work, we designed two distinct series of compounds combining chalcogens and coumarins. One series incorporates a 1,2,3-triazole group, while the other is based on direct coupling with diorganoyl dichalcogenides. In the first series, the introduction of the 1,2,3-triazole ring was a strategic choice due to its high chemical stability and its well-established role as a bioactive linker capable of enhancing interactions with biological targets.In the second series, the direct coupling approach allows a more straightforward incorporation of chalcogen atoms, potentially modulating electronic and lipophilic properties and, consequently, biological activity.[2b] The synthetic route began with the propargylation of coumarins, a strategy that allowed us to obtain the desired products in 80% yield.[2a] Subsequently, triazole derivatives were obtained through the CuAAC reaction between propargylated coumarins and chalcogen-containing azides derived from dichalcogenides.[2b] Simultaneously, a second series was synthesized through the direct coupling of dichalcogenides with propargylated coumarins using copper iodide in dimethyl sulfoxide (Scheme 1).[2c] These approaches allowed access to structurally diverse hybrids, which were subjected to biological evaluation, triazole derivatives for antimalarial assays and chalcogen-coupled compounds for anticancer studies, highlighting their potential as promising bioactive structures.



Scheme 1. General synthetic route for the preparation of the target compounds.

Acknowledgements: UFF, CAPES, FAPERJ, CNPQ

References:

1. a) Kaushik C. P.; Chahal M. *Monatsh. Chem.* **2021**, *152*, 1001. b) Gomes L. S.; *Future Med. Chem.* **2025**, *17*, 1363.
2. a) Ferreira, T.M.; *Chem. Eur. J.* **2025**, 31, e202403987. b) Gomes L. S.; *Bioorganic & Medicinal Chemistry* **2025**, 132, 118447 c) Gomes L. S.; *ACS Omega* **2024**, *9*, 21948

Microwave-assisted synthesis of tetrasubstituted 2-pyridones from allylic β-ketoesters and primary amines mediated by $NaBH_4$

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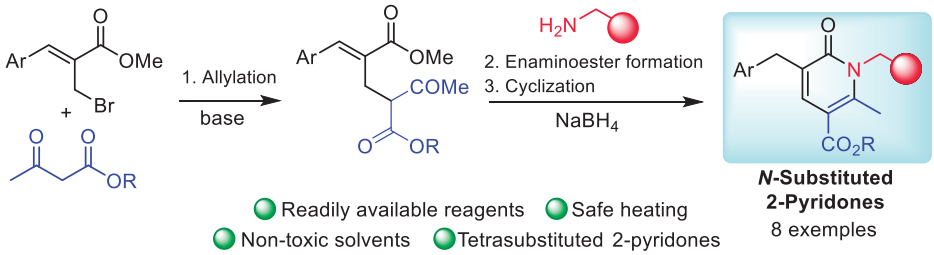
N-Substituted 2-pyridones are privileged heterocyclic scaffolds widely found in natural products and biologically active molecules,[1] exhibiting important pharmacological properties such as anticancer, anticonvulsant, and anti-inflammatory activities.[2] Owing to their synthetic and medicinal relevance, the development of efficient methods for their preparation remains highly desirable. In this context, we investigated the use of Morita–Baylis–Hillman (MBH)-derived allylic bromides as versatile building blocks for the synthesis of functionalized pyridones. Regioselective allylation of ethyl acetoacetate with MBH bromides under microwave irradiation afforded key 1,5-diester intermediates, which were subsequently subjected to a one-pot sequence involving treatment with primary amines to generate β-enaminoesters, followed by sodium borohydride-mediated cyclization under mild acidic conditions. This operationally simple approach avoids the isolation of unstable intermediates and enables rapid access to 1,3,5,6-tetrasubstituted *N*-substituted 2-pyridones in moderate overall yields from allylic bromides. Remarkably, $NaBH_4$ promoted cyclization without reduction of ester or olefinic functionalities, suggesting an unusual activation pathway, possibly involving *in situ* generated borane species. Control experiments are currently underway to better understand the mechanistic role of $NaBH_4$ in the cyclization step. This study represents the first use of MBH-derived allylic bromides as precursors for highly substituted 2-pyridones of synthetic and potential pharmacological relevance.



Scheme 1: synthesis of 2-pyridones.

Acknowledgements: CAPES, CNPq, FAPESC and INCT-Catálise

References:

1. a) Verma, K. K.; Kapoor, S.; Kushwaha, V. K.; Mishra, A.; Upadhyay, A. *Lett. Drug Design Discov.* **2024**, *21*, 1617-1631. b) Asmaa, K.; Fatima, B.; Zahira, K.; Noureddine, C.-B. *Mini-Rev. Org. Chem.* **2023**, *20*, 358-371. c) Amer, M. M. K.; Aziz, M. A.; Shehab, W. S.; Abdellattif, M. H.; Mouneir, S. M. *J. Saudi Chem. Soc.* **2021**, *25*, 101259.
2. a) Lehmann, M.; Kolb, M. *Eur. Respir. J.* **2023**, *61*, 2300240. b) Watts, J. M.; Shaw, S. J.; Jonas, B. A. *Curr. Treat. Opt. Oncol.* **2024**, *25*, 1345–1353.
3. Moro, P. A. M.; Russo, T. V. C,; Viana, F.R.; Sá, M. M. *Tetrahedron Letters* **2026**, *181*, 156124.

Visible light-mediated cyclization of Sulfoxonium ylides: Synthesis of trisubstituted furans

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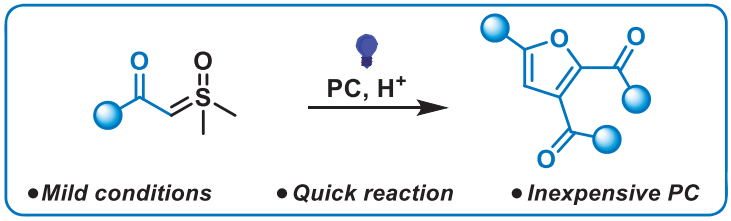
Since their first appearance in the early 1930s, sulfoxonium ylides have steadily expanded in both synthetic utility and chemical relevance. This trend is also evident in the context of photocatalytic transformations, particularly in recent years. The application of sulfoxonium ylides in visible-light-mediated reactions has enabled the synthesis of a wide variety of structurally complex and synthetically valuable compounds, including, but not limited to, tetralones, sultines, modified peptides, and other relevant molecular scaffolds[1].

In this work, we demonstrate that the combination of sulfoxonium ylides with a suitable photocatalyst possessing sufficiently high oxidation potential, in the presence of a proton source, enables the one-pot synthesis of trisubstituted furans (Scheme 1). It is noteworthy that, although new methodologies for the synthesis of trisubstituted furans have recently been reported,[2] this is the first time that these types of furans can be reached from sulfoxonium ylides.

Furans are well recognized for their importance in materials science, particularly in the development of biodegradable polymers and, more recently, in applications related to organic light-emitting diodes (OLEDs).[3] In addition, numerous furan-derived molecules exhibit significant biological activity, including commercial drugs such as Furosemide and Tanshinone I[4].

In summary, beyond enabling the one-pot synthesis of trisubstituted furans, the methodology described herein represents a novel and significant contribution to the chemistry of sulfoxonium ylides.



Scheme 1: Synthesis of Trisubstituted furans from sulfoxonium ylides

Acknowledgements: We thank the São Paulo Research Foundation (FAPESP) for financial support (2023/02675-7) . We also thank the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for financial support in the form of a fellowship to K.C.C (403690/ 2022-6).

References:

1. a) WAN, Chuan; HOU, Zhanfeng; YANG, Dongyan; *et al*. The thiol-sulfoxonium ylide photo-click reaction for bioconjugation. **Chemical Science**, v. 14, n. 3, p. 604–612, 2023; b) XIAN, Ning; LI, Zihao; JI, Xiaochen; *et al*. Tetralone Formation through Visible-Light-Driven Photocyclization of Aryl Sulfoxonium Ylides with Unactivated Alkenes. **Organic Letters**, v. 27, n. 33, p. 9310–9315, 2025; c) HUANG, Hongyin; GUI, Mengqi; ZHANG, Guoqiang; *et al*. Modular and Direct Synthesis of γ-Sultines From Simple Unactivated Alkenes. **Angewandte Chemie International Edition**, v. 65, n. 14, p. e22431, 2026.
2. a) FAN, Jian; ZU, Yanhong; ZHENG, Zhimin; *et al.* A silver-mediated radical process of β-keto sulfones for the synthesis of 2,3-diacyl furans. **Organic & Biomolecular Chemistry**, v. 22, n. 9, p. 1770–1774, 2024; b) GAO, Benxuan; LIANG, Tongwei; KUSCH, Lucas M. P.; *et al*. Copper-Catalyzed Cascade Cross-Coupling/Cyclization of Silyl Enol Ethers for Synthesis of Polysubstituted Furans. **Organic Letters**, 2026.
3. BIELSKI, Roman; GRYNKIEWICZ, Grzegorz. Furan platform chemicals beyond fuels and plastics. **Green Chemistry**, v. 23, n. 19, p. 7458–7487, 2021.

4. a) ROUSH, George C.; KAUR, Ramdeep; ERNST, Michael E. Diuretics: A Review and Update. **Journal of Cardiovascular Pharmacology and Therapeutics**, v. 19, n. 1, p. 5–13, 2014.
b) HUANG, Xing; JIN, Lili; DENG, Hao; *et al*. Research and Development of Natural Product Tanshinone I: Pharmacology, Total Synthesis, and Structure Modifications. **Frontiers in Pharmacology**, v. 13, 2022.

Synthesis of novel biomass-derived sulfur ylides

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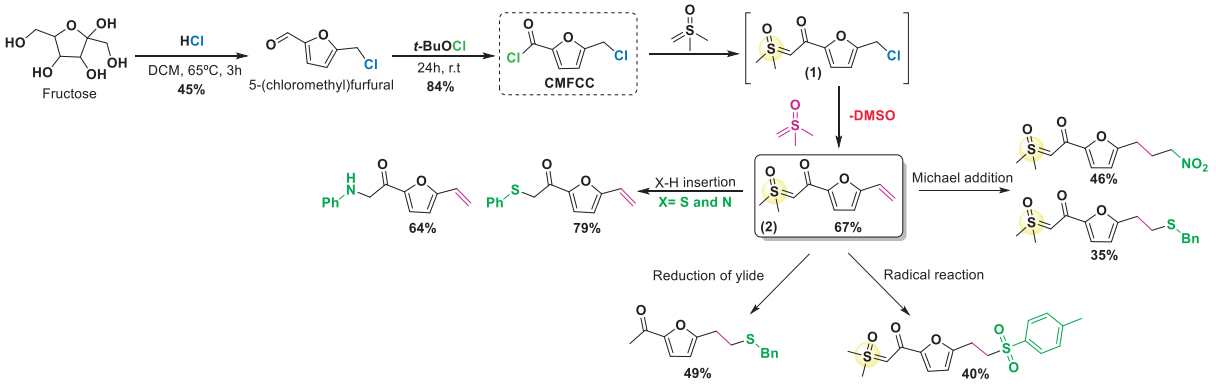
Furans are heterocycles of great relevance across various fields, particularly in the pharmaceutical industry and in materials science.[1] In addition, they stand out as versatile intermediates in the synthesis of industrially relevant molecules.[1] Many furanic compounds can be obtained from renewable sources, such as carbohydrates, making them particularly attractive from the perspective of sustainable chemistry.[2] Despite advances in this area, the application of furan derivatives in the synthesis of sulfur ylides (SY) remains unexplored. SY are important intermediates in synthetic transformations, particularly as precursors to carbene species.[3] In this context, this work describes the development of a new methodology for the synthesis of α-carbonyl sulfur ylides from 5-(chloromethyl)furan-2-carbonyl chloride (CMFCC). The CMFCC was obtained through the oxidation of 5-(chloromethyl)furfural, a fructose-derived compound, in yields of up to 84% (Scheme 1). Subsequently, this intermediate was employed in the synthesis of the new sulfur ylide (2), with yields of up to 67%. It was observed that the formation of this compound occurs via the intermediate ylide (1).From ylide (2), X–H insertion reactions (X = S and N) were carried out via metal–carbene intermediates, affording the corresponding products in good to excellent yields. Michael addition reactions with different nucleophiles also led to the formation of new functionalized ylides, with yields of up to 46%. Furthermore, radical reactions were also explored, resulting in addition to the double bond and the formation of another functionalized ylide, with yields of up to 40%.These results highlight the versatility of this system, demonstrating that a single biomass-derived furanic ylide, such as (2), can provide access to a variety of functionalized furanic compounds, thereby expanding its potential in organic synthesis.



Scheme 1: Synthesis of New Biomass-Derived Sulfur Ylides.

Acknowledgements: We thank Sao Paulo State Research Foundation – FAPESP for fellowship for J.R.S. (grant number 25/06191-0) and financial support to A.C.B.B. (25/21337-0).

References:

1. a) *Gut*, **1983**, 24, 418-420. b) *Green Chem.*, **2021**, 23, 7458-7487
2. a) *ACS Sustainable Chem. Eng.* **2019**, 7, 6, 5588–5601. b) *Green Chem.*, **2014**,16, 516-547.
3. a) *Chem. Sci.,* **2022**, 13,1192. b) *Org. Lett.* **2011**, 13, 20, 5480–5483.

Optimization and application of Ullmann Reaction in *N*-arylation of 4-aminopyrrolo[2,1-*f*]triazine

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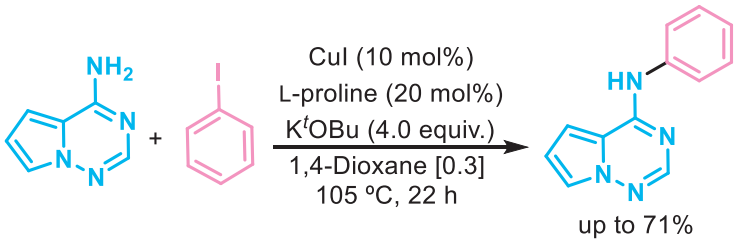
Metal catalyzed-coupling reactions play an important role in organic chemistry, as they permit the synthesis of diverse molecules that can serve as building blocks for a range of compounds, such as pharmaceuticals, dyes, and agricultural products. Among these reactions, those involving copper catalysts deserve special attention, since they represent a cheaper and greener alternative when compared to those involving catalysts made of more precious metals. In this scenario, the Ullmann reaction is remarkable, allowing the production of arylamines.[1] This reaction has been widely reported in the literature, being investigated for a series of heterocycles, however, methods aiming to obtain the arylated 4-aminopyrrolo[2,1-*f*]triazine heterocycle via the Ullmann reaction have not yet been extensively investigated. This heterocycle deserves special attention, since is a component of several drugs with potential biological activity, such as Avapritinib and Rogaratinib, and has recently attracted attention due to its presence in Remdesivir, an antiviral used in the treatment of COVID-19.[2]

In this work, we report a method to *N*-arylate pyrrolotriazine via the Ullmann reaction, using a methodology that was optimized for this heterocycle, aiming to achieve a series of analogues that can be potential building blocks in the construction of new molecules. Initially, we investigated conditions such as solvent, temperature, reagent equivalents, and solvent concentration, allowing the reaction yield to increase from 22% to 71%. Furthermore, a scope of molecules is being constructed to verify the generality of this protocol and thus obtain a series of compounds.



Scheme 1: Optimized reaction condiction.

Acknowledgements: We thank FAPEMIG, CAPES (Finance code 001), CNPq (301820/2025-2, 400077/2023-0, 401402/2025-8 and 407577/2024-6) for their financial support.

References:

1. a) Ullmann, F. Chemische Berichte, v. 36, n. 2, p. 2382–2384, 1903. b) Mao, J. et al. Tetrahedron, v. 64, p. 1383-1387, 2008.
2. Pereira, V. R. D et al. European Journal of Organic Chemistry, v. 28, n. 42, 2025.

