7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

ABSTRACT BOOK

PARTNERS

SHIMADZU
Excellence in Science

MERCK

CIC
SOLUÇÕES GRÁFICAS

Programa de Pós-Graduação em Ciências Farmacêuticas

FACULDADE DE CIÊNCIAS FARMACÊUTICAS DE RIBEIRÃO PRETO · USP ·

FAPESP

CAPES

ORGANIZING COMMITTEE – General

- Prof. Dr. Giuliano Cesar Clososki, Department of BioMolecular Sciences, FCFRP, University of São Paulo.
- Prof. Dr. Flavio da Silva Emery, Department of Pharmaceutical Sciences, FCFRP, University of São Paulo.
- Prof. Dr. Carlos Roque Duarte Correia, Department of Organic Chemistry, Chemistry Institute, Unicamp.
- Prof. Dr. Marcus Mandolesi Sá, Department of Chemistry, Federal University of Santa Catarina.

ORGANIZING COMMITTEE - local

- Dr. Thiago dos Santos, FCFRP, University of São Paulo.
- Msc. Raul Marques Novais, FCFRP, University of São Paulo.
- Msc. Gabriel de Paula Bueno, FCFRP, University of São Paulo.

SCIENTIFIC COMMITTEE

- Prof. Dr. Antônio Carlos Bender Burtoloso, São Carlos Institute of Chemistry, University of São Paulo.
- Prof. Dr. Cinthia Duarte de Freitas Milagre, Chemistry Institute, São Paulo State University.
- Prof. Dr. Rodrigo Octavio M. Alves de Souza, Department of Organic Chemistry, Federal University of Rio de Janeiro.
- Prof. Dr. Kleber Thiago de Oliveira, Department of Chemistry, Federal University of São Carlos.
- Prof. Dr. Vicente Gotor-Fernández, Department of Organic and Inorganic Chemistry, University of Oviedo.
- Prof. Dr. María Consuelo Jiménez, Industrial Engineering School, Polytechnic University of Valencia.

- Prof. Dr. Jose Maria Lassaletta, Spanish National Research Council (CSIC), Sevilla.
- Prof. Dr. Fernando Cossio, University of the Basque Country, Leioa, Guipúzcoa.

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Monday, 10 July 2023		
14:00-16:00	Conference Registration	
16:00-16:30	Opening remarks	
Session 1 **Chair: Prof. Dr. Carlos Roque Duarte Correia**		
16:30-17:15	Dr. Vicente Gotor-Fernandez – *University of Oviedo* "Merging gold and enzyme catalysis for asymmetric synthesis"	PL - 1
17:15-18:00	Dr. Monica Tallarico Pupo – *University of Sao Paulo* "Natural products discovery from symbiotic systems"	PL - 2
18:00-18:45	Dr. Aitziber López Cartajarena – *CIC biomaGUNE* "Engineered protein-based biocatalysts, nanozymes, and biomaterials"	PL - 3
19:00–21:30	Welcome reception	

Tuesday, 11 July 2023		
Session 2 **Chair: Prof. Dr. Vicente Gotor-Fernández and Prof. Dr. Marcus Mandolesi Sá**		
09:00-09:45	Dr. Julio Cezar Pastre – *State University of Campinas* "Enabling technologies for the sustainable chemical synthesis of high added-value compounds from renewable sources"	PL - 4
09:45-10:00	**Ilana Sganzerla Rosário - *São Paulo State University (UNESP)*** **"Synthesis and photopolymerization of quinoline derivatives containing methacrylate group with potential application in biomaterials"**	**FP - 1**
10:00-10:15	**Daniel Gedder Silva - *University of São Paulo (USP-RP)*** **"Synthesis of heterocyclic compounds as potential anti-Infectives agents"**	**FP - 2**
10:15-10:30	**Luiz P. M. O. Leão - *UNICAMP*** **"The Second Generation of the In-tandem Enantioselective Heck-Matsuda Arylations of Unactivated Olefins Directly from Anilines and Nitroarenes"**	**FP - 3**
10:30-11:00	Coffee break	
11:00-11:45	Dr. Rosario Fernández Fernández – *University of Seville* "Development of New Catalytic Systems. Applications in Asymmetric Catalysis"	PL - 5

11:45-12:00	**Thaynan A. B. Chagas - *UNICAMP*** **"Development of an asymmetric version of the Morita-Baylis-Hillman reaction using vinyl-1,2,4-oxadiazoles as nucleophilic partners"**	**FP - 4**
12:00-12:15	**Camilla D. Buarque - *PUC-Rio*** **"Ecofriendly synthesis of 4-acyl-1,2,3-triazoles as precursors for novel p.Phe508del-CFTR traffic correctors"**	**FP - 5**
12:15-12:30	**Carla C. Decandio – *Merck Brazil*** **"Innovation for Sustainable Development"**	**FP - 6**
12:30–14:00	Lunch	
	Session 3 **Chair: Prof. Dr. Fernando P. Cossío and Prof. Dr. Rosario Fatima Fernandez Fernandez**	
14:00-14:45	Dr. Josiel Domingos – *Federal University of Santa Catarina* "Palladium-triggered Deprotection Chemistry for Small Molecule Activation in Living Systems"	PL - 6
14:45-15:30	Dr. Jose L. Vicario - *University of the Basque Country* "Organocatalytic Enantioselective Reactions Driven by the Release of Ring Strain"	PL - 7
15:30-15:45	**Giovana da S. Ramos – *UFSC*** **"Synthesis of 2-hydrazono-3-thiazolines through a novel one-pot multicomponent/rearrangement process from 2-substituted oxazoles"**	**FP - 7**
15:45-16:00	**Matheus Fernandes Alves – *Unifal-MG*** **"Metabolic fingerprint of Ocotea diospyrifolia: A integrated strategy to achieve reliable annotation"**	**FP - 8**
16:00-16:45	**Coffee break & Poster Session 1**	
16:45-17:30	Dr. Paulo Schneider – *Federal University of Rio Grande do Sul* "New approaches to the synthesis of polysubstituted aromatic compounds containing chalcogens"	PL - 8
17:30-18:15	Dr. Martín Fañanás-Mastral – *University of Santiago de Compostela* "Catalytic Approaches for Stereoselective Hydrocarbon Difunctionalization"	PL - 9
18:15-18:30	**Victor C. S. Santana - *UNICAMP*** **"Selective late-stage oxidation of C–H bonds in the synthesis of complex natural diterpenes"**	**FP - 9**
20:00-22:30	Conference dinner (*by adhesion*)	

Wednesday, 12 July 2023		
Session 4 **Chair: Prof. Dr. Jose Maria Lassaletta and Prof. Dr. Antônio Carlos Bender Burtoloso**		
09:00-09:45	Dr. Ângelo de Fátima – *Federal University of Minas Gerais* "Why to inhibit ureases from agricultural and medicinal perspectives?"	PL - 10
09:45-10:30	Dr. Manuel Alcarazo - *University of Göttingen* "From ligand design to the synthesis of biologically active molecules"	PL - 11
10:30-11:15	**Coffee Break & Poster Session 2**	
11:15-12:00	Dr. Fernando P. Cossío - *University of the Basque Country* "Bicolor Fluorescent Sensors for Barium Tagging in the Neutrinoless Double Beta Decay Reaction of Xe-136"	PL - 12
12:00-12:45	Dr. Marcio Weber Paixão – *Federal University of São Carlos* "Visible-Light-Driving Organic Chemistry: Synthesis of Small Molecules and Biomolecules Modifications"	PL - 13
12:45-13:15	Closing ceremony	
14:00–17:00	Barbecue (*by adhesion*)	

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Synthesis and investigation of the chemosensory action of 1,4-dihydro-1,2,4,5-tetraarylpyrrolo[3,2-*b*]pyrrole derivatives

Lucas Michelão Maratins,[1*] Lais Cristina Augusto, [1] Vitor Fernandes Moreno,[1] Julia Lopes Rodrigues[1] and Luiz Carlos da Silva Filho[1]

1) Department of Chemistry, São Paulo State University (UNESP), School of Sciences, 17033-360, Bauru, São Paulo, Brazil

****e-mail: lm.martins@unesp.br***

Keywords: *pyrrolo[3,2-b]pyrroles, chemosensors, fluorescence.*

ABSTRACT

Chemosensors (CS) are substances that can signal a chemical or physical alteration that occurs in the presence of an analyte. Colorimetric and fluorescent CS present some advantages such as high sensitivity and versatility. In 2016 Wu and coworkers demonstrated that a pyrrolo[3,2-b]pyrrole (PP) derivative can be used as a simple halocarbon qualitative chemosensor.[1]

Based on that we synthesized, using a previously developed method in our group,[2] PPs that could be investigated as CS for different solvents. A solvatochromic study was made for two PPs, and we found that although they suffer different effects from the solvents, none of them could easily be used as a colorimetric or fluorescent sensor.