Iodine-promoted selenylation of pyrrolo[2,1-*f*][1,2,4]triazin-4-amine

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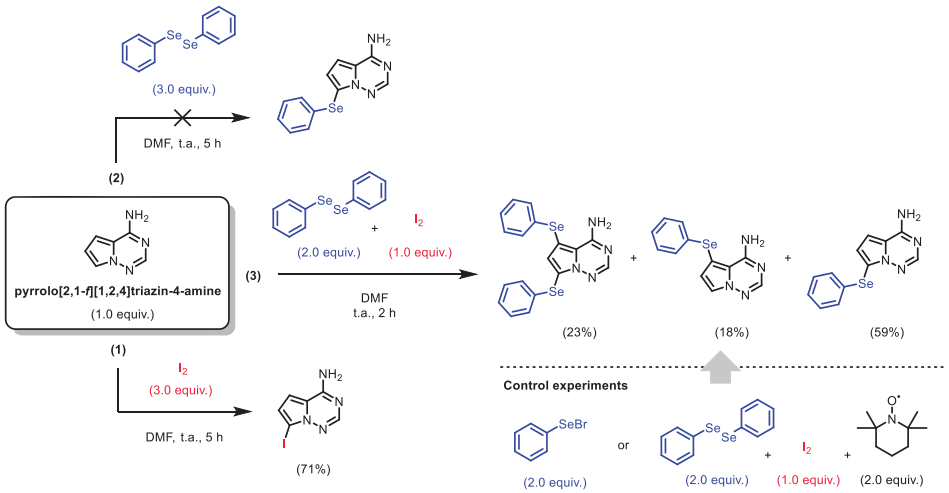
In a previous study published by our research group, we described an optimized synthetic route for the preparation of the *N*-heterocycle pyrrolo[2,1-*f*][1,2,4]triazin-4-amine, as well as alternative methodologies for its functionalization at the C7 position and the exocyclic amino group (NH_2). Among the investigated strategies, we highlight the selective halogenation at C7 through the reaction with molecular iodine (I_2) under mild conditions (**Scheme 1, eq 1**). However, under analogous conditions, the reaction with diphenyl diselenide (Ph_2Se_2) did not promote heterocycle functionalization, suggesting a delicate balance between the electrophilicity of the reactive species and the nucleophilicity of the substrate (**Scheme 1, eq 2**).[1] To gain further insight into this reactivity, we investigated the reaction of the heterocycle with Ph_2Se_2 in the presence of I_2. Notably, this system proved highly reactive, enabling selective functionalization at both the C7 and C5 positions as well as the concurrent formation of disubstituted derivatives (**Scheme 1, eq 3**). Control experiments employing phenylselenyl bromide (PhSeBr) alone or Ph_2Se_2 and I_2 in the presence of the radical scavenger TEMPO afforded identical results. These findings suggest that the halogen promotes the *in situ* generation of highly electrophilic selenium species, such as PhSeI and PhSeBr, thereby supporting the involvement of a likely non-radical reaction pathway. Furthermore, new diaryl diselenides bearing different substitution patterns will be synthesized to evaluate the scope and generality of the developed methodology.[2]



Scheme 1: Conditions for the iodine-promoted selenylation of pyrrolo[2,1-*f*][1,2,4]triazin-4-amine.

Acknowledgements: We thank FAPEMIG, CAPES (Finance code 001), CNPq (301820/2025-2, 400077/2023-0, 401402/2025-8 and 407577/2024-6) for their financial support.

References:

1. Pereira, V. R. D.; et al. Eur. J. Org. Chem. **2025**, 28, e202500512.
2. Kommula, D.; et al. Synth. Commun. **2020**, 50, 1026.

From Hit to Lead: Optimization of Imidazo-Fused Heterocycles as Trypanocidal Agents with Enhanced Pharmacokinetic Properties

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Trypanosomiasis is a neglected tropical disease (NTD) caused by protozoa of the genus *Trypanosoma,* including *T. b. gambiense* and *T. b. rhodesiense* (sleeping sickness, sub-Saharan Africa) and *T. cruzi* (Chagas disease, the Americas). Current therapeutic options are limited and frequently associated with adverse effects. [1a-e] Safer and more effective treatment alternatives are needed.Previously, our group identified a hit compound from the imidazo[1,2-c]pyrimidine scaffold with *in vitro* activity against *T. cruzi* (EC_{50} = 0.09 μM) and *T. brucei* (EC_{50} = 0.02 μM), along with metabolic stability in mouse liver microsomes ($t_1/_2$ > 60 min) and high plasma protein binding (unbound fraction of 9.9%), and a favorable pharmacokinetic profile. However, its low solubility under gastric (0.7 μM), intestinal (2.4 μM), and physiological (1.9 μM) pH conditions indicated the need for structural optimization.[2] This work developed new imidazo[1,2-*a*]pyridine and imidazo[1,2-*c*]pyrimidine derivatives to improve aqueous solubility while maintaining trypanosomicidal activity and optimizing the pharmacokinetic profile. Twenty compounds containing an fluorinated/non-fluorinated aromatic rings were synthesized (**Figure 1**), with yields ranging from 7 to 82%. Single-crystal X-ray diffraction confirmed an orthorhombic system, in agreement with ^1H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry. *In silico* pharmacokinetic analysis identified two distinct clusters based on lipophilicity and solubility. *In vitro* assays demonstrated established structure–activity relationships that will guide the design of subsequent series. The next series will incorporate saturated sp3-renriched fragments to improve aqueous solubility and overall pharmacokinetic.

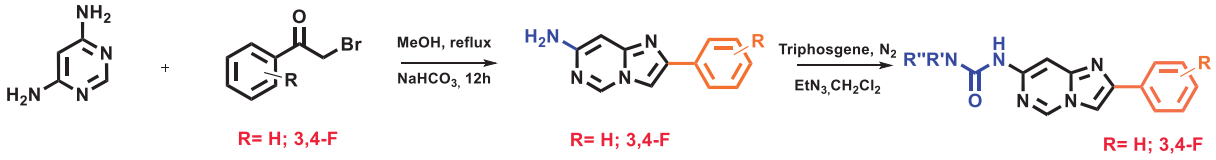

Figure 1: Synthetic route used to obtain the imidazopyrimidines.

Acknowledgements: We thank FAPESP, CRAFT, QHETEM and LMPH.

References:

1. a) World Health Organization. Trypanosomiasis, human African (Sleeping Sickness). b) Franco, J., Scarone, L., & Comini, M. A. *Annual Reports in Medicinal Chemistry*, **2018**, 51, 97-133. c) Dickie, E. A., Giordani, F., Gould, M. K., Mäser, P., Burri, C., Mottram, J. C., ... & Barrett, M. P. *Tropical medicine and infectious disease*, **2020**, 5, 1, 29. d) World Health Organization. Chagas disease (also known as American trypanosomiasis). e) Venturelli, A., Tagliazucchi, L., Lima, C., Venuti, F., Malpezzi, G., Magoulas, G. E., ... & Costi, M. P. *Microorganisms*, **2022**, 10, 7, 1298.
2. Silva, D. G., et al. ACS Medicinal Chemistry Letters, **2017**, 8, 7, 766-770.

Sustainable visible-light-driven selective chalcogenocyclization of juglone

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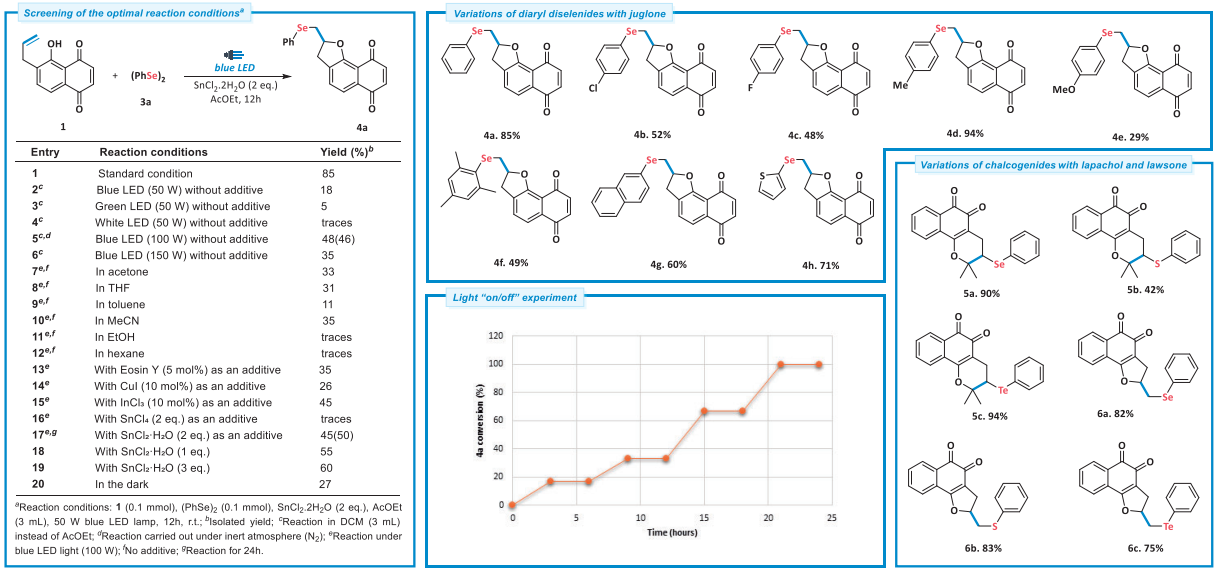
Naphthoquinones are redox-active scaffolds widely recognized for their ability to generate reactive oxygen species (ROS) and for their broad range of biological and photophysical properties.[1] In parallel, chalcogen-containing compounds, particularly those bearing sulfur, selenium, and tellurium, have attracted considerable attention due to their capacity to modulate electronic, redox, and optical properties, thereby enhancing biologically relevant activities.[2] Herein, we report a sustainable visible-light-assisted methodology for the selective cyclization and chalcogen functionalization of naphthoquinones under mild conditions. Using juglone as a model substrate and diphenyl diselenide as the coupling partner, the reaction was optimized under blue LED irradiation (50 W, 12 h) in the presence of $SnCl_2 \cdot 2H_2O$ (200 mol%) in CH_2Cl_2, affording selenonaphthoquinone derivatives in yields of up to 94%. The optimized conditions enabled the preparation of a diverse series of selenium-containing derivatives from juglone, while extension of the methodology to other naphthoquinone scaffolds, including lawsone and lapachol, proved compatible with sulfur-, selenium-, and tellurium-based reagents, significantly broadening the structural diversity of the products obtained. Mechanistic investigations, including light on/off experiments, confirmed the essential role of visible-light irradiation throughout the transformation, supporting a photoinduced chalcogen-radical pathway (Scheme 1). Overall, the developed protocol provides an efficient and versatile platform for accessing structurally diverse chalcogen-functionalized naphthoquinones under sustainable conditions.



Entry	Reaction conditions	Yield (%)[b]
1	Standard condition	85
2[c]	Blue LED (50 W) without additive	18
3[c]	Green LED (50 W) without additive	5
4[c]	White LED (50 W) without additive	traces
5[c,d]	Blue LED (100 W) without additive	48(46)
6[c]	Blue LED (150 W) without additive	35
7[e,f]	In acetone	33
8[e,f]	In THF	31
9[e,f]	In toluene	11
10[e,f]	In MeCN	35
11[e,f]	In EtOH	traces
12[e,f]	In hexane	traces
13[e]	With Eosin Y (5 mol%) as an additive	35
14[e]	With CuI (10 mol%) as an additive	26
15[e]	With $InCl_3$ (10 mol%) as an additive	45
16[e]	With $SnCl_4$ (2 eq.) as an additive	traces
17[e,g]	With $SnCl_2 \cdot H_2O$ (2 eq.) as an additive	45(50)
18	With $SnCl_2 \cdot H_2O$ (1 eq.)	55
19	With $SnCl_2 \cdot H_2O$ (3 eq.)	60
20	In the dark	27

[a]Reaction conditions: **1** (0.1 mmol), $(PhSe)_2$ (0.1 mmol), $SnCl_2.2H_2O$ (2 eq.), AcOEt (3 mL), 50 W blue LED lamp, 12h, r.t.; [b]Isolated yield; [c]Reaction in DCM (3 mL) instead of AcOEt; [d]Reaction carried out under inert atmosphere (N_2); [e]Reaction under blue LED light (100 W); [f]No additive; [g]Reaction for 24h.

Scheme 1. Reaction optimization, substrate scope, and light "on/off" experiments for the visible-light-mediated synthesis of chalcogen-functionalized naphthoquinones.

Acknowledgements: We thank UFF, CAPES, FAPERJ and CNPq.

References:

1) Mone, N. S.; Syed, S.; Ravichandiran, P.; Satpute, S. K.; Kim, A. R.; Yoo, D. J. *ChemMedChem* **2023**, *18*, e202200471.
2) Khan, J.; Rani, A.; Aslam, M.; Pandey, G.; Pant, B. N. *Results Chem.* **2023**, *6*, 101138.

4,7-Dichloroquinoline–Organochalcogen Hybrids: Integrated Photophysical, Electrochemical, and DNA-Interaction Studies

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Fluorescent organic dyes are key to advanced luminescent materials due to their tunable optics, high efficiency, and need for well-designed, photostable chromophores.[1] Within this context, quinoline scaffolds emerge as an alternative due to their rigid π-conjugated framework and tunable electronic properties, which enable fine control over optical behavior.[2] In this context, incorporation of selenium-containing chalcogen units further modulates excited-state dynamics through enhanced spin–orbit coupling,[4] while 1,2,3-triazole linkers provide structural stability and favorable electronic and biological interactions, making them attractive components in fluorescent molecular architectures.[5] Based on these considerations, the present work aimed at the synthesis of a series of new molecular hybrids derived from 4,7-dichloroquinoline and organochalcogens, using the 1,2,3-triazole core as a linker. Initially, alkynes **1a-l** were synthesized from diorganyl dichalcogenides through a sequence involving copper-catalyzed coupling followed by a retro-Favorskii reaction, affording yields ranging from 20 to 90%. Azide **2** was obtained in 90% of yield. After that, The two blocks were combined via CuAAC reaction to afford a library of 11 hybrid molecules **3a-l** with yields of **15–80%** in which the oxidized selenium derivative was also obtained. Additionally, photophysical studies were carried out, revealing a pronounced heavy-atom effect when comparing derivatives **3a**, **3h**, and **4a (Fig. 1b).** Computational results suggest preferential minor groove binding for all quinoline derivatives, with compounds **3c** and **3e** showing the strongest DNA interactions **(Fig. 1c)**. In conclusion, the present work is at an advanced stage, with final experiments underway.

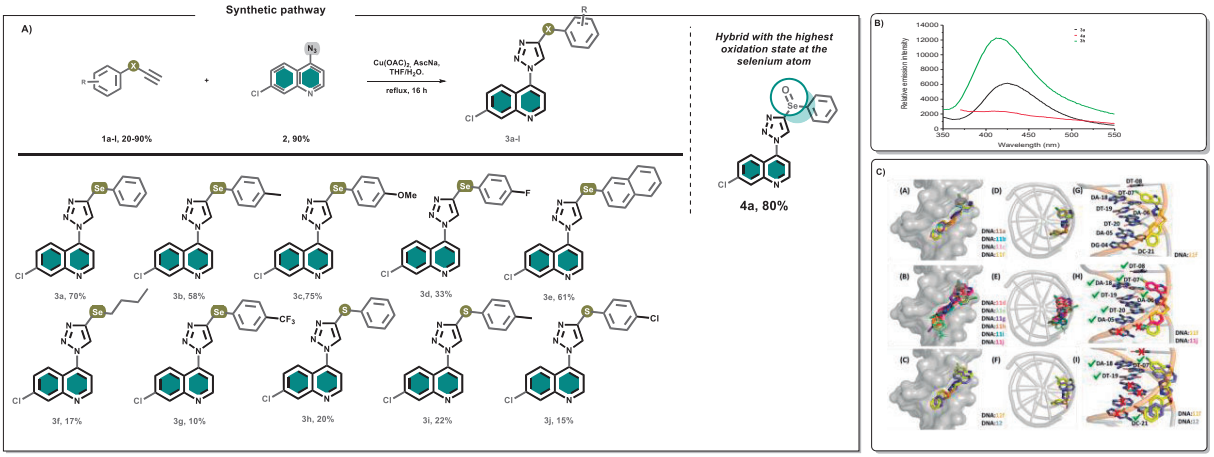

Fig 1. A) Synthetic route for the molecular hybrids; B) Photophysical assays ; C) Molecular docking studies.

Acknowledgements: UFF, CAPES, FAPERJ, CNPq, ppgq-uff

References:

1. Tian, X. *et al. Chem. Sci. 12* (10), 3406–3426, 2021, 2. Dos Santos, G. C. *et al.* J Fluoresc, 27 (5), 1709–1720, 2017
3. Yadav, P. *et al.* Bioorg Chem, 109, 104639. 2021 4. Mahmood, A. *et al.* Polym. Chem. 13 (42), 5993–6001. 2022
5. Bozorov, K.*et al.* Bioorganic & Medicinal Chemistry, 27 (16), 3511–3531. 2019

Semi-synthesis of new heterocyclic compounds derived from a flavanone glycoside and biological evaluation

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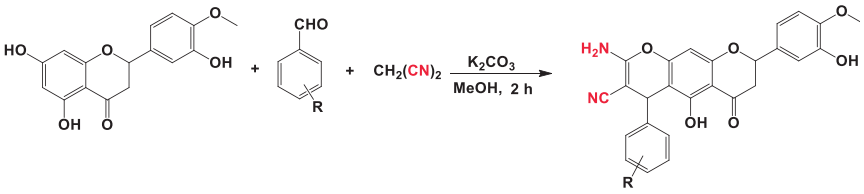
Plant-derived flavonoids are a class of naturally-occurring phenyl chromenes that are widely-distributed in edible plants, and possess a range of biological activities, including those of the anti-inflammatory, antiallergic, antiproliferative, antibacterial, antidiabetic, antiviral, antimutagenic, antithrombotic, anticarcinogenic, estrogenic, hepatoprotective, insecticidal, and antioxidant varieties.[1] Hesperetin (5,7,3′-trihydroxy-4′-methoxyflavonone), a flavonoid abundant in immature citrus fruits and attracted considerable research interest due to its antimicrobial, antifungal, antioxidant, chemopreventive and antitumor potential.[2,3] In view of the significance of the frameworks of chromene-based compounds, efficient synthesis of 2-amino 3-cyano chromene derivatives are of great interest as part of our program on the synthesis of heterocyclic derivatives and screening of their biological activities.[4] In the light of the wide range of biological activities associated with the 2-amino 3-cyano chromene derivatives we focused on the synthesis of novel 2-amino 3-cyano pyrano[2,3*H*]hesperitin analogues via one-pot multi-component reactions (MCRs) (**Scheme 1**), and investigation of their in vitro cytotoxicity on tumor cells and on intracellular amastigotes of *Leishmania amazonensis* and *T. cruzi*.



Scheme 1: Synthesis of target compounds.

Acknowledgements: We woud like to thank the Brazilian National Research Council CNPq and CAPES for financial support of our research.

References:

1. Assirey E.; Alsaggaf A.; Naqvi A.; Moussa Z.; Okasha R.M.; Afifi T.H.; Abd-El-Aziz A.S. *Molecules*. **2020**, *25*, 544.
2. Verma A.; Bakshi J.; Kumar G.; Kamboj H.; Verma R.; Vijayaraghavan P.; Singh A. *J Pure Appl Microbiol.* **2025**;19 (1) 594-600.
3. Sohel M.; Sultana H.; Sultana T.; Al Amin Md, Aktar S.; Ali Md C.; Rahim Z. B.; Hossain Md A. *Heliyon*. **2022**. 8, 08815.
4. Martin E. F.; Mbaveng A. T.; de Moraes M. H.; Kuete V.; Biavatti M. W. *Archiv der Pharmazie*. **2018**. 351 (10) 1800100.

SUSTAINABLE SYNTHESIS OF PYRIMIDO[1,2-*a*]BENZIMIDAZOLE HYBRIDS THROUGH A3 COUPLING REACTIONS

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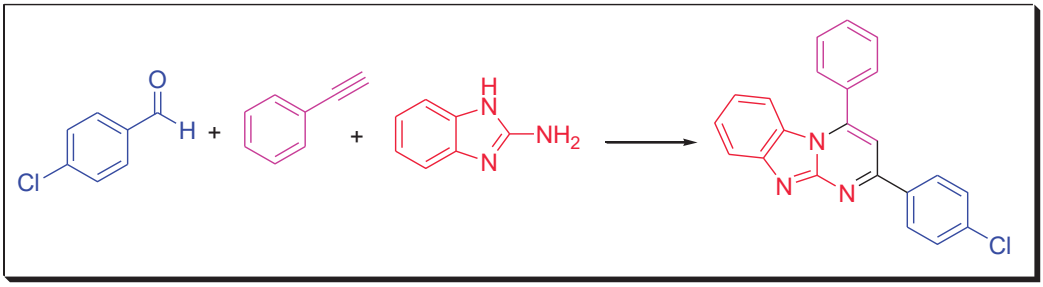
Nitrogen-fused heterocyclic molecules may exhibit significant potential for the protection and modulation of biological systems.[1] In this context, pyrimidobenzimidazoles have attracted considerable pharmacological interest due to their wide range of reported biological activities, including antihypertensive, antidiabetic, anti-inflammatory, antirheumatic, and antibacterial properties. Therefore, the study of heterocyclic chemistry represents an important tool for understanding the mechanisms of drug action and for the development of new therapeutic agents, constituting a research field that is continuously expanding worldwide. In this context, the present study aims to synthesize pyrimido[1,2-a]benzimidazole derivatives through A^3-type multicomponent reactions,[3] employing methodologies aligned with the principles of green chemistry in order to achieve more sustainable, efficient, and environmentally friendly synthetic processes. For the synthesis, 1 mmol of 4-chlorobenzaldehyde, 1 mmol of phenylacetylene, and 1 mmol of 2-aminobenzimidazole were added under reflux conditions at 100 °C for 24 hours. The catalyst and solvent were also added to the reaction system, as shown in Scheme 1 below.

Scheme 1. Synthesis of Pyrimido [1,2-a] Benzimidazole derivative.



The synthesis of pyrimido[1,2-a]benzimidazole hybrids proved to be efficient, providing yields ranging from 20% to 80%. The best reaction conditions were achieved under solvent-free conditions using an AgCl/CuI catalytic system.

Acknowledgements: We thank CNPq, FINEP, CAPES, UEG e LaQuiMeSO.

References:

1. Kumar, A.; Kumar, M.; Maurya, S.; Khanna, R. S.; *J. Org. Chem.* **2014,** 79 (15), 6905–6912.

2. Kumar, p. v.;Roopan, S. M.; Madhumitha, G. *Catalysis Letters,* **2025**, 155 (5) 181 .

3. Seenivasan,V. T.; Chen, N. Q.; Govindan, K.; Jayaram, A.; Lin, Y. C.; Li, C. H.; Lin, W. Y. *J. Org. Chem.* **2025**, 90 (11), 4018-4027.

Lophine-benzazole dyads: synthesis, photophysics and BSA interaction

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The benzazole and imidazole nuclei stands out in heterocyclic chemistry due to the chemical, farmacological and photophysical properties presented by their derivatives.[1] Herein, we describe the synthesis of novel lophine-benzazole dyads, as well as their photophysical characterization and interaction studies with bovine serum albumin (BSA). The *N*-alkylaminolophine intermediates were synthesized through a tetracomponent reaction between an appropriate diamine, benzaldehyde, benzil and ammonium acetate under microwave irradiation (300 W), employing EtOH at 110°C for 5 h. On the other hand, the benzazole intermediates were synthesized in two steps. First, the cyclocondensation between 5-amino-2-hydroxybenzoic acid and *o*-amino(thio)phenol was carried out in polyphosphoric acid at 200 °C for 4 h. The aminobenzazoles obtained were then treated with $SCCl_2$ in acetone at room temperature for 3 h, giving the desired NCS derivatives. Ultimately, the lophine and benzazole nuclei were connected through a thiourea linker. The reaction was performed in dichloromethane at 40 °C for 20 h, affording the benzoxazole derivatives in 66 - 91% yield and the benzothiazole derivatives in 65 - 95% yield. The photophysical characterization of the 14 dyads synthesized were performed in three different solvents: dichloromethane, methanol and dimethyl sulfoxide. In the fluorescence emission spctra, it was possible to observe a dual emission related to the lophine core (~380 nm) and the keto form of benzazole unit (~520-550),[2] demonstrating the potential of these compounds as optical sensors in solution. Four lophine-benzazole dyads were chosen as models for the BSA interaction studies. After the addition of different amounts of the dyads to the BSA solution, quenching of the protein fluorescence emission was observed. Molecular docking calculations were perfomed to better understand the dyad-protein interactions. The results suggest a static fluorescence quenching mechanism occurring mainly in the binding pocket of site III (subdomain IB) , where Trp-134 residue is located, due to the highest docking score values.

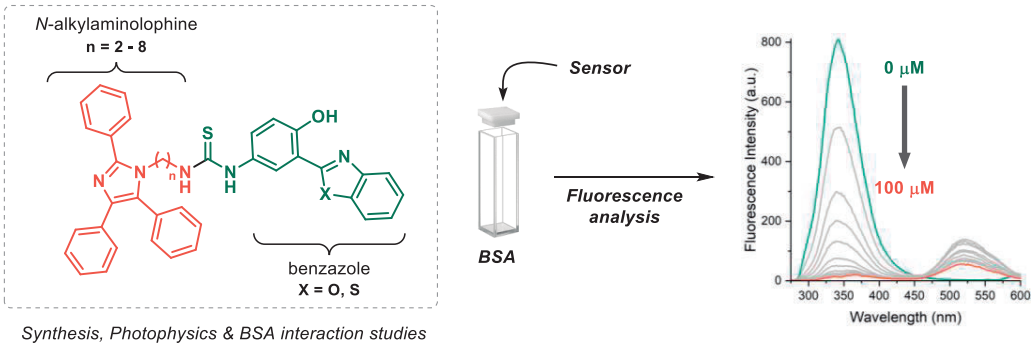

Figure 1: Lophine-benzazole dyads.

References:

1. a) Siwach A.; Verma P.K. *Bmc Chem.* **2021**, *15*, 12. b) Bansa S. *Mini-Rev. Org. Chem.* **2021**, *18*, 383.
2. Câmara V.S.; Debia N.P.; Junior H.C.S., Ceschi M.A.; Rodembusch F.S. *J. Mol. Liquids* **2024**, *398*, 124231.

Synthesis and Pharmacological Potential of Novel Phthalimide-Linked Zidovudine Derivatives

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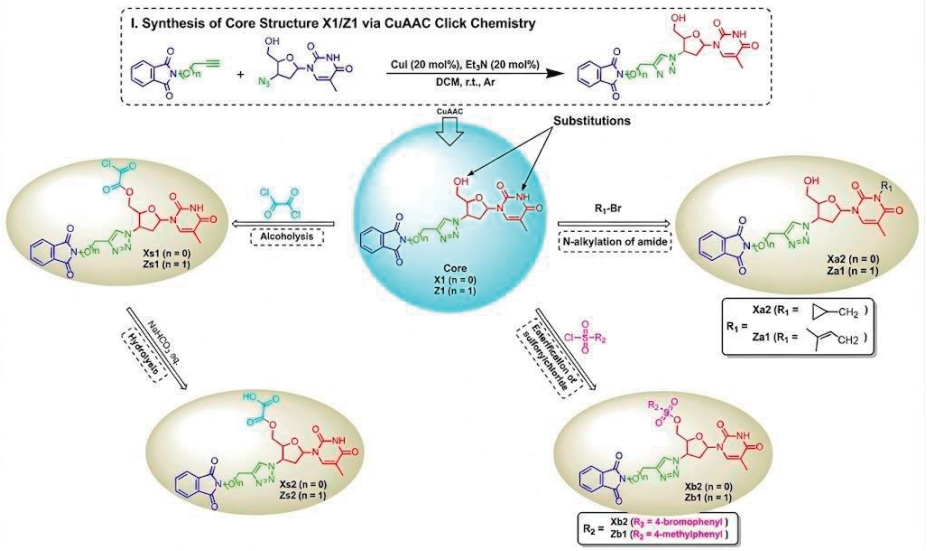
The copper-catalyzed azide–alkyne cycloaddition (CuAAC), commonly known as 'click chemistry', is a powerful and environmentally friendly strategy for the rapid construction of biologically relevant molecules.[1] Inspired by the therapeutic importance of Zidovudine (AZT) and the broad pharmacological potential of phthalimide derivatives, we designed and synthesized a new series of phthalimide-linked AZT hybrids connected through a 1,2,3-triazole linker. The study aimed to generate multifunctional compounds with potential antimalarial activity through targeting Plasmodium falciparum heat shock protein 90 (PfHSP90). Two key intermediates, **X1** and **Z1**, were successfully obtained in high purity using optimized CuAAC conditions. Subsequent structural diversification was achieved through N-alkylation of amide functions, alcoholysis, esterification, sulfonylation, and hydrolysis reactions, affording a focused library of novel derivatives (**Scheme 1**). The synthetic route provided efficient access to structurally diverse compounds while maintaining the desirable features of both AZT and phthalimide pharmacophores. [2]
Computational investigations, including drug-likeness prediction, molecular docking, and molecular dynamics simulations against *PfHSP90* (PDB ID: 3K60), indicated favorable binding profiles for several derivatives. Biological evaluation was performed through in vitro antimalarial assays against the PfHB3 strain and cytotoxicity assessment using the PC12 cell line (MTT assay). The results identified **X1** and **Z1** as promising antimalarial drug-like scaffolds, while derivatives Xa2, Xb2, Za1, and Zb1 displayed particularly encouraging computational and biological profiles. Overall, this work demonstrates the utility of click chemistry for the generation of innovative AZT–phthalimide hybrids and highlights their potential as lead structures for future antimalarial drug development.[3]



Scheme 1: Graphical abstract scheme of the designing phthalimide-linked pyrimidinones.

Acknowledgements: We thank the Chinese Gov. Scholarship CSC and UNESCO-TWAS-FAPESP Postdoc-Fellowship Program

References:

1. a) Kolb, H.C.; et.al. *Angew. Chem., Int. Ed. Engl*. **2001**, 40, 2004. b) Singh, G.; et.al. *Tetrahedron Lett*. **2014**, 55, 903.
2. a) Hibbard, J.P.; et.al. *J. Org. Chem*. **2022**, 87, 12036. b) Mittersteiner, M.; et.al. *J. Org. Chem*. **2022**, 87,4590.
3. a) Hou, Y.; et.al. *J. Agric. Food Chem*. **2019**, 67, 8227. b) Bhrdwaj, A.; Abdalla, M.; et.al. *Appl. Biochem. Biotechnol*. **2023**, 1, 26.

Carquejol as a Renewable Chiral Handle for the Synthesis of Dihydropyrimidinone Scaffolds via the Biginelli Reaction

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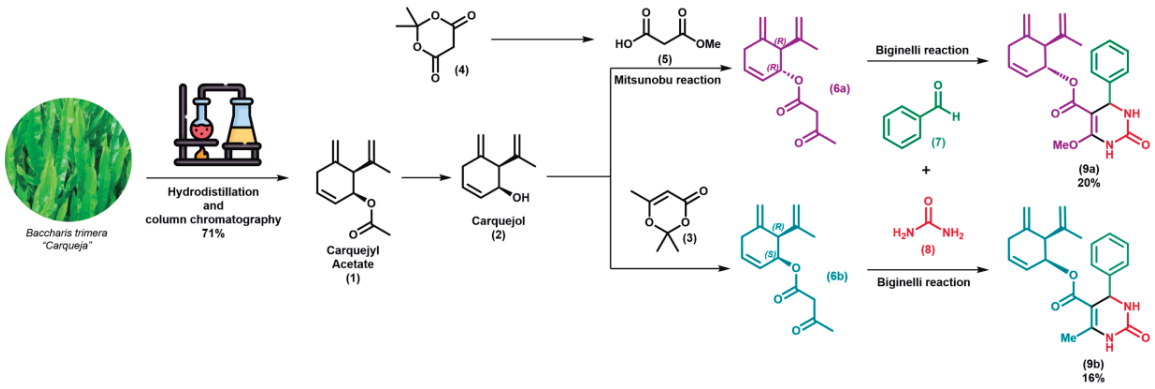
The incorporation of stereochemically defined fragments into heterocyclic scaffolds is a valuable strategy for generating structurally complex molecules with potential biological relevance. Dihydropyrimidinones (DHPMs), classically accessed through the Biginelli multicomponent reaction, are an important family of nitrogen-containing heterocycles associated with diverse biological activities.[1] In this work, carquejol, a rare *o*-menthane obtained from carquejyl acetate, a major constituent of *Baccharis trimera* essential oil and a distinctive irregular monoterpenoid from this plant, was explored as a renewable, locally abundant, and enantiopure source of chirality for the construction of terpene-functionalized DHPMs.[2,3]

Carquejol was converted into two diastereomeric 1,3-dicarbonyl derivatives designed to act as chiral β-dicarbonyl components in the Biginelli reaction. Diastereochemical divergence was achieved by selecting complementary stereochemical routes: the *syn* derivative was obtained through rapid acetylation using TMD, while the *anti* derivative was accessed through a Mitsunobu protocol. The resulting 1,3-dicarbonyl compounds were then employed in multicomponent condensations with urea and aromatic aldehydes, affording DHPM scaffolds bearing a terpene-derived chiral handle (**Scheme 1**).