So the next step will be studying these compounds in other types of analytes, such as acid-base conditions or in the presence of salts, using a methodology from the literature.[3]

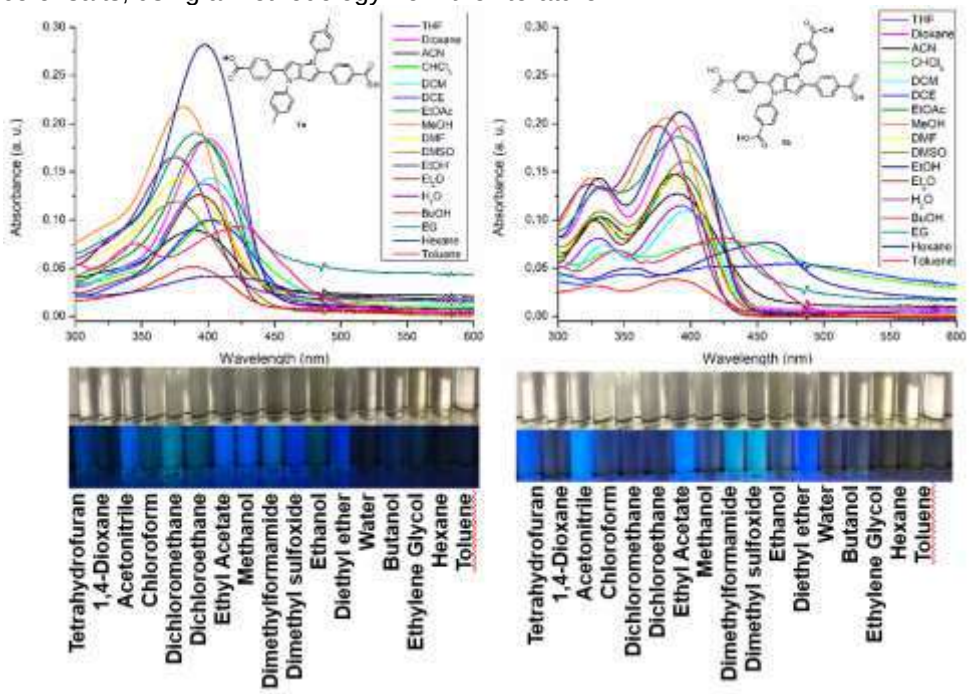


Figure 1. PP derivatives and their solvatochromism study with UV-Vis spectra.

ACKNOWLEDGEMENTS

The authors would like to thank FAPESP (2018/14506-7), CAPES (88882.330148/2019-01) and FEPAF for their financial support.

REFERENCES

[1] Wu, J.-Y.; Yu, C.-H.; Wen, J.-J.; Chang, C.-L.; Leung, M. *Anal. Chem.* **2015**, *88* (2), 1195–1201.

[2] Martins, L. M.; de Faria Vieira, S.; Baldacim, G. B.; Bregadiolli, B. A.; Caraschi, J. C.; Batagin-Neto, A.; da Silva-Filho, L. C. *Dye Pigm.* **2018**, *148*, 81–90.

[3] dos Santos, G. C.; Rodrigues, J. L.; Moreno, V. F.; da Silva-Filho, L. C. *J. Mol. Struct.* **2021**, *1235*, 130260.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Synthesis and photopolymerization of quinoline derivatives containing methacrylate group with potential application in biomaterials

Ilana Sganzerla Rosário,[1*] Vitor Fernandes Moreno,[1] Luiz Carlos da Silva Filho[1]

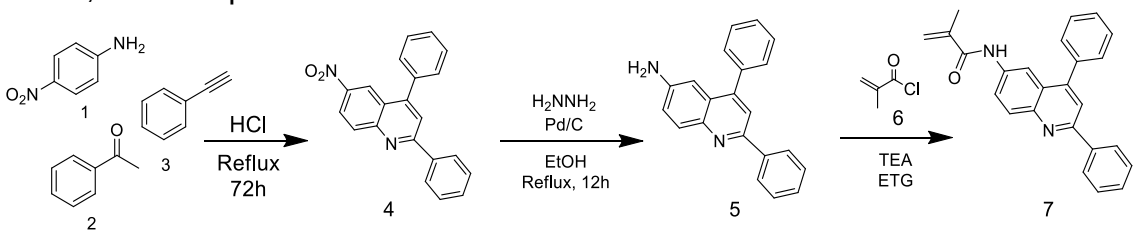
1) Department of Chemistry, São Paulo State University (UNESP), School of Sciences, 17033-360, Bauru, São Paulo, Brazil

****e-mail: ilana.sganzerla@unesp.br***

Keywords: *quinoline derivatives, photopolymerization, photoinitiator, luminescent polymers, biomaterials*.

ABSTRACT

The objective of this work is the synthesis of different quinoline derivatives (Scheme 1) that have the ability to act as Type I (absence of co-initiator) and Type II (presence of co-initiator) photoinitiators in the photopolymerization reaction with urethane dimethacrylate (UDMA) which is widely used as a monomer in photoreactions applied in resins for dental restoration.1-3 Through studies of photolysis using these derivatives, it was notable that the formation of reactive species occurred from the first second of exposure to light, evidencing the photosensitivity of these molecules. Furthermore, polymers with a degree of conversion of up to 60% were obtained in about 50 seconds, these results being interesting since they are close to those presented by camphorquinone. It is noteworthy that the materials obtained have fluorescent characteristics (Figure 1), which may be relevant when applied to the dental area, for example.



Scheme 1. Synthesis of quinoline derivatives

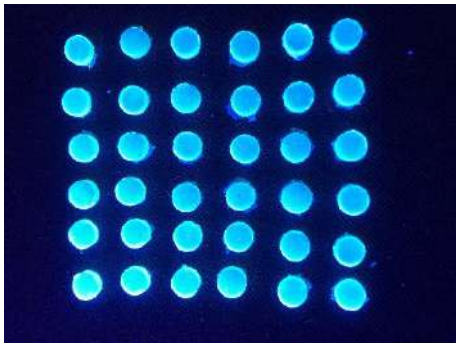


Figure 1. Polymers using UDMA and quinoline photoinitiators

ACKNOWLEDGEMENTS

The authors would like to thank FAPESP (2018/09235-4 and 2018/14506-7), CAPES (88887.827622/2023-00), and Pró-Reitoria de Pesquisa da UNESP (PROPe-UNESP) for their financial support.

REFERENCES

[1]. Moszner, N.; Völkel, T.; Fischer, U. K.; Klester, A.; Rheinberger, V., *Angew. Makromol. Chem*. 1999, 265 (1), 31–35.
[2]. Alarcon, R. T.; dos Santos, G. C.; de Oliveira, A. R.; da Silva-Filho, L. C.; Bannach, G., *J. Appl. Polym. Sci*. 2019, 136 (19), 47461.
[3]. Fouassier, J. P.; Lalevée, *J. Photoinitiators for Polymer Synthesis*; John Wiley & Sons, 2013.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Evaluation of vasorelaxant potential of lupeol esters

Matheus Emanuell Andrade dos Santos,[1] Rita de Cássia Vilhena da Silva,[2] Priscila de Souza,[2] Aline Teixeira Maciel e Silva,[3] Lucienir Pains Duarte[3] and Cássia Gonçalves Magalhães[1*]

1) Departamento de Química, Universidade Estadual de Ponta Grossa, 84030-900
2) Núcleo de Investigações Químico-Farmacêuticas,* Universidade do Vale do Itajaí*, 88302-202
3) Departamento de Química, Universidade Federal de Minas Gerais, 31270-901
****e-mail: cgmagalhaes@uepg.br***

Keywords: lupeol esters*, M. salicifolia, anti-hypertensives*

ABSTRACT

Hypertension is directly associated with cardiovascular diseases, requiring the discovery of new anti-hypertensive drugs. In this context, natural products comprise a relevant source of lead structures that can direct the synthesis of new bioactive compounds.[1] Lupeol, a pentacyclic triterpene found in plants from *Monteverdia* genus (Celastraceae) has been show cardioprotective effects.[2] This work describes the study of the potential vasorelaxant activity of aromatic (**1**, **2**, **3**) and aliphatic (**4**, **5**) esters (Figure 1), obtained by semi-synthesis, using lupeol isolated from *M. salicifolia*.[3] The assay was conduced by the thoracic aortic rings model, using acetylcholine as positive control. The esters 1, 2, 4 and 5 exhibited a discreet vasorelaxant activity, in the range of 14% to 30%. The compound 3 was inactive. These results refuse a direct action of these esters in the blood vessels, contrasting with the benefits showed by lupeol and other analog esters evaluated by different mechanisms.

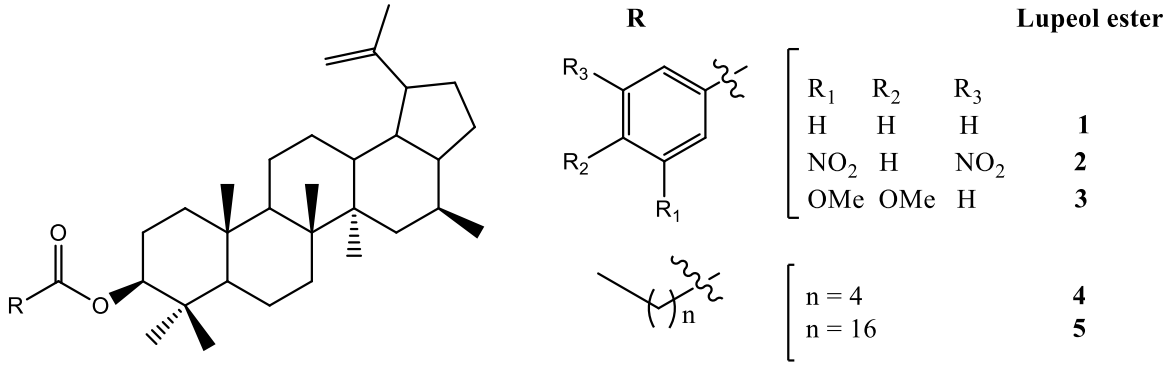


Figure 1. Structure of Lupeol esters.

ACKNOWLEDGEMENTS

PIBIC-UEPG, CAPES

REFERENCES

[1] Xavier, F. J. S., Lima Júnior, C. G., Vasconcellos, M. L. A. A., Oliveira, R. *Rev Virt Quím*, **2019**, *11*, 1-12.

[2] Sharma, N., Palia, P., Chaudhary, A., Verma, K., Kumar, I. *J Drug Deliv Ther* **2020**, *10*, 325-332.

[3] Silva, A. T. M., Magalhães, C. G., Duarte, L. P., Mussel, W. N., Ruiz, A. L. T. G., Shiozawa, L., Carvalho, J. E., Trindade, I. C., Vieira, S. A. *Braz J Pharm Sci*, **2017**, *53*, 251-351.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Design and synthesis of boronics acids derivatives and benzoboroxoles with antifungal activity.

João Lucas Bruno Prates,[1*] Samanta de Matos Silva,[2] Ana Marisa Fusco-Almeida.[2] and Jean Leandro dos Santos.[1*]

1) Department of Drugs and Medicines, School of Pharmaceutical Sciences, São Paulo State University, 14801-902

2) Department Clinical Analisys, School of Pharmaceutical Sciences, São Paulo State University, 14801-902

****e-mail: joao.prates@unesp.br***

Keywords: *Boronic acids, Benzoboroxole, T. rubrum.*

ABSTRACT

Boronic acids and benzoboroxole belong to a class of compounds called organoboron and are being highlighted in the recent years in the fields of medicinal and organic chemistry. These compounds present the ability of making a reversible covalent bond to amino acid residues, being used in the structure of inhibitors for the development of new compounds for the treatment of infectious diseases, such as tuberculosis and onychomycosis.[1] Tavaborole is an example of benzoboroxole that was approved by the FDA in 2016 for the treatment of onychomycosis.[2]

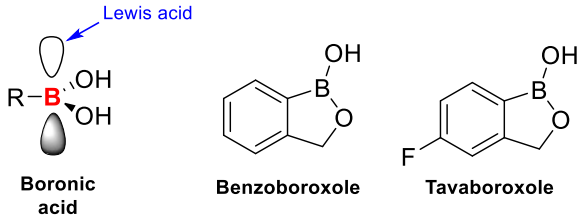
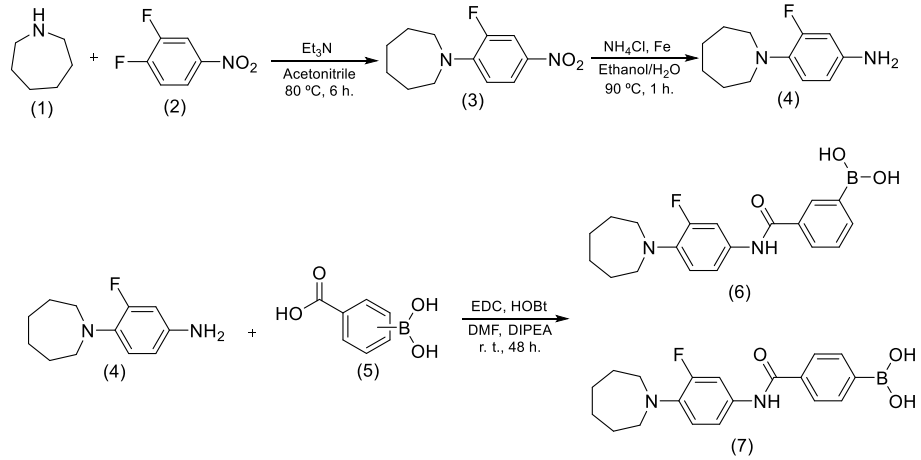


Figure 1. Chemical structure of boronic acid, benzoboroxole and Tavaborole.

In this work, fourteen derivatives of boronic acids and benzoboroxoles were synthesized in yields ranging from 22% to 62% and evaluated against the fungus *Trichophyton rubrum* (*T. rubrum*). Two of these compounds, 6 and 7, presented promisor results with MIC_{50} values of 87.7 µM, which was 2.4-fold more active than the standard drug fluconazole (209.8 µM) (Scheme 1).



Scheme 1. Synthetic methodology for obtaining boronic acid derivatives.

ACKNOWLEDGEMENTS

Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) – Finance Code 001.

REFERENCES

[1]. Kahlert, J. Austin, C. J. D. Kassiou, M. Rendina, L. M. *Aust. J. Chem.* **2013**, *66*, 1118-1123.
[2]. Rock, F. L. Mao, W. Yaremchuk. A. et. al. *Sci.* **2007**, *316*, 1759-1761.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

In silico study of novel 2-aminobenzamide derivatives as HDAC3 inhibitors designed as Latency Reversing Agents

Lívia da Rocha Fernandes,[1*] Jean Leandro dos Santos[1]
1) Department of Drugs and Medicine, Faculty of Pharmaceutical Sciences, UNESP, 14800903
****e-mail: livia.fernandes@unesp.br***

Keywords: *HIV, Latency Reversal Agents, Molecular Docking.*

ABSTRACT

Latency-Reversing agents (LRAs) targeting the HIV reservoir, is an useful approach to achieve the functional cure[1]. Among the epigenetic strategies those involving the HDAC-3 inhibition seems to be promising as 'shock' therapy to activate latent viral genome in the CD4+ T cells reservoir[2]. So, this study aims to design and evaluate in silico new HDAC-3 inhibitors as potentials LRAs for HIV. This study was performed on Schrodinger Maestro molecular modeling environment. A series of BRD3308 was designed and the molecular docking study was carried out according to previous procedures[3] with HDAC-3. Among the series, based on the pose, interactions, and the docking score (DS) values we have selected 4 scaffolds to be explored, where the DS values were: **(1)** -9.208; **(2)** -8.369; **(3)** -8.363; and **(4)** -6.954 kcal/mol. Compound **(1)** have shown the best DS among and main interactions in agreement with BRD3308, and will be used for further optimization.

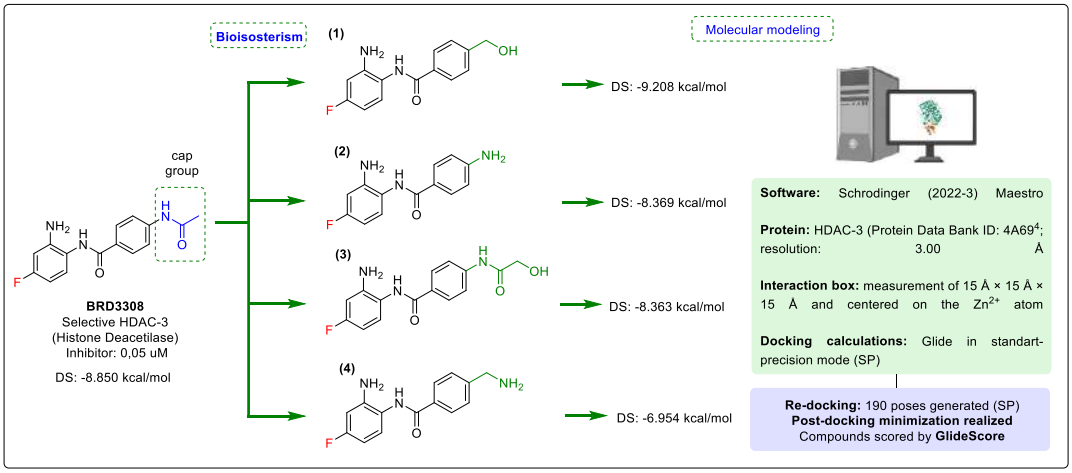


Figure 1. Structural planning of HDAC-3 inhibitors candidates as LRAs, their docking scores and molecular modeling development.