This approach demonstrates the potential of carquejol as an abundant natural source of chirality for heterocycle diversification. By merging a renewable monoterpene fragment with the biologically relevant DHPM core, this work provides a platform for the synthesis of chiral, structurally enriched dihydropyrimidinones and supports further exploration of carquejol-derived building blocks in heterocyclic and medicinal chemistry.



Scheme 1: Isolation of carquejyl acetate from *Baccharis trimera* essential oil, conversion to carquejol, and further use as a renewable chiral building block for the synthesis of 1,3-dicarbonyl derivatives and dihydropyrimidinone (DHPM) scaffolds via the Biginelli reaction.

Acknowledgements: The authors would like to thank Matologia Research Group at Universidade Federal do Paraná for supplying the *Baccharis trimera* plant material, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Fundação Araucária for funding.

References:

1. Kappe, C. O. *European Journal of Medicinal Chemistry* **2000**, 35, 1043.
2. Naves, Y. R. *Helvetica Chimica Acta* **1962**, *45*, 1598
3. Minteguiaga, M.; Dellacassa, E.; Iramain, M. A.; Catalán, C. A. N.; Brandán, S. A. *Journal of Molecular Structure* **2017**, *1150*, 8.

Sonochemical optimization of the α-azidation step in the two-step synthesis of β-keto-1,2,3-triazoles from 2-bromoacetophenones

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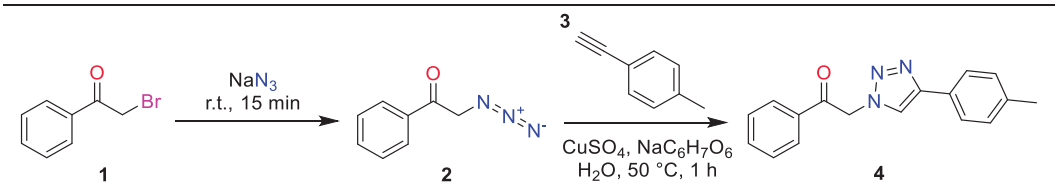
The 1,2,3-triazole scaffold has been widely recognized as a pharmacologically privileged motif in medicinal chemistry, with 1,4-disubstituted derivatives bearing a carbonyl group at the β-position demonstrating documented antiproliferative activity against multiple human cancer cell lines, as well as dual antimicrobial and anticancer potential.[1] The copper-catalyzed azide-alkyne cycloaddition (CuAAC) has been established as the principal route for the regioselective synthesis of these β-keto-1,2,3-triazoles, including via sequential two-step protocols in which α-bromoacetophenones undergo nucleophilic azidation prior to cycloaddition with terminal alkynes under conventional stirring conditions.[2] Sonochemical protocols for the synthesis of 1-benzyl-1,2,3-triazoles have already been explored and reported[3], but the application of ultrasonic irradiation to assist both the α-azidation and the subsequent cycloaddition steps for β-keto-1,2,3-triazoles has not been systematically investigated. Herein, we report the ultrasound-assisted optimization of the synthesis of 1-phenyl-2-(4-(p-tolyl)-1H-1,2,3-triazol-1-yl)ethan-1-one (**4**) in two steps: first, azidation reactions were executed under different solvent (ethanol, methanol, acetone, chloroform) and power (800, 720, 640 W) conditions, using 2-bromoacetophenone (**1**) (1 mmol) and sodium azide (3 mmol) for 15 min, room temperature (r.t.) with yields between 40-85%. Then the 2-azido-1-phenylethanone (**2**) was used to obtain the triazole compound **4** in click chemistry conditions: 0.5 mmol **2**, 0.75 mmol 1-ethynyl-4-methylbenzene (**3**), pentahydrated copper sulfate (5 mol %), sodium ascorbate (10 mol %), 1 h, 50 °C in distilled water with a 98% yield. The obtained compounds **2** and **4** were characterized by FTIR and ^{1}H and ^{13}C NMR. The results demonstrate that ultrasonic irradiation effectively promotes both steps of the synthesis, affording compound 4 in good yield under mild conditions, with further optimization of the CuAAC step currently underway.



Entry	Solvent	Power (W)	Yield[1] (%)	Yield[2] (%)
1a	EtOH	800	85	98
2a	MeOH	800	80	-
3a	Acetone	800	40	-
4a	Chloroform	800	68	-
5a	EtOH	720	83	-
6a	EtOH	640	60	-

[1] Yields obtained under ultrasonics conditions
[2] Yield under conventional conditions

Table 1: Ultrasound-assisted synthesis conditions optimization of β-keto-1,2,3-triazole.

Acknowledgements: We would like to thank the financial support obtained from CNPq, Capes and FAPEAP.

References:

1. a) Maleki, S.; Bakherad, M.; Nasr-Isfahani, H.; Dehghanibavani, E.; Tamardash, L. K. *Monatsh Chem.* 2025, *156*, 655. b) Queiroz T. M.; Orozco E. V. M.; Silva V. R.; Santos L. S.; Soares M. B. P.; Bezerra D. P.; Porto A. L. M. *Heliyon* 2019, *5*, e02408
2. a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; K.B. Sharpless, K. B. *Angew. Chem. Int. Ed.* 2002, *41*, 2596. b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* 2002, 67, 3057 c) Vantikommu, J.; Palle, S.; Reddy, P. S.; Ramanatham, V.; Khagga, M.; Pallapothula, V. R. *European J. Med. Chem.* 2010, 45, 5044
3. Naeimi, H.; Dadashzadeh, S.; Moradian, M. *Res Chem Intermed* 2015, 41, 2687.

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Synthesis of Coumarin-Oxadiazole Hybrids for Alzheimer's Disease Treatment: Development of Innovative Therapeutic Agents

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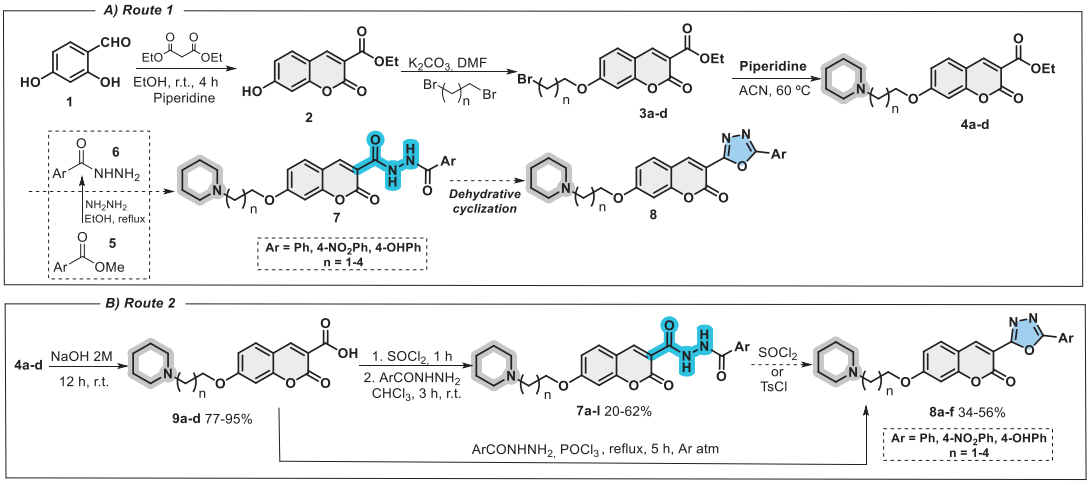
The search for novel drugs capable of reducing the morbidity and mortality associated with neurodegenerative diseases, such as Alzheimer's disease (AD), is a cornerstone of organic synthesis applied to medicinal chemistry. Advances in understanding AD mechanisms have driven the development of inhibitors targeting cholinesterases and Aβ peptide aggregation, a scenario in which coumarins stand out due to their broad therapeutic applicability.[1,2] In this work, we propose the synthesis of novel coumarin-1,3,4-oxadiazole hybrids, and the evaluation of their anti-Alzheimer potential through enzyme inhibition assays and antioxidant activity.

In order to obtain hybrids **8**, the synthesis of intermediate **2** was required, which was prepared via a Knoevenagel condensation starting from 4-hydroxybenzaldehyde (**1**) and diethyl malonate in the presence of piperidine (Scheme 1). Subsequently, **2** was reacted with the corresponding dibromoalkane. Intermediates **3** were then treated with piperidine to afford intermediates **4**, which were subsequently reacted with acylhydrazides **6**; however, this step did not yield the desired product. Proceeding with the synthesis, the alkylated derivatives **4** were hydrolyzed using 2M NaOH and converted into the respective diacyl intermediates **7** (20–62%). These compounds were subjected to dehydratative cyclization conditions, but the target products were not obtained. Alternatively, the gradual addition of phosphoryl chloride to a mixture of **4a–d** and benzohydrazides **6** was tested (Scheme 1, Route 2), successfully affording the desired products (34–56%). Overall, 31 substances were obtained in satisfactory yields, 22 of which are novel compounds.

The biological activity of intermediates **7** was also evaluated. In the assays against AChE, several compounds demonstrated significant inhibition percentages; most notably, two derivatives exhibited 94.1% and 93.5% inhibition, outperforming the positive control (donepezil, 92.9%). Complementing Ellman method, AChE assays were conducted using an IMER system. Screening identified three compounds as the most potent inhibitors, displaying IC_{50} values ranging from 150 to 715 nM, with all three exhibiting a competitive inhibition mechanism and K_i values ranging from 137 to 720 nM. Further oxadiazole evaluations are currently underway, reinforcing the importance of SAR studies in optimizing drug candidates for AD.



Scheme 1: Proposed synthetic route for the preparation of coumarin–oxadiazole compounds.

Acknowledgements: Capes, CNPq, and FAPERJ

References: 1. Tripathi A.; Choubey P. K.; Sharma P.; Seth A.; Saraf P.; Shrivastava S. K. *Bioorg. Chem.* **2020**, 95, 103506.

2. Fouad R.; Saif, M.; Mashaly M. M.; Zekrallah M. *J. Mol. Struct.* **2023**, 1284, 135421.

Glycosides of fluorinated p-nitrophenol offer improved sensitivity for detection of β-galactosidase and β-glucuronidase in *Escherichia coli* and other *Enterobacterales*

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We describe the synthesis and evaluation of six halogenated nitrophenyl glycosides for detection of β-galactosidase and β-*glucuronidase enzyme activity among Enterobacterales ("coliforms") and Escherichia coli, respectively. These were evaluated alongside the established substrates; o*-nitrophenyl-β-*D-galactopyranoside (ONPG), p*-nitrophenyl-β-*D-galactopyranoside (PNPG) and p*-nitrophenyl-β-*D*-glucuronide (PNP-GUR).[1,2] The evaluation was performed using 30 isolates of *Enterobacterales* including 19 isolates of *E. coli*. Hydrolysis of 2-fluoro-*p*-nitrophenyl-β-*D*-galactopyranoside (2-fluoro-PNPG) yielded a significantly stronger yellow colouration after a six-hour incubation period compared to hydrolysis of ONPG and PNPG, potentially allowing for a more sensitive detection of *Enterobacterales*. Similarly, hydrolysis of the novel substrate 2-fluoro-*p*-nitrophenyl-β-*D*-glucuronide sodium salt (2-fluoro-PNP-GUR Na) by producers of β-glucuronidase also yielded a significantly stronger yellow colouration, potentially allowing for a more sensitive detection of *E. coli*. The yellow chromophore 2-fluoro-*PNP retained high colour intensity at reduced pH when compared to o-nitrophenol and p*-nitrophenol. Both substrates potentially offer enhanced sensitivity for the detection of *Enterobacterales* and *E. coli* in environmental samples as markers of faecal pollution.[3]

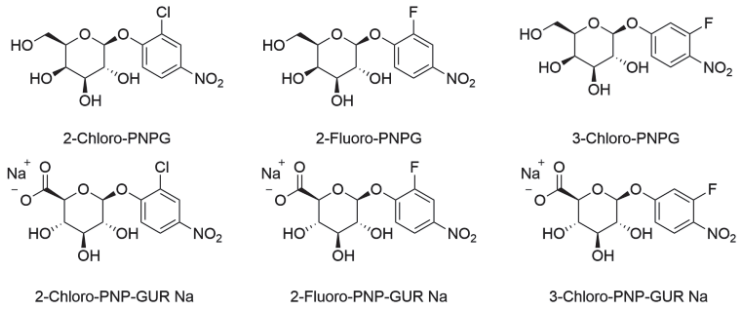

Figure 1: The six chromogenic substrates based on glycosides of halogenated nitrophenol evaluated in this study. Abbreviations: PNPG, p-nitrophenyl-β-*D-galactopyranoside; PNP, p*-nitrophenol; GUR, glucuronide.

Acknowledgements: This work was funded by Glycosynth Ltd. and was carried out at Glycosynth Ltd., Northumbria University, and Freeman Hospital.

References:

1. Lederberg, J. The β-*D*-galactosidase of *Escherichia coli*, strain K-12. *J. Bacteriol.* 1950, 60, 381–392.
2. Kilian, M.; Bülow, P. Use of a β-glucuronidase detecting agar medium (PGUA agar) for the identification of *Escherichia coli* in primary cultures of urine samples. *Acta Path. Microbiol. Scand.* 1979, 8, 271–276.
3. Edberg, S. C.; Allen, M. J.; Smith, D. B. Defined substrate technology method for rapid and specific simultaneous enumeration of total coliforms and *Escherichia coli* from water: collaborative study. *J. Assoc. Off. Anal. Chem.* 1991, 74, 526–529.

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Synthesis and evaluation of the trypanocidal activity of new 5-(1*H*-1,2,3-triazol-1-yl)-1,4-naphthoquinones

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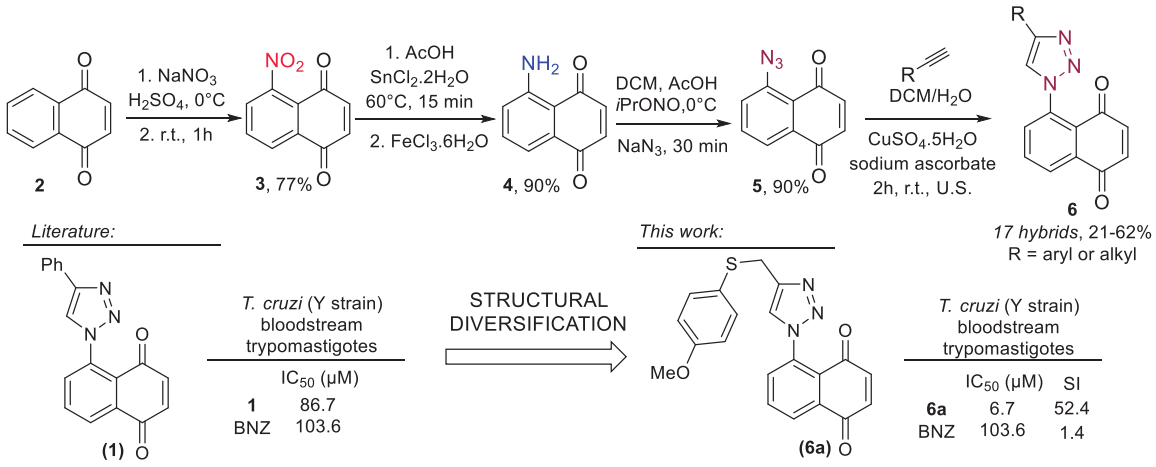
Naphthoquinones are a class of compounds extensively studied due to their diverse biological activities. A naphthoquinone-triazole hybrid **(1)** linked through the aromatic ring of the naphthoquinone moiety, has shown promising trypanocidal activity.[1] However, as this compound represents the only reported analogue of this type, SAR studies could not be performed, leaving the biological potential of this structural modification largely unexplored. In addition, the reported synthesis of compound **1** employs relatively high-cost catalysts and starting materials. Accordingly, this work aimed to synthesize novel naphthoquinone–1*H*-1,2,3-triazole hybrids through a synthetic route employing more accessible catalysts and reagents and evatuate their trypanocidal activity. The synthesis began with the nitration of compound **2**, followed by reduction to afford **4** (**Scheme 1**).[2] This intermediate underwent diazotization and subsequent nucleophilic aromatic substitution to yield **5**, and a Cu(I)-catalyzed cycloaddition with commercially available and synthetic alkynes afforded triazole derivatives **6**.[3] A total of 17 derivatives of type **6** were synthesized, 16 of which are novel, and their trypanocidal activity was evaluated. Among them, **6a** was more potent against trypomastigotes than the prototype **1** and demonstrated approximately 37-fold greater selectivity than benznidazole (BNZ).