ACKNOWLEDGEMENTS

CAPES - Coordination for the Improvement of Higher Education Personnel
LAPDESF - Drug Research and Development Laboratory

REFERENCES

(1) Cillo, A. R.; Mellors, J. W. Which Therapeutic Strategy Will Achieve a Cure for HIV-1? *Curr. Opin. Virol.* **2016**, *18*, 14–19. https://doi.org/10.1016/j.coviro.2016.02.001.

(2) Keedy, K. S.; Archin, N. M.; Gates, A. T.; Espeseth, A.; Hazuda, D. J.; Margolis, D. M. A Limited Group of Class I Histone Deacetylases Acts To Repress Human Immunodeficiency Virus Type 1 Expression. *J. Virol.* **2009**, *83* (10), 4749–4756. https://doi.org/10.1128/JVI.02585-08.

(3) Urias, B. S.; Pavan, A. R.; Albuquerque, G. R.; Prokopczyk, I. M.; Alves, T. M. F.; de Melo, T. R. F.; Sartori, G. R.; da Silva, J. H. M.; Chin, C. M.; Santos, J. L. Dos. Optimization of Resveratrol Used as a Scaffold to Design Histone Deacetylase (HDAC-1 and HDAC-2) Inhibitors. *Pharmaceuticals* **2022**, *15* (10), 1260. https://doi.org/10.3390/ph15101260.

(4) Watson, P. J.; Fairall, L.; Santos, G. M.; Schwabe, J. W. R. Structure of HDAC3 Bound to Co-Repressor and Inositol Tetraphosphate. *Nature* **2012**, *481* (7381), 335–340. https://doi.org/10.1038/nature10728. PDB DOI: https://doi.org/10.2210/pdb4a69/pdb.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Anti-inflammatory activity of microbial naphthoquinone and its novel derivatives.

Vitor Tassara Moraes,[1*] Franco Jazon Caires,[1] Pedro V. da Silva-Neto,[2] Carlos Arterio Sorgi,[2,3] Luiz Alberto Beraldo de Moraes,[3] Giuliano Cesar Clososki[1*]

1) Núcleo Pesquisas em Produtos Naturais e Sintéticos, Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo-USP, Ribeirão Preto, 14040-903, SP, Brazil.

2) Departamento de Química, Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto-FFCLRP, Universidade de São Paulo-USP, Ribeirão Preto 14040-901, SP, Brazil.

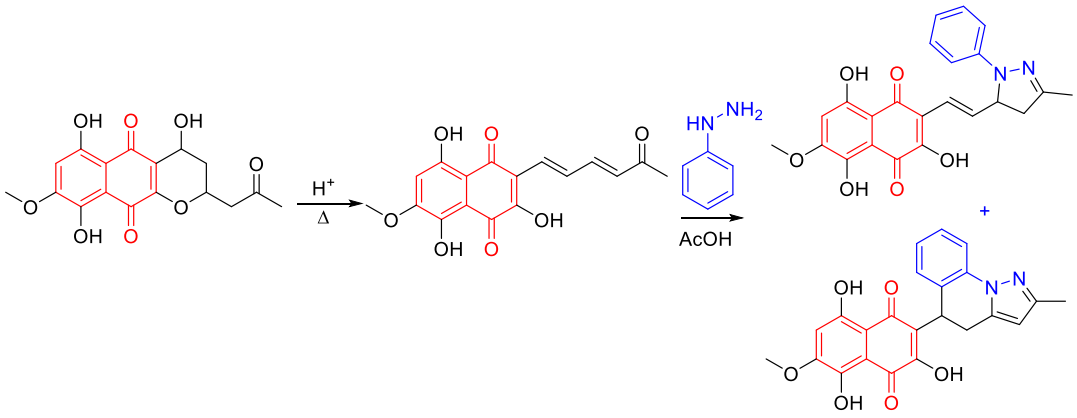
3) Departamento de Bioquímica e Imunologia, Faculdade de Medicina de Ribeirão Preto-FMRP, Universidade de São Paulo-USP, Ribeirão Preto 14040-900, SP, Brazil.

****e-mail: vtmx00@usp.br; gclososki@usp.br***

Keywords: *Natural product, Heterocycles, anti-inflammatory*

ABSTRACT

Inflammation is a complex set of interactions between soluble factors and cells, mediated by a variety of mechanisms.[1] When out of control, the inflammatory process can harm the organism, bringing the necessity of using drugs to inhibit or control the process. Many natural products possess anti-inflammatory activity as a valuable characteristic, naphthoquinones included.[2] In this context, they can be used as a starting point to develop new anti-inflammatory drugs. This work aimed at structural modifications in a microbial naphthoquinone (3,5,8-TMON) in order to generate a potential drug candidate with anti-inflammatory activity. 3,5,8-TMON was obtained from the fermentation of the fungus *Cordyceps* sp.[3] and reactions with phenyl hydrazine were carried out in acetic acid under different conditions. Cytotoxic activity was evaluated using RAW 264.7 and THP-1 monocytic macrophages and pro-inflammatory cytokine production was evaluated by ELISA. We could obtain a pure naphthoquinone and novel products with interesting anti-inflammatory activity.



Scheme 1. Obtaining the naphthoquinone and further modification.

ACKNOWLEDGEMENTS

Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, PIBIC No 119964/2021-0)
Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, No. 2022/05327-7 e 2022/16916-3)
Coordenação de aperfeiçoamento de Pessoal de Nível Superior (CAPES)

REFERENCES

1. Medzhitov, R. *Nature* **2008**, 454, 428–435.
2. Aminin, D.; Polonika, S. *Chem. Pharm. Bull.* **2020**, 68, 46-57
3. Unagul, P.; Wongsa, P.; Kittakoop, P.; Intamas, S.; Srikitikulchai, P.; Tanticharoen, M. *J Ind Microbiol Biotechnol* **2005**, 32, 135-140.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Design and synthesis of new indolizines with potential antiproliferative activity.

Victor Hugo Catricala Fernandes,[1*] Maitê Bueno Giometti,[1] and Giuliano Cesar Clososki[1]

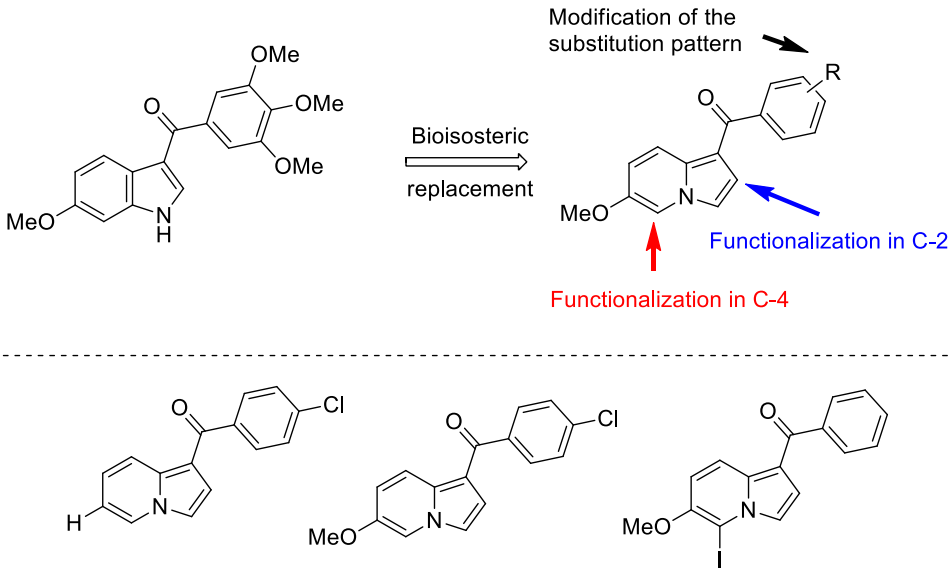
1) Department of Biomolecular Sciences, Faculty of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo.

****e-mail: catricala@usp.br***

Keywords: *Indolizine, C-H Functionalization, Antiproliferative activity.*

ABSTRACT

Indolizines, characterized by the fusion of a pyridine ring and a pyrrole ring, possess chemical properties derived from both rings [1]. This unique molecular structure has led to their widespread utility in material chemistry, photochemical processes, and medicinal chemistry. Indolizines have exhibited notable pharmacological activities, including anti-proliferative, anti-inflammatory, anti-tuberculosis, and larvicidal effects [2]. While substituted indolizines have demonstrated significant antiproliferative potential, resulting from the bioisosteric replacement of a lead compound, there remains a scarcity of studies focusing on the impact of their substituents [3]. To contribute to the field and unravel structure-activity relationships, our study aimed to synthesize two promising indolizines suitable for C-H functionalization, including 1-substituted and 1,5-disubstituted derivatives. Notably, we explored alternative organometallic bases such as magnesium and zinc, which exhibit considerable potential as substitutes for lithium bases based on the preliminary results obtained thus far. By developing synthetic methodologies to access new analogs, we have gained valuable insights into their functional properties and their potential for therapeutic applications.



Scheme 1. Strategy for achieving new candidates with potential anti-proliferative activity

ACKNOWLEDGEMENTS

FAPESP (2022/06051-5 and 2022/05327-7), CAPES and CNPq.

REFERENCES

[1] KATRITZKY, A. R.; RAMSDEN, C. A.; JOULE, J. A.;Zhdankin, V. V. Handbook of Heterocyclic Chemistry, 3ª Ed.; Oxford Elsevier, **2010.**

[2] SINGH, G. S.; MMATLI, E. E.. *Eur. J. Med. Chem.*, **2011,** 46 (11), p. 5237–5257.

[3] TUNG, Y. S. et al. *Journal of Medicinal Chemistry*, **2011,** v. 54, n. 8, p. 3076–3080.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Design of quinazolinone-based compounds as new *Hs*DHODH inhibitors with antiviral potential against SARS-CoV-2

Jéssica D. Bueno[1,2] Bruna F. Godoi[1,2] Thiago dos Santos[1,3] Aline D. Purificação[2,3] Maria C. Nonato[2,3] Flávio da S. Emery[1,3]

1) Laboratory of Heterocyclic and Medicinal Chemistry (QHETEM), School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo (FCFRP/ USP), Brazil

2) Laboratory of Protein Crystallography (LCP/RP), *School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo (FCFRP/ USP), Brazil*

3) Center for the Research and Advancement of Fragments and Molecular Targets (CRAFT), FCFRP/USP, Brazil

Keywords: *Quinazolinones, SARS-CoV-2, HsDHODH*

ABSTRACT

The pandemic of COVID-19 in 2020 was caused by the virus SARS-CoV-2.Considering that the virus is an obligate intracellular parasite, the human dihydroototate desydrogenase enzyme (*Hs*DHODH) emerges as a target because it is essential in the biosynthesis of pyrimidine nucleotides.[1,2] According to previous studies in which the quinazolinone heterocyclic scaffold takes important interactions of hydrogen bonds with the enzyme HsDHODH (QHM989 IC_{50} = 29uM and QHM990 IC_{50} = 50uM), thus, 2-amino-substituted quinazolinones were synthesized with different spacer groups in order to evaluate their importance to the activity, as in the Figure 1.

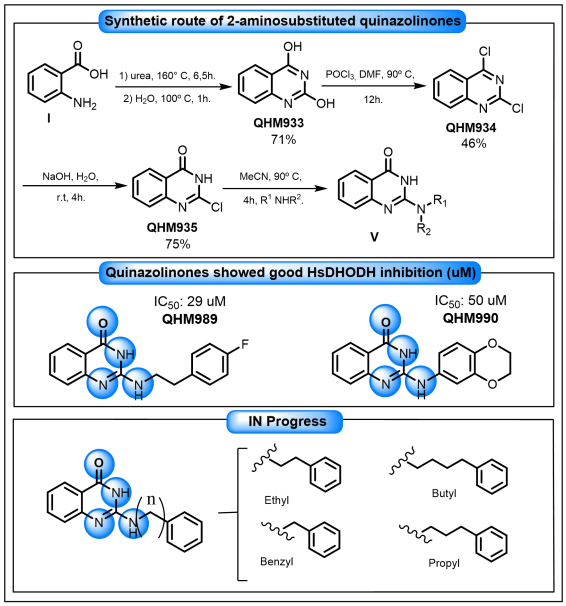


Figure 1. 2-aminosubstituted quinazolinones synthesis

ACKNOWLEDGEMENTS

This work was supported by CNPq and CAPES.

REFERENCES

1. Zuo Z, Liu X, Qian X, et al. Erratum: Bifunctional Naphtho[2,3- d][1,2,3]triazole-4,9-dione Compounds Exhibit Antitumor Effects in Vitro and in Vivo by Inhibiting Dihydroorotate Dehydrogenase and Inducing Reactive Oxygen Species Production (7633−7652) *J Med Chem*. 2020;63(18).

2. Jiang N, Zhai X, Zhao Y, et al. Synthesis and biological evaluation of novel 2-(2-arylmethylene)hydrazinyl- 4-aminoquinazoline derivatives as potent antitumor agents. *Eur J Med Chem*. 2012;54:534-541.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Synthesis and biological evaluation of new uracil derivatives inhibitors of dihydroorotate dehydrogenase from *Leishmania braziliensis* (*Lb*DHODH)

Pedro Ivo Palacio LEITE[1,3], Dr. Thiago dos SANTOS[1, 3], Dra. Thamires Quadros FROES,[2,3] Dr. Daniel Gedder SILVA[1,2], Profa. Dra. Maria Cristina NONATO[2,3], Prof. Dr. Flavio da Silva EMERY[1,3].

[1] QHetem - Research group in Heterocyclic and Medicinal Chemistry, Department of Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences (FCFRP), University of São Paulo (USP-RP), Brazil.
[2]Laboratory of Protein Crystallography, Department of Biomolecular Sciences, Faculty of Pharmaceutical Sciences (FCFRP), University of São Paulo (USP-RP), Brazil.
[3]Center for the Research and Advancement of Fragments and Molecular Targets (CRAFT), USP-RP, Brazil.
***e-mail: palaciopip@usp.br**

Keywords: Leishmania brazilienses, Dihydroorotate dehydrogenase, Uracil.

INTRODUCTION

Synthetic nucleosides are a class of compounds that are capable of mimicking natural nucleosides in a variety of metabolic pathways and, therefore, constitute models attractive for studies of interactions with molecular targets.[1] Dihydroorotate dehydrogenase from *Leishmania braziliensis* (*Lb*DHODH) is a member of Class 1A DHODHs, enzymes which use fumarate to oxidize dihydro flavin mononucleotide (FMNH2).[2] The potential of *Lb*DHODH as a drug target against mucocutaneous leishmaniasis has been validated,[3] Thus, this work aims to develop selective unprecedented inhibitors of *Lb*DHODH via a FBDD (fragment-based drug design) strategy comprising varied Uracil-based fragments which are obtained by selected functionalization protocols.

RESULTS/DISCUSSIONS/CONCLUSION

Figure 1: Synthesized library of uracil-containing compounds as potential LbDHODH..

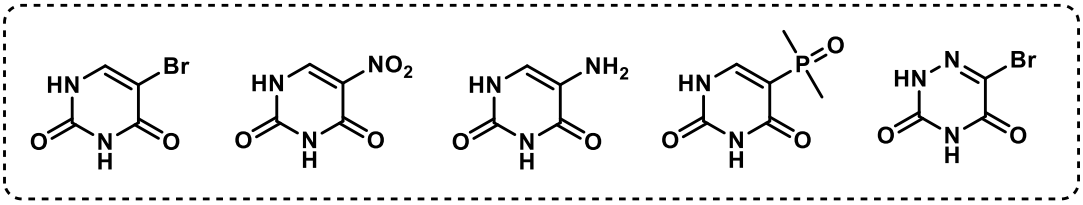
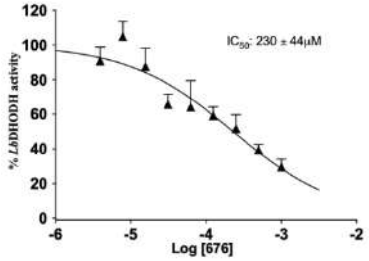


Figure 2: dose-response curve obtained for QHM-676.



Among the five molecules tested, one displayed promising inhibitory activity towards LbDHODH. Figure 2 presents the dose-response curve most potent molecule, with QHM-676 considered a powerful fragment. Such data will be extremely important for identifying a HIT and optimizing its properties while growing the identified fragment-based.

ACKNOWLEDGEMENTS

CAPES (88887.596040/2020-00), CNPq and CRAFT.