Scheme 1: Synthetic route for the production of new triazole-naphthoquinone hybrids and **6a** trypanocidal activity.

Acknowledgements: We thank CAPES, CNPq, FAPERJ and PPGQ-UFF

References:

1. Carvalho, R. L et al. *Chem. - Eur. J.*, **2018**, *24*, 15227.
2. Ivashkina, N. V. et al. *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, **1984**, *33*, 2345.
3. Pacheco, P. A. F. et al. *Bioorg. Med. Chem.*, **2019**, *10* ,1016.

Synthesis and photocatalytic three-component ring-opening of 3-substituted-1-azabicyclo[1.1.0]butanes towards 3,3-disubstituted *N*-sulfonylazetidines

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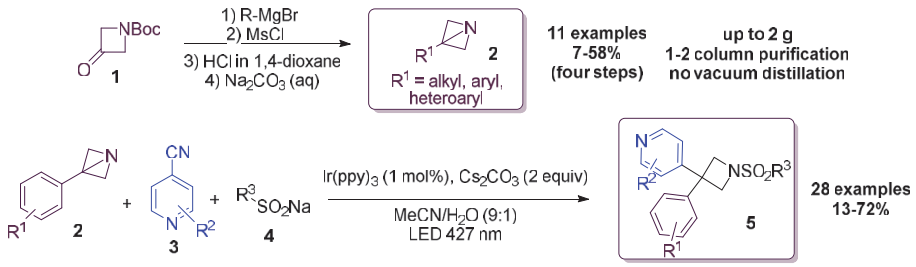
Azetidines exhibit a wide range of biological activities and are present in several approved drugs and drug candidates.[1,2] The azitidine core can act as a bioisostere for a variety of groups and incorporation of such motifs often results in improved physicochemical and pharmacokinetic properties.[3] An emerging strategy to prepare azetidines is the ring-opening reaction of 1-azabicyclo[1.1.0]butanes (ABBs).[4] Many polar methods have been developed,[5] however the first photocatalytic radical difunctionalization using ABBs was only reported in 2024.[6] Following this report, other related methods emerged, all relying on the attack of an electrophilic sulfur-centered radical to the electron-rich nitrogen atom. Despite these advances, preparation of 3,3-diaryl-substituted azetidines remain a synthetic challenge. Another major challenge in advancing this chemistry is the lack of convenient methods to prepare 3-aryl-1-azabicyclo[1.1.0]butanes, hampering their broader adoption as convenient starting materials. In this report, we aim to tackle both problems by developing a new route to the preparation of 3-aryl-ABBs **2** and their application in the photocatalytic and modular three-component preparation of 3,3-diaryl-*N*-sulfonylazetidines **5** (Scheme 1).



Scheme 1: Synthesis and photocatalytic three-component ring-opening of ABBs **2** towards *N*-sulfonylazetidines **5**.

Starting from commercially available ketone **1,** and using a four-step sequence, 11 ABBs were prepared, with yields in the range of 7-58% (over four steps), without need for column chromatography purification in the last two steps. Using the ABBs **2** in combination with cyanopyridines **3** and sodium sulfinates **4**, a three-component photocatalytic reaction was developed. Under optimized conditions, 28 examples of 3,3-diaryl-*N*-sulfonylazetidines **5** with yields in the range of 13–72% were prepared.

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References:

1. Parmar, D. R.; Soni, J. Y.; Guduru, R.; Rayani, R. H.; Kusurkar, R. V.; Vala, A. G. *Arch. Pharm.* **2021**, *354* (11), 2100062. 2. Pattanayak, P.; Sethy, K. *ChemistrySelect* **2025**, *10* (24), e06100. 3. Bauer, M. R.; Di Fruscia, P.; Lucas, S. C. C.; Michaelides, I. N.; Nelson, J. E.; Storer, R. I.; Whitehurst, B. C. *RSC Med. Chem.* **2021**, *12* (4), 448–471. 4. Andresini, M.; Degennaro, L.; Luisi, R. *Org. Biomol. Chem.* **2020**, *18* (30), 5798–5810. 5. Bielecki, M.; Nassir, M.; Sharma, H. A.; Truax, N. J.; Raheja, N.; Thompson, T. M.; El-Hayek Ewing, T.; Melillo, B.; Cravatt, B. F.; Baran, P. S. *J. Am. Chem. Soc.* **2025**, *147* (25), 22209–22218. 6. Rodríguez, R. I.; Corti, V.; Rizzo, L.; Visentini, S.; Bortolus, M.; Amati, A.; Natali, M.; Pelosi, G.; Costa, P.; Dell'Amico, L. *Nat. Catal.* **2024**, *7* (11), 1223–1231.

Photoredox-Catalyzed Synthesis of a Novel Class of Fluoroalkyl Pyrazolones

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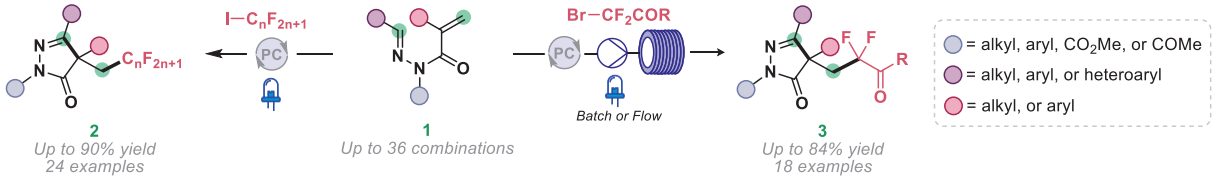
N-Heterocyclic compounds are of major importance due to their widespread presence in biological systems and their diverse pharmacological activities, with 82% of FDA-approved small-molecule drugs (2013–2023) containing at least one nitrogen heterocycle.[1] Among these, pyrazolones, especially 2-pyrazolin-5-ones, are privileged scaffolds in medicinal chemistry, displaying a broad range of biological activities and enabling structural diversification, including enantioenriched and 4,4-disubstituted derivatives with therapeutic potential.[2]

Despite significant progress in the synthesis of fluoroalkyl pyrazoles, the regio- and chemoselective construction of fluoroalkyl-containing 2-pyrazolin-5-ones remains underexplored. Existing approaches rely mainly on electrophilic or nucleophilic fluorination,[3] or on modification of preformed pyrazolones,[4] while the selective incorporation of fluorinated groups such as difluoromethylene (–CF_2–) and perfluoroalkyl (–C_nF_{2n+1}) units remains challenging, despite their strong impact on physicochemical and pharmacokinetic properties of potential pharmaceuticals.[5]

Herein, we present a robust and regioselective strategy for the synthesis of fluorinated 2-pyrazolin-5-ones via radical cascade cyclization of (*E*)-*N*'-benzylidene-*N*-methacryloyl-hydrazides (Scheme 1, **1**).[6] These readily accessible and modular substrates enable rapid structural diversification, making them particularly attractive for synthetic applications. By employing perfluoroalkyl halides as radical precursors, the transformation proceeds under mild, transition-metal-free conditions, enabling the efficient incorporation of both polyfluoroalkyl (**2**) and difluoromethylene groups (**3**). The methodology demonstrates broad substrate scope, accommodating both aryl and alkyl derivatives, and performs effectively in both batch and continuous flow systems, underscoring its robustness and scalability. Overall, this approach significantly expands the synthetic utility of hydrazide-based platforms and provides streamlined access to fluorinated heterocycles with promising applications in drug discovery and materials science.



Scheme 1. General representation of the synthesis of perfluoroalkylated pyrazolones via a photocatalysis-driven radical cascade.

Acknowledgements: Gratitude is expressed to the Brazilian funding agencies CNPq (INCT Catálise), and CAPES - Financial code 001. This study was financed, in part, by the São Paulo Research Foundation (FAPESP), Brasil. Process Numbers 2022/04597-0, 2023/12718-5 and 2024/09943-0. This project was supported by the BMBF Cluster4Future Electrifying Technical Organic Synthesis (ETOS, 03ZU1205AC).

References:

[1] Marshall, C. M.; Federice, J. G.; Bell, C. N.; Cox, P. B.; Njardarson, J. T. *J. Med. Chem.* **2024**, 67, 11622−11655.
[2] Ghulam, M.; Zia-ur-Rehman, M.; Sumrra, S. H.; Ashfaq, M.; Zafar, W.; Ashfaq, M. *J. Mol. Struct.* **2022**, 1262, 133044.
[3] Wang, Y.; Wang, S.; Wu, Y.; Zhao, T.; Liu, J.; Zheng, J.; Wang, L.; Lva, J.; Zhang, T. *Org. Chem. Front.* **2023**, 10, 2226–2233.
[4] (a) Li, D.; Zhang, W.; Zhang, S.; Sun, W.; Zhao, J.; Wang, B.; Qu, J.; Zhou, Y. *Org. Lett.*, 2021, **23**, 5804 – 5808.
[5] (a) Sap, J. B. I.; Meyer, C. F.; Straathof, N. J. W.; Iwumene, N.; am Ende, C. W.; Trabanco, A. A.; Gouverneur, V. *Chem. Soc. Rev.* **2021**, 50, 8214–8247; (b) Gaines, L. G. T. *Am. J. Ind. Med.* **2023**, 66, 353–378.
[6] Pissinati, E. F.; Azizzade, M.; Opatz, T.; Paixão, M. W. *Adv. Synth. Catal.,* **2025**, 367, e70118.

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1,1-Difluoroallenes as Versatile Platform for Syntheses of Ring-Fluorinated Oxacycles

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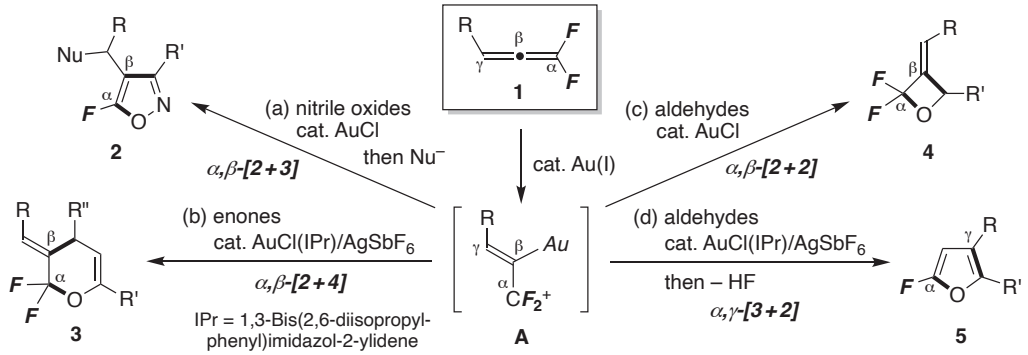
Ring-fluorinated heterocyclic compounds have great potential in pharmaceuticals and agrochemicals owing to their unique bioactivities. Consequently, efficient methods for their synthesis are highly desirable. We have previously developed synthetic routes based on [4 + 1] cycloaddition of free or metal difluorocarbenes with four-atom units.[1] Herein, we report gold(I)-catalyzed syntheses of ring-fluorinated oxacycles using 1,1-difluoroallenes[2] as a versatile synthetic platform.

In the presence of an AuCl catalyst, 1,1-difluoroallenes **1** undergo α,β-selective [2 + 3] cycloaddition with nitrile oxides, followed by S_N2'-type fluorine substitution to afford 5-fluoroisoxazoles **2** (**Scheme 1a**).[3] We propose that regioselective metallation of **1** generates gold(I)-bearing difluoroallylic cations **A**, which are stabilized by the fluorine substituents, and thereby promote regioselective cycloaddition at the α position. When enones are used instead of nitrile oxides, 1,1-difluoroallenes **1** participate in an α,β-selective [2 + 4] cycloaddition under AuCl(IPr)/$AgSbF_6$ catalysis to furnish 3-alkylidene-2,2-difluoro-3,4-dihydro-2H-pyranes **3** (**Scheme 1b**).[4] In the presence of an AuCl catalyst, 1,1-difluoroallenes **1** also undergo α,β-selective [2 + 2] cycloaddition with aldehydes to afford 3-alkylidene-2,2-difluorooxetanes **4** (**Scheme 1c**). In contrast, in the presence of the AuCl(IPr)/$AgSbF_6$ catalyst, 1,1-difluoroallenes **1** react with aldehydes via α,γ-selective [3 + 2] cycloaddition, followed by efficient dehydrofluorination to provide 2-fluorofurans **5** (**Scheme 1d**).[5]



Scheme 1: Syntheses of ring-fluorinated oxacycles **2**–**5** from 1,1-difluoroallenes **1**.

Acknowledgments: We thank Tosoh Finechem Corporation for the generous gift of CF_3CH_2I, which was used for the preparation of 1,1-difluoroallenes via difluorovinylidenation of aldehydes and ketones.[2]

References:

1. Fuchibe, K.; Ichikawa, J. *Chem. Commun.* **2023**, *59*, 2532.
2. Fuchibe, K.; Abe, M.; Oh, K.; Ichikawa, J. *Org. Synth.* **2016**, *93*, 352; Fuchibe, K.; Ichikawa, J. *Org. Synth*. **2022**, *99*, 113.
3. Fuchibe, K.; Sakon, K.; Suto, K.; Eto, R.; Nakazono, S.; Ichikawa, J. *Org. Lett.* **2023**, *25*, 7258.
4. Miyazaki, D.; Eto, R.; Ichikawa, J.; Fuchibe, K. *Chem. Commun.* **2025**, *61*, 4563.
5. Miyazaki, D.; Kudo, K.; Fujiki, Y.; Watanabe, N.; Matsui, T.; Ichikawa, J.; Fuchibe, K. *Org. Lett.* **2025**, *27*, 3807.

Sacrifice of Diorganyl Diselenide Enables Cyclization of Aryl Propargyl Ethers in the Synthesis of 3-Organoselenyl Chromenones

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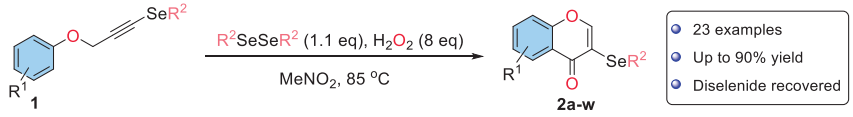
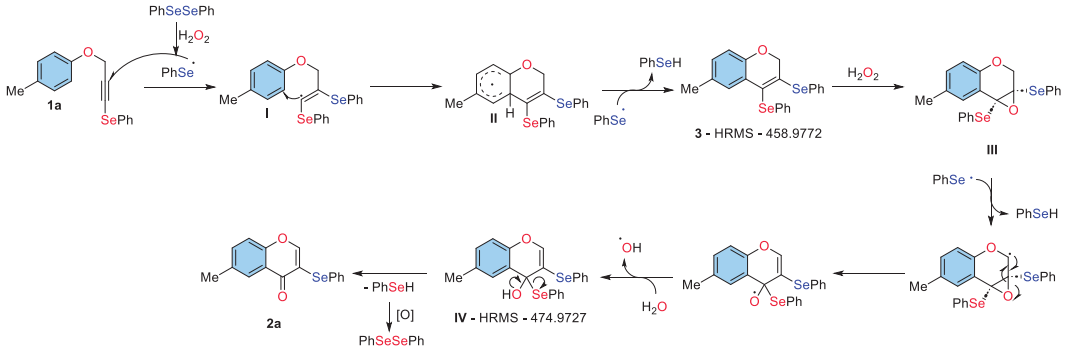
We report the synthesis of 3-organoselenyl chromenones **2** via a cascade cyclization of organoselenyl aryl propargyl ethers **1** (**Scheme 1**). The transformation is promoted by diorganyl diselenides and hydrogen peroxide. In this process, the diselenides are first activated by hydrogen peroxide to generate reactive selenium species. These selenium species then add to the terminal alkyne group of the propargyl ether, leading to alkyne functionalization. Subsequent intramolecular nucleophilic attack by the aryl oxygen onto the activated alkyne intermediate triggers cyclization. During this cyclization step, a carbonyl group is incorporated in situ, forming the chromenone scaffold without pre-installed carbonyl functionalities.[1] Although the diselenide acts sacrificially, it is regenerated and can be recovered at the end of the reaction, underscoring the sustainability and atom economy of this protocol.