REFERENCES

[1] McDonald, C. A.; Palfey, B. A. Substrate binding and reactivity are not linked: grafting a proton-transfer network into a class 1A dihydroorotate dehydrogenase. Biochemistry, 2011,50(14), 2714-2716.
[2]. Carter, N. S., Yates, P., Arendt, C. S., Boitz, J. M., & Ullman, B. Purine and pyrimidine metabolism in Leishmania. Drug targets in kinetoplastid parasites, 2008, 141-154.
[3]. Boncel, S., Gondela, A., Mączka, M., Tuszkiewicz-Kuźnik, M., Grec, P., Hefczyc, B., & Walczak, K. Novel 5-(N-alkylaminouracil) acyclic nucleosides. *Synthesis*, *2011*(04), 603-610.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Multitarget strategy as tool in the development of new compounds against triple negative breast cancer: Entinostat-based carbamate derivatives to seek dual inhibition

Lucas Melero Gavilha,[1*] Raul Marques Novais,[1] Thiago dos Santos,[1] Flavio da Silva Emery,[1*]
Department of Pharmaceutical Sciences, School of Pharmaceutical Sciences of Ribeirão Preto – FCFRP-USP, São Paulo, Brazil

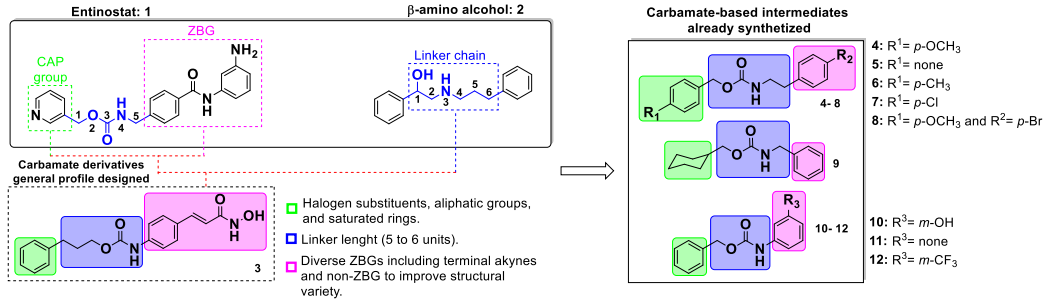
****e-mail: flavioemery@usp.br***

Keywords: *carbamate derivatives, TNBC, multitarget strategy.*

ABSTRACT

Triple-negative breast cancer (TNBC) is characterized by the lack of progesterone and estrogen receptors, and the amplification absence of the HER2 gene. It is the most lethal subtype with the worst prognosis among the other breast cancer types and has no targeted therapy.[1] The minor groove DNA and histone deacetylases enzymes (HDACs) are promising targets against TNBC, based on the anti-cancer activity of minor groove binders (MGBs) and HDACs inhibitors.[2,3] Therefore, through a multitarget strategy,[4] this work focused on the design and synthesis of bioinspired carbamate derivatives on Entinostat, an HDACs inhibitor while preserving structural aspects from *β*-amino alcohols, which were previously investigated as MGBs.[2] Thus, the design and synthesis of the compounds consisted of the combination of a five to six-unit-linked chain with an aromatic ring containing a zinc-binding group (ZBG) as highlighted in **Figure 1**. For the aromatic ring from our carbamate derivatives, different substitution patterns will be explored including electron-donating and withdrawing groups, as well as its replacements by aliphatic chains. Modifications for the linker chain will be also studied in order to obtain greater complementarity with the desired biological targets through a structure-activity relationship approach. We hope to contribute to the discovery of novel anti-cancer drugs scenario regarding TNBC.

Figure 1. The design and general profile of carbamate derivatives and already synthetized compounds.



ACKNOWLEDGEMENTS

FAPESP, CAPES and CRAFT for research support and grants awarded.

REFERENCES

[1] Li, X, et al. Triple-negative breast cancer has worse overall survival and cause-specific survival than non-triple-negative breast cancer. Breast cancer res. treat., **2017,** V.161(2), p.279–287,
[2] Vaidergorn, et al. β-amino alcohols and their respective 2-phenyl-N-alkyl aziridines as potential DNA minor groove binders. Eur. J. Med. Chem., **2018**, V.157, p.657-664.
[3] Zhang, L, et al. Zinc binding groups for histone deacetylase inhibitors. J Enzyme Inhib Med Chem, **2018**, Vol. 33, p. 714–721.
[4] Bass, A. K. A, et al. Comprehensive review for anticancer hybridized multitargeting HDAC inhibitors. Eur. J. Med. Chem., **2021,** V.209.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Novel Arylated Flavones Related to Natural Products as Promising Anti-Chikungunya Agents

Edgar Schaeffer,[1] Luana G. de Souza,[1]* Stephany da S. Costa,[2,3] Larissa E. C. Constant,[3] Nathasha C. de Oliveira,[1] Diego Allonso,[2] and Alcides J. M. da Silva[1]*

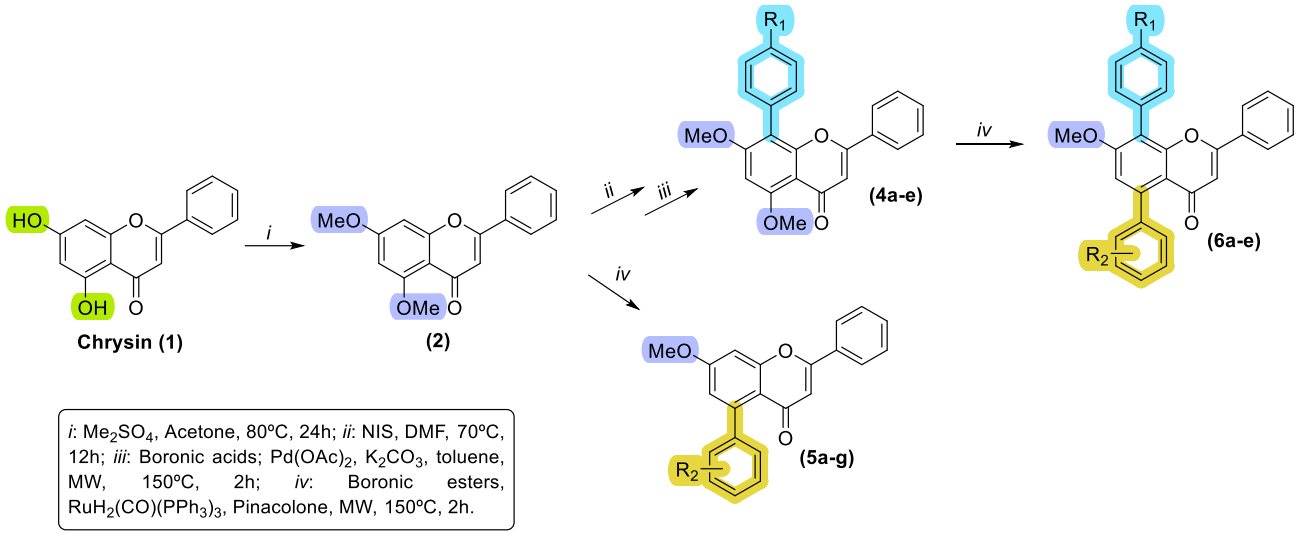
1) Laboratório de Catálise Orgânica (LCO), IPPN/UFRJ; 2) Laboratório de Biotecnologia e Doenças Infecciosas, FF/UFRJ; 3) Laboratório de Biotecnologia e Bioengenharia Estrutural, IBCCF/UFRJ

e-mail: luanagoncalvessouza10@gmail.com; alcides@ippn.ufrj.br

Keywords: *Flavonoids, Flavones, Synthesis, ADMET, Molecular docking*

ABSTRACT

Chikungunya fever is a tropical disease transmitted by the mosquito of Aedes sp infected by the chikungunya virus (CHIKV).[1-3] In this work, a series of aryl-chrysin derivatives were made. The flavones were synthesized from chrysin by a semi-synthetic route. The new 5-aryl-flavones, 8-aryl-flavones or 5,8-bisaryl-flavones were obtained with good yields (up to 99%) by palladium[5] and ruthenium[6] catalysis (Scheme 1). These arylated flavones were directed for an *in silico* analysis of molecular docking assay in target enzyme, the non-structural protein 2 (nsP2).[4] In addition, a prediction of the drug-likeness, the physicochemical properties, and the pharmacokinetic profile of all compounds were made, and the results were satisfactory. The compounds are being tested against Chikungunya virus against mammalian cells line, evaluating the anti-viral and the cytotoxic activity. In general, all substances were not toxic for human cells.



Scheme 1. Synthesis of the methoxy-chrysin derivatives

ACKNOWLEDGEMENTS

Financial support from CAPES (grant 8888.506711/2020-01), FAPERJ (grant E-26/210.152/2019). L.G.S. acknowledges the scholarship from CAPES (grants 88887.717857/2022-00).

REFERENCES

[1] Martins, D.O.S.; Santos, I.A.; Oliveira, D.M.; Grosche, V.R.; Jardim, A.C.G. *Viruses* **2020**, 12, 272
[2] Varikkodan, M.M.; Chen, C.-C.; Wu, T.-Y. *Int. J. Mol. Sci.* **2021**, 22, 7891
[3] Kaur, P.; Chu, J.J.H. *Drug Disc. Today* **2013**, 18, 969-983
[4] Narwal, M.; Singh, H.; Pratap, S.; Malik, A.; Kuhn, R.J.; Kumar, P.; Tomar, S. *Int. J. Biol. Macromol.* **2018**, 116, 451-462
[5] Basílio, N.; Lima, J.C.; Cruz, L.; Freitas, V.; Pina, F.; Ando, H.; Kimura, Y.; Oyama, K-I.; Yoshida, K. *Eur. J. Org. Chem.* **2017**, 5617-5626
[6] Frota, L.C.R.M.; Schneider, C.; Amorim, M.B.; Silva, A.J.M.; Snieckus, V. *Synlett* **2017**, 28, 2587-2593.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Synthesis, Antileishmanial Activity and *in silico* studies in the cytosolic tryparedoxin peroxidase (cTXNPx) target of New Sulfonamide-chalcones

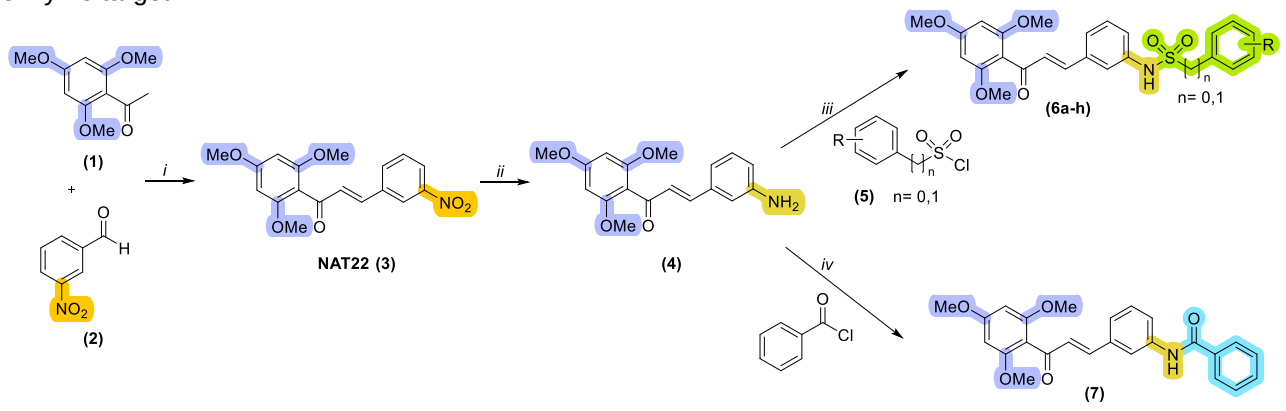
Nathalia S. de Oliveira,[1*] Luana G. de Souza,[1] Edgar Schaeffer,[1] Arielly R. R. Barreto,[2] Felipe Carvalho-Gondim,[2] Vitor M. de Almeida,[3] Osvaldo A. Santos-Filho,[3] Bartira Rossi-Bergmann,[2] Alcides J. M. da Silva[1,*]

1) Laboratório de Catálise Orgânica (LCO), IPPN/UFRJ;
2) Instituto de Biofísica Carlos Chagas Filho IBCCF/UFRJ;
3) Laboratório de Modelagem Molecular e Biologia Estrutural Computacional, IPPN/UFRJ.
****e-mail: nathalia.oliveira@ufrj.br; alcides@ippn.ufrj.br***

Keywords: *Sulfonamide-chalcones, Synthesis, Leishmaniasis, Molecular docking, Molecular dynamics.*

ABSTRACT

Leishmaniasis is an emerging tropical infectious disease caused by a protozoan parasite of the genus *Leishmania*.[1] In this work, the molecular hybridization between a trimethoxy chalcone and a sulfonamide group was used to generate a series of sulfonamide-chalcones.[2,3] The chalcones were synthesized from 2',4',6'-trimethoxyacetophenone (**1**) and 3-nitro-benzaldehyde (**2**) through the Claisen-Schmidt condensation, followed by the chemoselective reduction of the NO_2 group and sulfonylation of the formed amine to make 8 new sulfonamide-chalcone hybrids with good yields (up to 95%). These sulfonamides-chalcones (**6a-h**) and *N*-benzoyl-chalcone (**7**) were tested against promastigotes of *L. amazonensis* and cytotoxicity against mouse macrophages. All chalcones presented good antileishmanial activity, with IC_{50} between 1.72 and 3.19 µM. Three of them that were also highly active against intracellular amastigotes (IC_{50} between 0.40 and 1.29 µM), and had good selectivity indexes (SI > 9) were selected for *in silico* analysis of molecular docking and molecular dynamics in the cytosolic tryparedoxin peroxidase (cTXNPx) parasite enzyme target.[3]



Scheme 1. Synthesis of the sulfonamide-chalcones derivatives (**6a-h)**, the synthetic intermediate amino-chalcone (**4**), and the *N*-benzoyl-chalcone (**7**).

ACKNOWLEDGEMENTS

Financial support from, CAPES (grant 8888.506711/2020-01), FAPERJ (E-26/210.152/2019). N.S.O. acknowledges the scholarship from CAPES (grant 88887.753015/2022-00). L.G.S. acknowledges the scholarship from CAPES (grants 88887.717857/2022-00).

REFERENCES

[1]. Santos, D. O. et al. *Parasitol. Res.* **2008**, *103,* 1-10.
[2]. Andrighetti-Fröhner, C. R. et al. *Europ. J. Med. Chem.* **2009**, *44*, 755-763.
[3]. Escrivani D. O. et al. *PLoS Negl Trop Dis*. **2021**, 15(11): e0009951.

7th Brazil-Spain Workshop on Organic Chemistry
BSWOC 2023
Ribeirão Preto - SP, Brazil
July 10-12, 2023

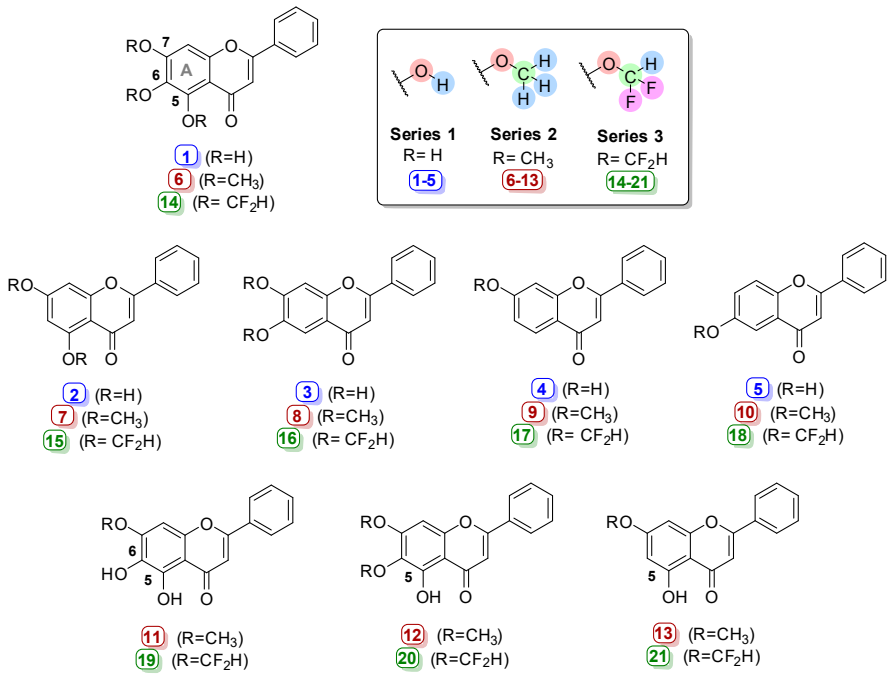
Synthesis of Baicalein Derivatives with Potential anti-SARS-CoV-2 Activity

Guilherme S. Caleffi,[1*] João L. S. Avelar,[1] Luana G. de Souza,[1] and Paulo R. R. Costa[1*]
[1]Laboratório de Química Bioorgânica (LQB), IPPN-UFRJ
**e-mail: guilherme.caleffi@gmail.com; prrcosta2011@gmail.com*

Keywords: *Antiviral, Flavonoids, Synthesis, ADMET, Molecular Docking.*

ABSTRACT

Baicalein was identified as a potent inhibitor of SARS-CoV-2 replication in infected Calu-3 cells[1] (EC_{50}= 1.2 μM) *via* non-covalent inhibition of its main protease (M^{pro}).[2] Starting from baicalein, we design three series of derivatives varying the number and position of the hydroxyl groups, as well as their derivatization by methyl and difluoromethyl groups, to establish a relationship between the substituents in the A ring and the efficacy against viral replication. The BOILED-Egg prediction model indicated that all designed compounds will probably present blood−brain barrier permeability and high human intestinal absorption. Twenty compounds were obtained (40-93% yield). Currently, the SARS-CoV-2 activity of these compounds in infected Calu-3 cells, as well as their inhibition of the SARS-CoV-2 M^{pro} enzyme, is being evaluated.