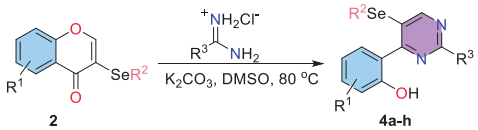
Scheme 1: Synthesis of 3-organoselenyl chromenones promoted by H_2O_2 and diorganyl diselenides.

This methodology provides access to 23 distinct 3-organoselenyl chromenones in yields up to 90%. Additionally, intermediate **3** was isolated and thoroughly characterized by NMR spectroscopy and X-ray diffraction.



Scheme 2: Proposed mechanism.

Moreover, the resulting 3-organoselenyl chromenones are not only robust end products but also versatile intermediates, as demonstrated by their use as starting materials for the synthesis of selenium-containing pyrimidines **4** in yields up to 95% (**Scheme 3**).



Scheme 3: Post-synthetic transformation of 3-organoselenyl chromenones into pyrimidine derivatives

Acknowledgements: We thank CAPES, CNPq (INCT SiPu21 No 409156/2024-8) and FAPERGS for financial support of this work.

References:

1. a) J. Cai, Z. Zeng, Q. Wang, W. Li, *Adv. Synth. Catal.* **2025**, 367, e202500210; b) W. Kan, Y. Piao, W. Song, X. Chen, C. Wang, Z. Wang, L. Wang, *Catalysts* **2024**, 14, 413.

Accessing novel heterocycles from Natural Products through Complexity-to-Diversity approaches

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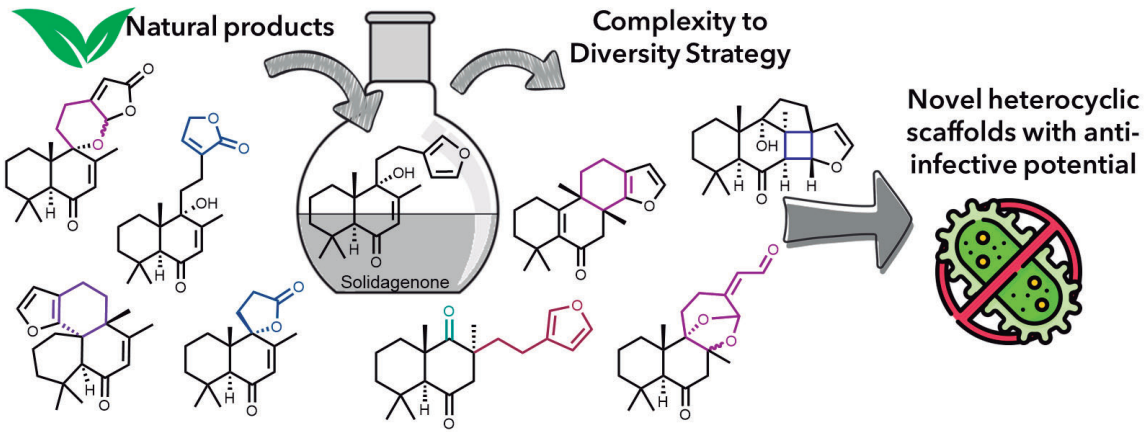
Natural products (NPs) are a privileged source of structural complexity and bioactive scaffolds.[1] However, their transformation into diverse heterocyclic frameworks is rarely addressed through conventional synthetic strategies. In this context, the Complexity-to-Diversity (CtD) approach provides a powerful platform to access novel heterocycles through ring distortion processes rather than de novo construction.[2]

Herein, we apply complementary CtD methodologies to terpenoid NPs, including diterpenes and sesquiterpene lactones isolated from their natural plant sources, enabling the rapid generation of structurally diverse libraries enriched in non-natural heterocyclic architectures.[3] Transformations such as oxidative rearrangements, acid-promoted skeletal reorganization, and chemoenzymatic and photochemical processes afford highly functionalized scaffolds in a limited number of steps. A central goal of this approach is the identification of biologically active compounds, with emphasis on anti-infective applications for the generation of new derivatives with improved efficacy, selectivity, and reduced toxicity (**Scheme 1**).

Notably, these strategies exploit the inherent complexity of NPs to generate unprecedented heterocyclic motifs, often inaccessible through classical synthetic routes. Many transformations reveal hidden or newly formed heterocyclic cores embedded within the original frameworks, expanding chemical space in terms of connectivity and three-dimensionality.

Overall, this work highlights CtD as a complementary paradigm in heterocyclic chemistry, linking NPs remodeling with the discovery of innovative and bioactive molecular architectures.



Scheme 1. Complexity-to-Diversity strategy applied to diterpenoid solidagenone for the generation of novel heterocyclic scaffolds with anti-infective potential.

Acknowledgements: The authors thank the funding entities ONR Global, CONICET, Secyt-UNC and ANPCyT.

References:

1. Lachance H.; Wetzel S.; Kumar K.; et al. *J. Med. Chem.* **2012**, *55*, 5989.
2. a) Furiassi L.; Tonogai E. J.; Hergenrother P. J. *Angew. Chem. Int. Ed*. **2021**, *60*, 16119. b) Motika S. E.; Hergenrother P. J. *Nat. Prod. Rep.* **2020**, *37*, 1395.
3) Adessi T. G.; Wagner P. M.; Bisogno F. R.; et al. Sci. Rep. 2024, 14, 14229. b) Tibaldi-Bollati M. L.; Nicotra V.; Oksdath-Mansilla G.; Nicotra, V.; García M. *ChemPlusChem* **2024**, *89*, 1.

Making Heterocycles using Wood, Light and Electricity

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At present, synthetic organic chemistry largely relies on fossil carbon sources. The presentation will highlight the alternative use of wood-based renewable chemical feedstocks and of photo- and electrochemical reagentless transformations in the synthesis of complex heterocyclic frameworks, including biologically active natural products such as morphinan, ergot, curare and strychnos alkaloids (**Figure 1**),[1]

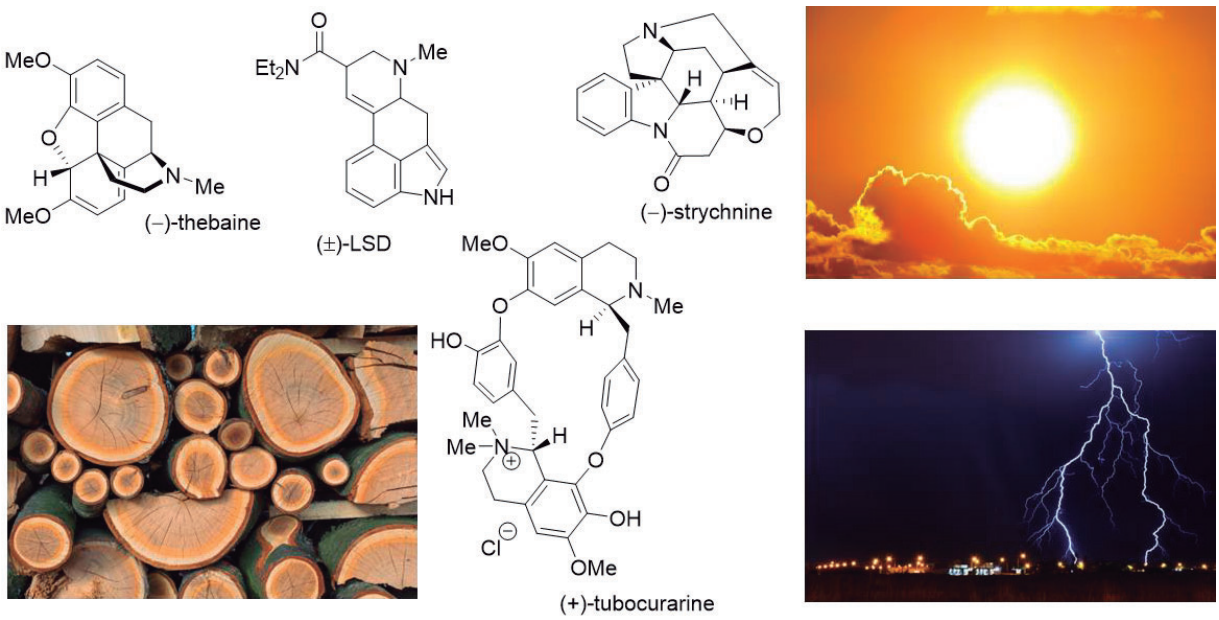

Figure 1: Synthesis of complex organic frameworks using wood-based starting materials, photo- and electrochemistry.

Acknowledgements: We thank Anthony Arduengo, III, Siegfried R. Waldvogel and Hans J. Schäfer for helpful discussions.

References:

1 a) D. Stubba, G. Lahm, M. Geffe, J. W. Runyon, A. J. Arduengo III, T. Opatz, *Angew. Chem. Int. Ed.* **2015**, *54*, 14187; b) N. Otto, D. Ferenc, T. Opatz, *J. Org. Chem.* **2017**, *82*, 1205; c) A. Lipp, D. Ferenc, C. Gütz, M. Geffe, N. Vierengel, D. Schollmeyer, H. J. Schäfer, S. R. Waldvogel, T. Opatz, *Angew. Chem. Int. Ed.* **2018**, *57*, 11055; d) A. Lipp, M. Selt, D. Ferenc, D. Schollmeyer, S. R. Waldvogel, T. Opatz, *Org. Lett.* **2019**, *21*, 1828; e) J. Brauer, R. Wiechert, A. Hahn, T. Opatz, *Org. Lett.* **2024**, *26*, 4314; f) R. Wiechert, L. Geske, J. Hammes, D. Tuncer, T. Opatz, *JACS Au* **2026**, *6*, 1822.

A Comprehensive Method for Reductive Amination under Electrosynthesis Conditions

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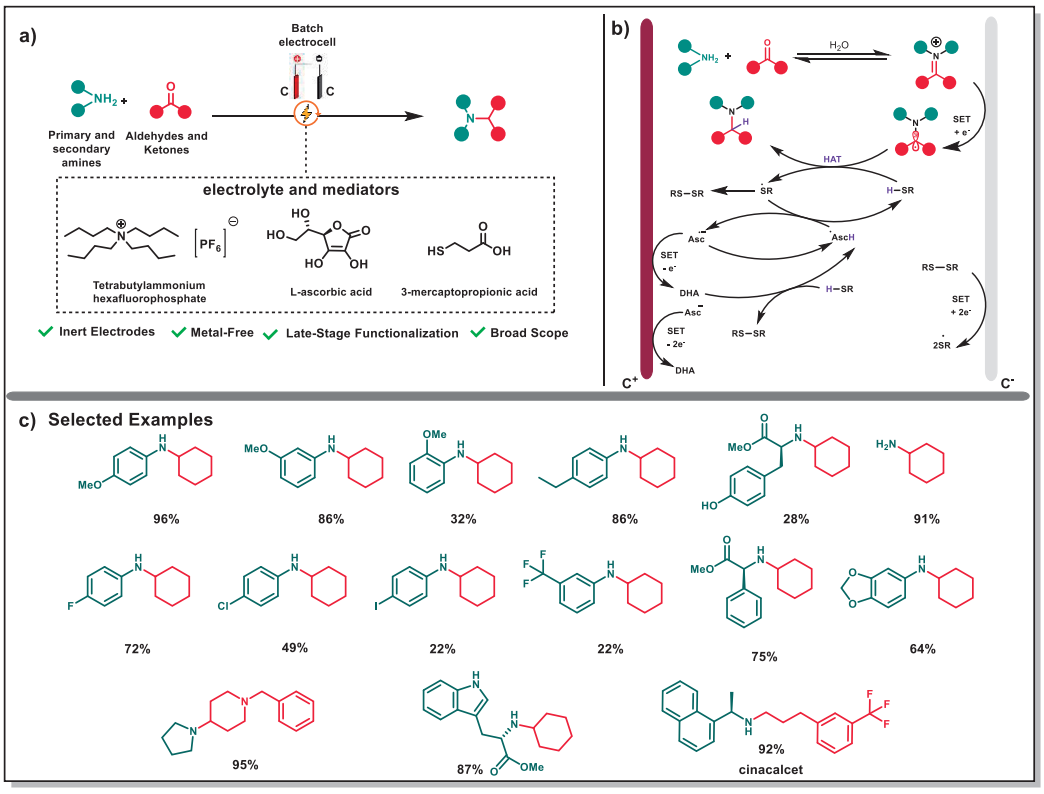
We present an investigation of the scope and robustness of our recently developed reductive amination method for aldehydes and ketones with primary and secondary amines under electrosynthetic conditions (Schemes 1a and 1b)[1]. Given the limited precedents of electrochemical methods[2] for reductive amination, especially those focused on the use of ketones, this research opens up new possibilities for sustainable and scalable applications. With optimized solvents, electrolytes, reagents, and their concentrations, and applied currents (in batch), we now extend this method to a broad range of molecules and valuable APIs[3], enabling access to a diverse chemical space (Scheme 1c).



Scheme 1. a) General reaction conditions; b) Proposed reaction mechanism; c) Substrate product scope.

Acknowledgements: We thank the São Paulo Research Foundation FAPESP (grant number 2023/04020-8 (K.T.O) and 2025/14388-8 (K.T.O)), Fellowships 2025/23071-8 (N.T) and 2024/11868-6 (G.H.S.R), as well as the Conselho Nacional de Pesquisa – CNPq (K.T.O research fellowship 303333/2022-7) and CAPES – Financial Code 001.

References:

1. Rosa, Gabriel H. S.; Teixeira, Nilo.; Da Silva, Gabriele. F.; Brocksom, Timothy J.; De Moraes, Fernando C.; De Oliveira, Kleber. T. unpublished results;
2. Hong, H.; Zou, Z.; Liang, G.; Pu, S.; Hu, J.; Chen, L.; Zhu, Z.; Li, Y.; Huang, Y. Org. Biomol. Chem. **2020**, 18 (30), 5832–5837.
3. Oleg I. Afanasyev, Ekaterina Kuchuk, Dmitry L. Usanov, and Denis Chusov. Chemical Reviews, **2019**, 119 (23), 11857-11911.

Enantioselective Titanium–BINOL Catalyzed IEDDA/ cheletropic cycloaddition of Thiophene *S,S*-Dioxides with Indenes

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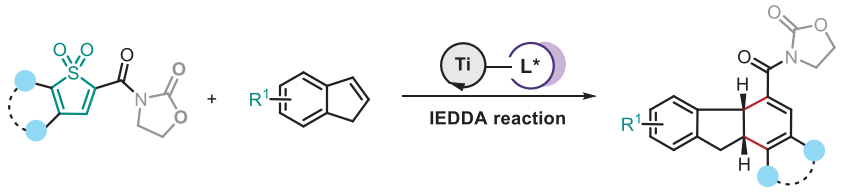
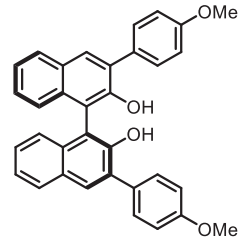
The Diels-Alder reaction was developed nearly a century ago, and numerous non-stereoselective and asymmetric variants have been reported; nevertheless, the demand for an ever-expanding library of synthetic and natural products continues to drive the development of new methodologies based on this transformation. By enabling the rapid assembly of polycyclic frameworks in a single step, the Diels-Alder has become a cornerstone in the synthesis of structurally intricate molecules such as terpenoids, alkaloids, and polyketides.[1] In this regard, thiophene *S,S*-dioxides (TDOs) have attracted considerable attention as highly reactive electron-deficient dienes in Diels-Alder reactions, affording adducts that readily undergo a [4+1] cheletropic extrusion of SO_2. Despite their promise as reactive dienes for IEDDA reactions, the use of TDOs remains an underexplored challenge, with relatively few reported examples achieving high levels of stereocontrol in the formation of new chiral centers.[2] Herein, we report the development of a highly enantioselective titanium–BINOL-catalyzed Diels–Alder reaction between TDOs and electronically unbiased indenes. This transformation exhibits broad substrate scope and remarkable functional group tolerance, enabling the asymmetric construction of complex polycyclic frameworks. Furthermore, the reaction is amenable to gram-scale synthesis, and the chiral ligand can be readily recovered and recycled with no deterioration in yield or enantioselectivity, demonstrating the practicality and sustainability of this protocol. Moreover, the resulting adducts serve as versatile synthetic intermediates, undergoing facile derivatization via hydrogenation, esterification, Suzuki coupling, and further Diels–Alder transformations.

Enantioselective Titanium–BINOL Catalyzed IEDDA/ cheletropic cycloaddition of Thiophene S,S-Dioxides with Indenes



- ***Commercially available and recyclable ligand***
- ***6/5/6 all carbon fused scaffold***
- ***Unactivated double bond***
- ***Up to 87% yield, 99:1 er***



L*, 166 USD / g

Acknowledgements: .We thank the EPSRC for support (EP/X028674/1) and the São Paulo Research Foundation (FAPESP) for financial support (2024/07727-8)

References:

1. Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. The Diels-Alder reaction in total synthesis. *Angew Chem Int Edit* **2002**, *41* (10), 1668–1698.
2. Park, K. H. 'Kenny,' Park, J., Frank, N., Zhang, H., Tian, P., Biddick, Y., Duarte, F., & Anderson, E. A. Collective asymmetric synthesis of the Strychnos alkaloids via thiophene S,S-dioxide cycloadditions. *Nature Chemistry* ***2026***, *18*(4), 782–789.

Synthesis of *N*-heterocycles *via* a multicomponent reaction with unprecedented reactivity

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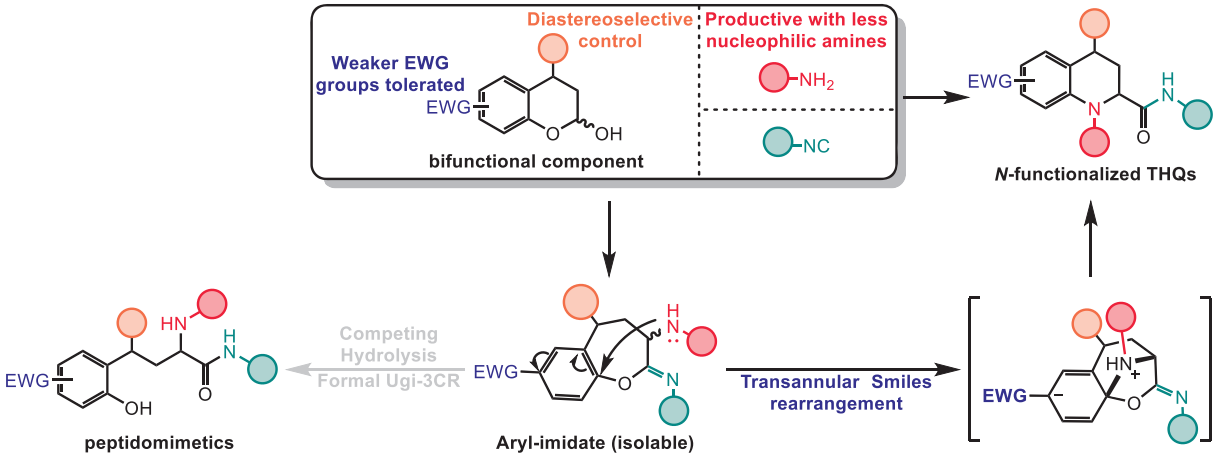
The ubiquitous presence of *N*-heterocycles in biologically relevant compounds is a constant source of inspiration towards the development of new synthetic methodologies. The privileged alkaloid core of 1,2,3,4-Tetrahydroquinolines (THQs), for example, has been the object of numerous synthetic approaches, among these, the hydrogenation of quinolines, the multicomponent Povarov reaction, and transition-metal catalyzed intermolecular C-N bond formation are particularly significant.[1]

Based on our previous works on isocyanide-based multicomponent reactions that explored hemiacetals as bifunctional components,[2] we envisioned that a variant of the Ugi-Smiles reaction could render modular access to THQs through an *N-arylative* cyclization (**Scheme 1**). This newly developed Ugi-Smiles 4C-3CR (four centers, three components) successfully generates *N*-functionalized tetrahydroquinolines under mild conditions, notably working with unproductive components of the original Ugi-Smiles 4C-4CR, such as anilines, α-branched primary amines, and less activated and sterically demanding phenols.[3] The origins of this unprecedented reactivity are currently under investigation using DFT calculations. Interestingly to note, peptidomimetics were also obtained *via* a competing Ugi-3CR pathway when those less reactive partners were employed.



Scheme 1: Multicomponent synthesis of 1,2,3,4-Tetrahydroquinolines.

Acknowledgements: This work was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001. The authors thank FAPESP (21/12394-0, 22/16188-8, 23/13505-5, 24/09943-0), and CNPQ (161524/2021-4) for grants and fellowships. CENAPAD-SP and CESUP are also gratefully acknowledged for computational resources.

References:

1. Muthukrishna. I.; Sridharan. V.; Menéndez J.C. *Chem. Rev*. **2019**, *119*, 5057.
2. a) Echemendía R.; de La Torre A.F.; Monteiro, J.L.; Pila, M.; Corrêa A.G.; Westermann B.; Rivera D.G.; Paixão M.W. *Angew. Chem. Int. Ed.* **2015**, *54*, 7621. b) Fernandes V.A.; Lima R.N.; Broterson Y.B. ; Kawamura M.Y.; Echemendía R.; de la Torre A.F.; Ferreira M.A.B.; Rivera D.G.; Paixão M.W. *Chemi Sci.*, **2021**, *12*, 15862.
3. Chéron N.; Ramozzi R.; El Kaïm L.; Grimaud L.; Fleurat-Lessard, P. *J. Phys. Chem. A* **2013**, *117*,8035.

Synthetic Exploration of Ethyl 7-oxo-1,6-naphthyridine Scaffolds and Their Analogues

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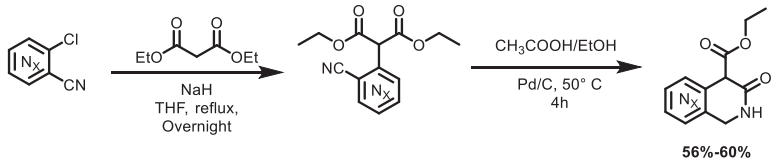
Underrepresented heteroaromatic scaffolds constitute a largely untapped source of chemical diversity for drug discovery[1-3]. Nitrogen-containing heterocycles are present in over 60% of FDA-approved small-molecule drugs, owing to their capacity to modulate electronic properties, polarity, and intermolecular interactions[4-6]. Among these, the 1,6-naphthyridine framework is a bicyclic motif that remains underexplored relative to its structural potential for fragment-based design and scaffold diversification. This work reports the synthesis and structural diversification of ethyl 7-oxo-1,6-naphthyridine scaffolds via a two-step route to yield fragment-like molecules in moderate overall yields. The 7-oxo functionality serves as the primary handle for further derivatization and potential engagement with biological targets, providing access to a set of fused [6,6] nitrogen heterocycles.



Scheme 1: General Scheme for their synthesis of the compounds

References:

1. Marshall, C. M.; Federice, J. G.; Bell, C. N.; Cox, P. B.; Njardarson, J. T. An Update on the Nitrogen Heterocycle Compositions and Properties of U.S. FDA-Approved Pharmaceuticals (2013–2023). *Journal of medicinal chemistry* **2024**, *67* (14). https://doi.org/10.1021/acs.jmedchem.4c01122.
2. Vitaku, E., Smith, D.; Njardarson, J. T. *Journal of Medicinal Chemistry*. **2014,** *57*(24), 10257–10274.
3. Hameed, A., Saeed, A., Uroos, M., Ali, S. F., Arshia, Ishtiaq, M., & Khan, K. M. *Expert Opinion on Therapeutic Patents*. **2018** https://doi.org/10.1080/13543776.2018.1432596
4. Pennington, L. D.; Moustakas, D. T. *J. Med. Chem.* **2017**, 60, 3552.
5. Shearer, J.; Castro, J. V.; Lawson, A. D. G.; MacCoss, M.; Taylor, R. J. K. *Journal of Medicinal Chemistry*. **2022**, *65*(13), 8699–8712. https://doi.org/10.1021/acs.jmedchem.2c00473
6. Taylor, R. J. K.; MacCoss, M.; Lawson, A. D. G. *Journal of Medicinal Chemistry*. **2014**, *57*(14), 5845–5859.

One-pot four-step sequential cohalogenation/oxidation/Hantzsch condensation/ multicomponent aza-Friedel–Crafts strategy for the synthesis of 2-aminoselenazole–indole hybrids

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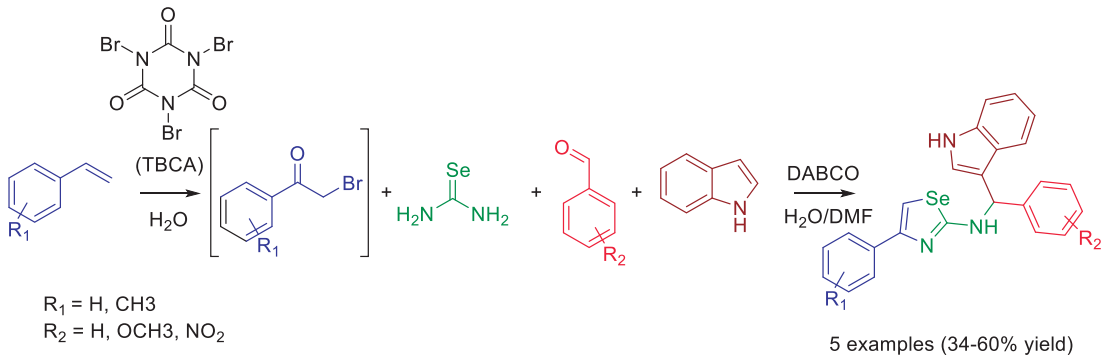
Multicomponent reactions (MCRs) have emerged as a fundamental strategy in modern synthesis, since they allow easy access to complex products from the combination of three or more reagents in a single process. Accordingly, eliminating the need for intermediate isolation typically results in greater molecular diversity and improved overall yields with less experimental effort. From a Green Chemistry perspective, MCRs are particularly attractive due to their intrinsic atom economy. In addition, they can drastically reduce energy consumption, execution time, and waste generation while bypassing purification steps.[1] 1,3-Selenazoles constitute an important class of compounds with broad applications in medicine and agriculture. Not surprisingly, considerable effort has been dedicated to the development of new synthetic methodologies to access 1,3-selenazole scaffolds.[2] Traditionally, these compounds are prepared via the Hantzsch synthesis; however, this methodology often relies on the use of brominated compounds that are lachrymatory and toxic, raising concerns regarding their handling and safety.To overcome these limitations, an interesting approach consists of generating α-bromo carbonyl compounds in situ using safer and easily handled sources of electrophilic bromine. Among them, tribromoisocyanuric acid (TBCA) has proven to be an efficient electrophilic brominating agent.[3] Through acid catalysis, the aza-FC reaction joins electron-rich aromatics to imines, establishing new C–C and C–N bonds. This process is fundamental for accessing polysubstituted amines of high pharmacological and biological relevance.[4] The present work, based on the studies of Gholami et al [5], describes the development of a one-pot, four-step telescoped approach to 2-aminoselenazole–indole hybrids, mediated by TBCA, starting from styrenes, through a consecutive co-bromination, oxidation, Hantzsch condensation, and a multicomponent aza-Friedel–Crafts reaction sequence. For instance, using substituted styrene and benzaldehyde, the selenazole was obtained in 34-60% yield after recristalizarion with water/ethanol (Scheme 1). Furthermore, the generality of the method is currently under investigatation to extend this protocol to β-dicarbonyl compounds, enabling access to structurally diverse hybrids with different substitution patterns.



Scheme 1: Multicomponent reaction for the synthesis of 2-amino-selenazoles-indoles hybrids

Acknowledgements: We thank the CNPq and FAPERJ for the financial support.

References:

1. a) Eifler-Lima, V. L. et al. *J. Braz. Chem. Soc*. **2024**, *10*, e-20240075. b) Ugi; Werner, B.; Dömling, A**. Molecules**. **2003**, *8*, 53. c) Mohlala, R.L.; Rashamuse, T.J.; Coyanis, E.M. *Front. Chem*. **2024**, 12:1469677.
2. a) Łączkowski, Krzysztof Z. et al. *J. Mol. Struct*. **2016**, *1108*, 427. b) Koketsu, M.; Ishihara, H. *Curr. Org. Chem*. **2003**, *7*, 175.
3. de Andrade, V. S. C.; de Mattos, M. C. S. *Synthesis*. **2019**, *51*, 1841.
4. Mohamed, A.H.; Masurier, N. *Org. Chem. Front*. **2023**, *10*, 1847.
5. F. Gholami et al. *J. Mol. Struct*. **2024**,*1299*,137061.

Enantioselective Multicomponent Carbonylative Heck–Matsuda Reaction from Anilines: Synthesis of Spiro-Heterocycles Containing Two Stereogenic Centers

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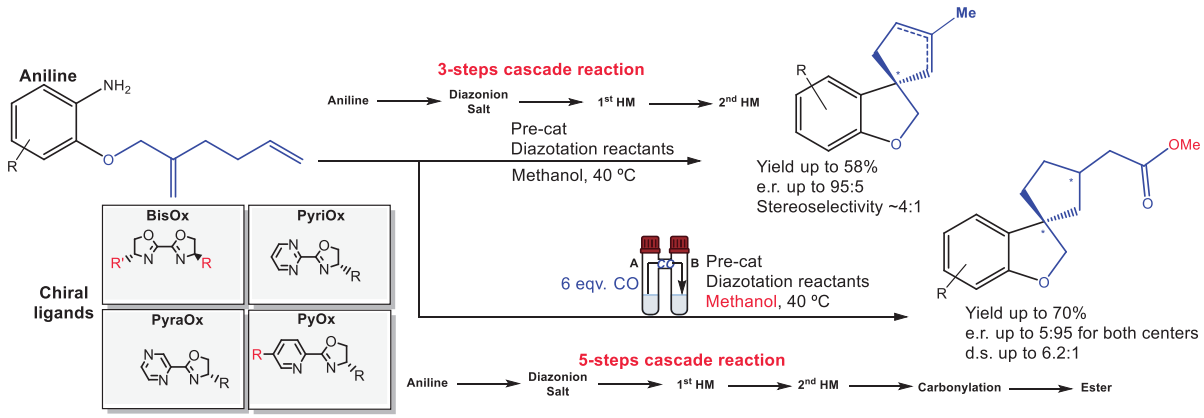
Palladium-catalyzed C–C couplings are versatile transformations widely used in organic synthesis and pharmaceutical chemistry.[1] The Heck-Matsuda (HM) reaction stands out for using aryldiazonium salts which readily undergo oxidative addition to Pd(0), forming reactive cationic intermediates under mild conditions. Using in-situ diazotization from anilines instead of preformed diazonium, in the presence of N,N-chiral ligands avoids unnecessary handling, improving safety and practicality of the overall reaction.[2,3] Herein, we describe an intramolecular and sequential Heck-Matsuda reaction to create enantioselective spiro heterocyclic compounds of biological and pharmaceutical relevance.[1]

Additionally, the capture of the reactive alkyl–palladium intermediates provides a practical strategy for introducing new functional groups, thereby expanding the scope of functionalized compounds while simultaneously generating new stereogenic centers through practical multistep one-pot cascade.[3]

In this context, the present work describes the development of an enantioselective cascade methodology for the synthesis of highly enantioenriched spiro-heterocycles from anilines bearing a non-conjugate diene in the carbon chain, enabling sequential migratory insertions (Scheme 1). Thus, these reactions were conducted with in-situ diazotation of the aniline, followed by a double-HM reaction, generating the spiro compounds from an eliminative HM to provide a mixture of two diastereomeric unsaturated spiro benzofurans. Furthermore, by employing controlled amounts of CO gas, it is selectively incorporated after the second migratory insertion step, affording ester-functionalized spirocyclic products bearing two stereogenic centers with high enantiomeric ratio (up to 5:95) in a carbonylative double HM reaction. This methodology enables the synthesis of enantioenriched spirocyclic scaffolds, opening synthetic possibilities for the synthesis of even more complex molecules.



Scheme 1: Cascade enantioselective intramolecular Heck-Matsuda for the obtention of functionalized spiro-heterocycles derivatives.

Acknowledgements: GHCM and CRDC thank FAPESP (2024/20078-9; 2025/08477-8).and CNPQ (408360/2024-0) for financial support.

References:

1. Basavaraja D.; Doddamani S. V.; Athira C. S.; Siby A.; Sreelakshmi V.; Ancy A.; Somappa S. B. *Tetrahedron* **2025**, *173*, 134468.
2. Kattela, S.; Heerdt, G.; Correia, C. R. D. *Adv. Synth. Catal.* **2017**, *359*, 260.
3. Chorro, T. H. D.; Kaussler, C.; Kolodiazhnaia, J. V.; Jensen, F.; Skrydstrup, T.; Correia, C. R. D. *Org. Chem. Front.* **2025**, *12*, 1257.

Automated direct-to-biology discovery of CDK-1 and CDK-2 inhibitor hits from an underexplored imidazo[1,2-a]pyrazine scaffold

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Protein kinases have emerged as one of the most prominent drug targets in the 21st century. These enzymes play central roles in cell signaling pathways, which are critically implicated in neoplastic and inflammatory diseases. In 2025, the FDA approved ten new kinase-inhibitor drugs, underscoring how drug-discovery is a hot topic [1]. Many of these drugs are small molecules featuring fused-ring scaffolds. For example, teletrectinib contains an imidazo[1,2-b]imidazopyridazine core. Similar cores can be accessed through multicomponent reaction strategies, such as Groebke-Blackburn-Bienaymé (GBB) reactions [2], a powerful tool for rapidly generating large libraries of structurally complex compounds from simple starting materials.

In this work, we report a direct-to-biology approach for the generation of potential CDK-1 and CDK-2 inhibitors via multicomponent reactions. 3-Chloropyrazin-2-amine was used as the amidine in GBB reactions to afford a new series of 8-chloroimidazo[1,2-a]pyrazine derivatives. Following the methodology optimization, 16 new GBB products were obtained in yields ranging from 10-38% (**figure 1**). Although the yields are modest, the workflow enables broad analogue generation and efficient exploration of previously underexplored kinase-focused chemical space. Subsequently, these compounds were subjected to nanoscale amination reactions in two 384-well plates. Aryl, heteroaryl, and aliphatic amines were employed, yielding 363 new imidazo[1,2-a]pyrazin-8-amine derivatives. Inhibition screening identified several hit compounds at 10 µM. Selected candidates will be synthesized on a large scale to confirm their inhibitory profiles and serve as starting points for the development of more potent kinase inhibitors.

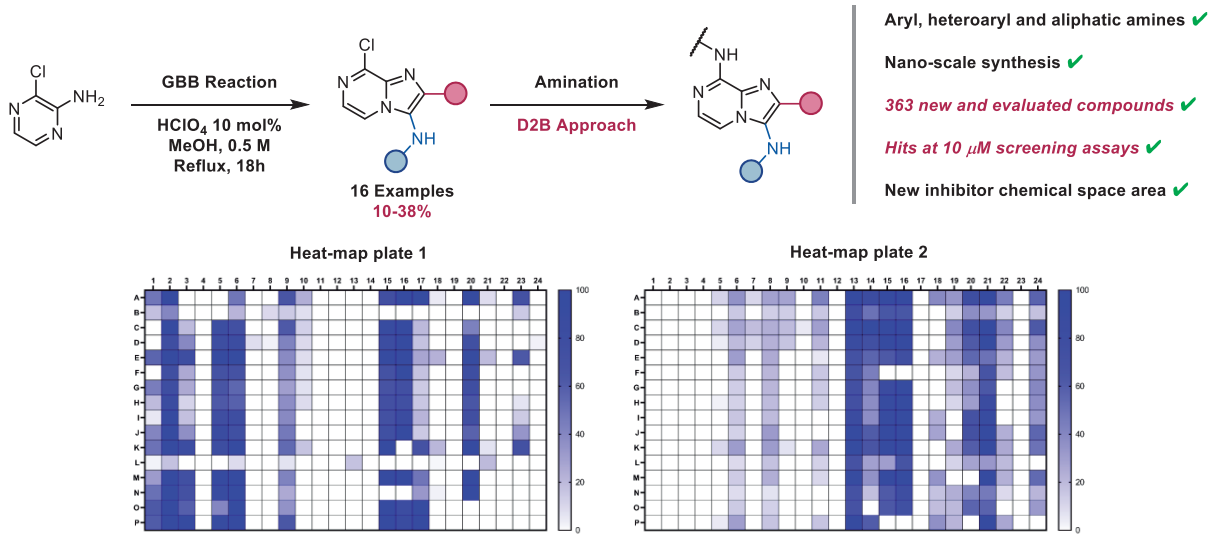

Figure 1. Synthesis in nanoscale of novel potential kinases inhibitors using a D2B approach

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References:

1. Roskoski R. *Pharmacological Research*, 224, **2026**, 108107;
2. Boltjes, A. and Dömling, A. *Eur. J. Org. Chem.*, **2019**, 7007-7049.

A Modular Acetamide-Based Triazole Synthetic Platform for the Diversity-Oriented Synthesis of Quinolones

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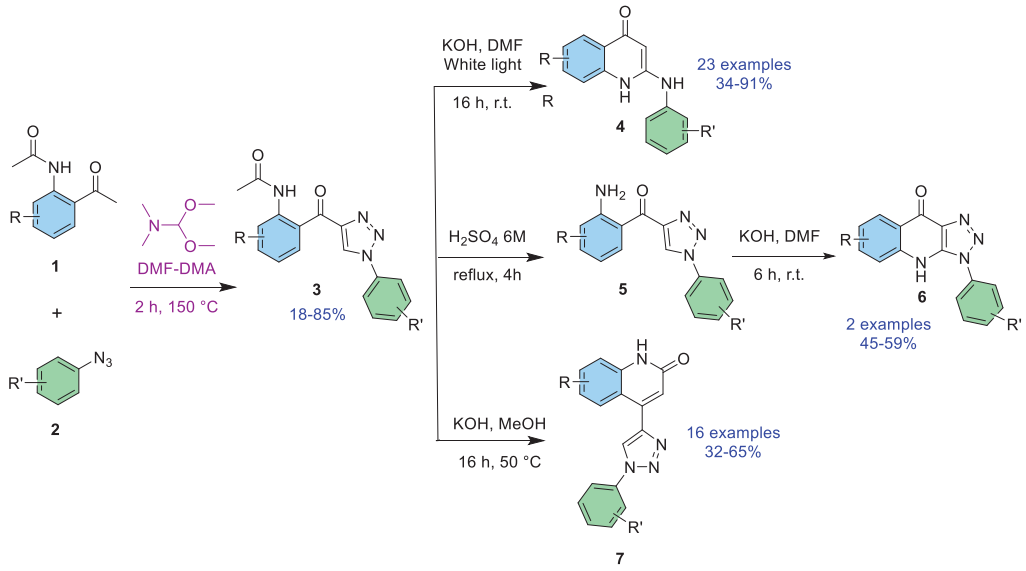
1,2,3-triazoles are versatile heterocyclic units with potential far beyond the formation of bioactive molecules. Among their derivatives, 4-acyl-1,2,3-triazoles stand out as multifaceted compounds, due to their straightforward synthesis and significant potential for generating new molecular entities. Despite their use for this purpose, reports in the literature of their use as key compounds to achieve new heterocycles, mainly quinolones, remain scarce.[1] Quinolones represent a privileged class of heterocycles, widely employed in the development of new drug candidates.[2] Based on LabSint's expertise in streamlined nitrogen-heterocycle synthesis with simple methodology and purification, this work explores acetamide-based 4-acyl-1,2,3-triazoles **3** as a versatile synthetic platform to achieve novel quinolone-based molecules via C-C and C-N cyclizations. The precursor compounds **3** were synthesized via a tandem enaminone-azide cycloaddition previously described by our research group, with yields up to 85%.[3] These were subsequently transformed into (arylamino)quinolin-4(1*H*)-ones **4** through C–N bond formation, followed by a ring-chain isomerization promoted by white-light irradiation in a basic medium (KOH/DMF), resulting in 23 new derivatives with yields ranging from 34% to 91%. Furthermore, by modulating reaction conditions to exclude light, we obtained fused quinolone-triazole hybrids **6**, from deprotected acyl-1,2,,3 triazol **5** affording only two initial examples in 45% and 59% yield. Finally, the 4-(1-aryl-1H-1,2,3-triazol-4-yl)quinolin-2(1H)-one **7** scaffold was efficiently synthesized under solvothermal conditions in methanol with KOH, yielding 17 new compounds (up to 65% yield) (Scheme 1).



Scheme 1: Convergent synthesis of quinolone-based structures from acetamide-based 4-acyl-1,2,3-triazoles

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References:

1. Motornov, V et al. RSC Adv 2023, 13 (49), 34646–34651.
2. Heeb, S. et al. FEMS Microbiol Rev., 2011, 35, 247–274
3. Azevedo, M.F.M.F.; Zeitune, D.C.; et. al. J. Mol. Struct., 2025, 1321, 139897.

Expanding Antiparasitic Chemical Space Through Miniaturized Synthesis of Nitrogen-Rich Heterocycles

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Neglected tropical diseases caused by trypanosomatid parasites still suffer from limited therapeutic options and a restricted diversity of validated chemotypes. In this context, we report integrated miniaturized medicinal chemistry strategies focused on the rapid synthesis and phenotypic evaluation of structurally diverse nitrogen-rich heterocycles against *Trypanosoma* and *Leishmania* species. Our approach combines microscale parallel synthesis (MPS), direct-to-biology concepts,[1] fragment-based drug design (FBDD), and heterocyclic scaffold expansion to accelerate antiparasitic hit discovery while reducing solvent consumption, purification steps, and experimental time (Figure 1). Different heterocyclic series were explored, including aminopyrazoles, pyrazolo[1,5-a]pyrimidines, indazoles, imidazopyrimidines, and Groebke–Blackburn–Bienaymé (GBB)-derived fused scaffolds. Aminopyrazole derivatives obtained through collaboration with DNDi and the Open Synthesis Network were diversified through urea formation, N-protection strategies, methylation, and piperazine incorporation, leading to compounds with promising activity against *Leishmania infantum*, including analogues displaying IC_{50} values below 1 μM and favorable selectivity profiles. In parallel, fragment-growing strategies based on 1H-indazole derivatives employed Sonogashira cross-coupling reactions to introduce alkynyl fragments and investigate structure–activity relationships. Among the synthesized compounds, selected N-protected indazole derivatives displayed low micromolar activity against *T. cruzi* and *L. infantum*, while carbamate-containing analogues improved selectivity by reducing cytotoxicity. Additionally, imidazopyrimidine-derived ureas and amides synthesized through MPS–MTS workflows demonstrated that crude reaction mixtures can reliably anticipate antiparasitic structure–activity trends after resynthesis and purification validation. The combined use of miniaturized synthesis, phenotypic screening, and heterocyclic diversification represents a sustainable and efficient strategy for rapidly expanding antiparasitic chemical space and identifying novel hit candidates for neglected tropical diseases.

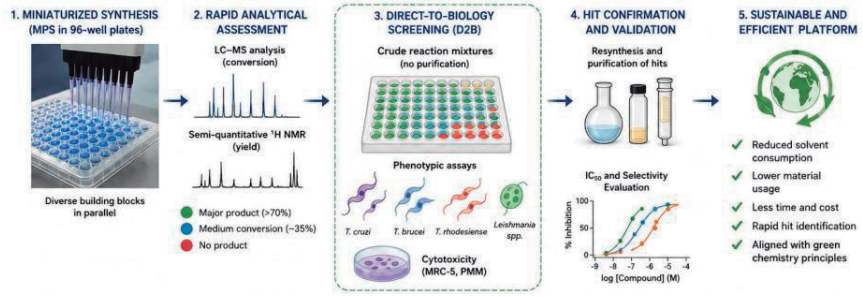

Figure 1. A Greener and Cost-Effective MPS–D2B Platform.

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References:

[1] Crispim, C. V. da S.; Lima, M. F. de; Abubakar, A.; da Silva, R. R. P.; da Silva, T. H. C.; Silva, D. G. J. Braz. Chem. Soc. accepted for publication.

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Spectroscopic and Structural Characterisation and Thermal Reactivity of Heavier Chalcogen Analogues of Pyran-4-one

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The four compounds pyran-4-one **1**, pyran-4-thione **2**, thiopyran-4-one **3** and thiopyran-4-thione **4** have been extensively studied by computational methods but certain key experimental data are lacking. For example only **3** has had its X-ray structure reported[1] and NMR data are incomplete. We report here the X-ray structures of compounds **1**, **2** and **4** which show interesting chalcogen–chalcogen interactions as well as a full NMR study of all four compounds.

The diphenyl compounds **5–10** have interesting optical properties and were prepared and studied by Detty and coworkers at Eastman-Kodak.[2,3] However again basic NMR and X-ray structural data are lacking. We have determined X-ray structures of all six compounds with that of **10** being the first of any telluropyranthione. The ^{13}C NMR spectra of **5–10** are also reported, most of them for the first time.

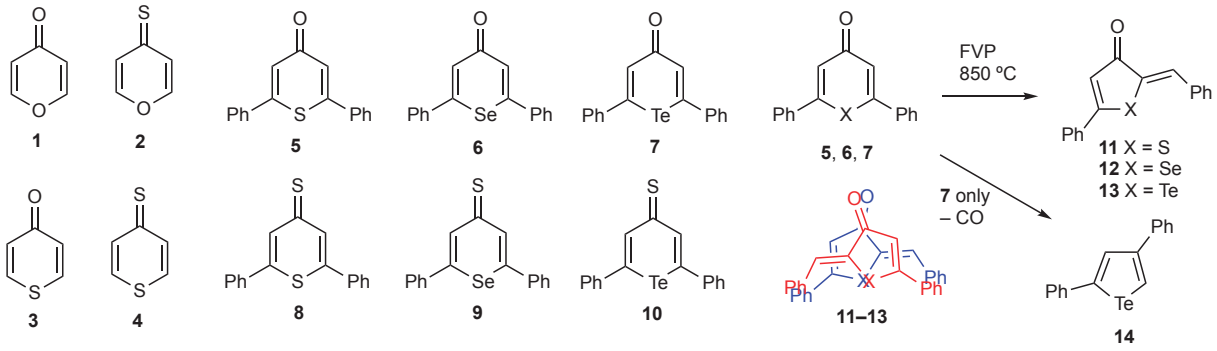

Figure 1: Structure of compounds studied

As far as we are aware the pyrolysis behaviour of such compounds has not been studied before. In a new thermal transformation we have found that flash vacuum pyrolysis (FVP) of carbonyl compounds **5–7** at 850 °C results in isomerisation into the five-membered ring products **11–13**. The X-ray structures of each of these show an interesting type of disorder with two alternative molecular orientations (red and blue) occuring together in the crystal. For the tellurium compound **7** an additional minor product (11%) from the pyrolysis is the diphenyltellurophene **14** formed by decarbonylation and rearrangement.

References:

1. Detty, M. R.; Luss, H. R. *Organometallics* **1992**, *11*, 2157–2162.
2. Detty, M. R.; Murray, B. J.; Seidler, M. D. *J. Org. Chem.* **1982**, *47*, 1969–1971.
3. Detty, M. R.; Murray, B. J. *J. Org. Chem.* **1982**, *47*, 1148–1150.

Abstract

Solid-phase peptide synthesis (SPPS) has long relied on iterative coupling and deprotection cycles separated by extensive solvent washing steps, resulting in significant reagent consumption and waste generation. CEM's Liberty platform introduces Ultra-Efficient SPPS (UE-SPPS), a microwave-assisted, wash-free methodology that eliminates all solvent washing steps between amino acid additions. By combining optimized microwave irradiation, CarboMAX™ coupling chemistry, and a one-pot deprotection/coupling process, UE-SPPS reduces solvent waste by up to 95% while maintaining — and often improving — crude purity and synthesis yield. The result is a faster, greener, and more cost-effective approach to peptide synthesis, capable of producing standard, complex, and long-sequence peptides with unprecedented efficiency. This technology represents a significant step forward in sustainable peptide manufacturing, with applications ranging from research-scale synthesis to GMP-compliant pharmaceutical production.