ACKNOWLEDGEMENTS

P.R.R.C thank the financial support from CAPES (98888.506711/2020-01) and FAPERJ (PRONEX - E-26/010.001.240/2016, CNE - E-26/201.179/2021). G.S.C. acknowledges the scholarship from FAPERJ (grant PDR10 - E-26/206.050/2022). L.G.S. acknowledges the scholarship from CAPES (grant 88887.717857/2022-00).

REFERENCES

[1] Zandi, K.; Musall, K.; Oo, A.; Cao, D.; Liang, B.; Hassandarvish, P.; Lan, S.; Slack, R. L.; Kirby, K. A.; Bassit, L.; Amblard, F.; Kim, B.; AbuBakar, S.; Sarafianos, S. G.; Schinazi, R. F. *Microorganisms* **2021**, *9*, 893 [2] Su, H.x.; Yao, S.; Zhao, W.f.; Li, M.j.; Liu, J.; Shang, W.j.; Xie, H.; Ke, C.g.; Hu, H.c.; Gao, M.n.; Yu, K.g.; Liu, H.; Shen, J.s.; Tang, W.; Zhang, L.k.; Xiao, G.f.; Ni, L.; Wang, D.w.; Zuo, J.p.; J. H.l.; Bai, F.; Wu, Y.; Ye, Y.; Xu, Y.c., *Acta Pharmacol. Sin.* **2020**, *41*, 1167.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Synthesis and biological evaluation of covalent inhibitors for dihydroorotate dehydrogenase of *Leishmania braziliensis* (*Lb*DHODH)

Jonathas dos Santos PAZINI[1], MSc. Pedro Ivo Palacio LEITE[1,3], Dr. Daniel Gedder SILVA[1,3], Dr. Thiago dos SANTOS[1, 3], Dr. Thamires Quadros FROES[2,3], Profa. Dra. Maria Cristina NONATO[2,3], Prof. Dr. Flavio da Silva EMERY[1,3].

[1] QHetem - Research group in Heterocyclic and Medicinal Chemistry, Department of Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences (FCFRP), University of São Paulo (USP-RP), Brazil.
[2]Laboratory of Protein Crystallography, Department of Biomolecular Sciences, Faculty of Pharmaceutical Sciences (FCFRP), University of São Paulo (USP-RP), Brazil.
[3]Center for the Research and Advancement of Fragments and Molecular Targets (CRAFT), USP-RP, Brazil.
e-mail: jonathaspazini@usp.br

Keywords: Leishmania brazilienses, Dihydroorotate dehydrogenase, indazole, covalent inhibitor.

INTRODUCTION

Leishmaniasis has a high annual incidence, about 12 million people are infected, and worldwide, 350 million people are at risk.[1] The development of new drugs is a need that has been widely discussed in the literature.[2] In this sense, understanding the mechanisms related to the virulence and pathogenesis of *Leishmania* sp. has become a great value in the search for novel antileishmanial agents. Dihydroorotate dehydrogenase of Leishmania braziliensis (LbDHODH) is a member of Class 1A DHODHs enzymes.[3] and, recently, our research group discovered 1-*H*-indazole as a promising hit in a fragment screening campaign against *Lb*DHODH. Thus, this work aims to develop covalent inhibitors for *Lb*DHODH.[4]

RESULTS/ DISCUSSIONS/CONCLUSION

Figure 1: Obtaining a library of covalent inhibitors derived from indazole.

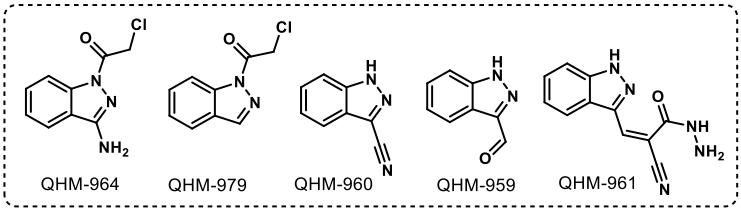
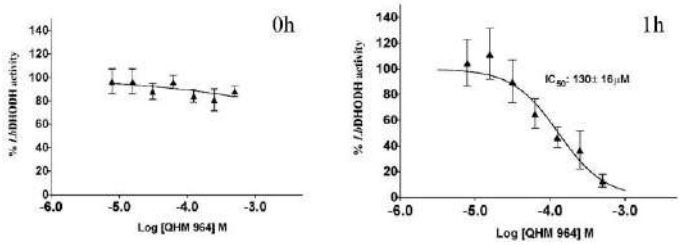


Figure 2: The obtained dose-response curves for QHM-964.



The molecules were purified by silica gel column chromatography and characterized by nuclear magnetic resonance (^{13}C and ^{1}H NMR) and high-resolution mass spectrometry. The isolated yields were satisfactory. The compounds were assayed against LbDHODH. Initially, a punctual assay was carried out at a concentration of 250 µM to verify molecules capable of inhibiting at least 50% of the enzymatic activity. These molecules showed good solubility. Our perspective is to optimize its properties while growing.

ACKNOWLEDGEMENTS

CAPES (88887.596040/2020-00), CNPq and CRAFT.

REFERENCES

[1] WORLD HEALTH ORGANIZATION. Leishmaniasis, **2009**. Available at: http://www.who.int/mediacentre/factsheets/fs375/en/. Accessed: June 8, 2023.

[2] Dumonteil, Eric. "Vaccine development against Trypanosoma cruzi and Leishmania species in the post-genomic era." Infection, Genetics and Evolution 9.6 (**2009**): 1075-1082.

[3] McDonald, Claudia A., and Bruce A. Palfey. "Substrate binding and reactivity are not linked: grafting a proton-transfer network into a class 1A dihydroorotate dehydrogenase." Biochemistry 50.14 (**2011**): 2714-2716.

[4] Aljoundi, A., Bjij, I., El Rashedy, A., & Soliman, M. E. *Covalent versus non-covalent enzyme inhibition: which route should we take? A Justification of the good and bad from molecular modelling perspective* **2020**. *The Protein Journal*, *39*, 97-105.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Synthesis of heterocyclic compounds as potential anti-Infectives agents

Daniel Gedder Silva[1*], Flavio da Silva Emery[1]

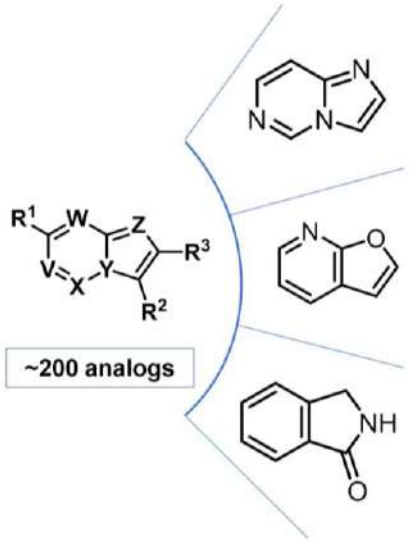
[1] *School of Pharmaceutical Sciences of Ribeirão Preto - University of São Paulo, Ribeirão Preto, São Paulo, Brazil - 14040-903*

e-mail: danielgedder@usp.br

Keywords: Anti-infectives, heterocyclic, medicinal chemistry

ABSTRACT

A large number of new heterocyclic compounds having different ring systems were synthesized using relatively simple synthetic pathways (low cost, few steps and good yields), such as condensation, Mannich and C−H activation reactions. Following, the fused rings were decorated with many functional groups, giving rise to a structurally diverse set of analogs (Scheme 1). New imidazopyridine/pyrimidine, furopyridine, and isoindole synthesized compounds that arose from medicinal chemistry optimization were evaluated in an integrated *in vitro* screen. By exploring the chemical diversity of three different heteroaromatic cores and introducing various groups at eight different positions of the general scaffold within this study, we were able to enlarge the chemical space of heterocycles as potential antitrypanosomal agents. The best replacements identified in this SAR studies, will guide the design and selection of the novel compounds that can be transitioned further into drug development for these parasitic infections.[1]



Scheme 1. Set of fused rings synthesized and assayed against *T. cruzi*, *T. brucei* and mammalian cells.

ACKNOWLEDGEMENTS

We are grateful to Fundacão de Amparo à Pesquisa do Estado de São Paulo (FAPESP) for funding (grant number: #2017/22001-0).

REFERENCES

[1] D. G. Silva, *ChemMedChem* **2020**, 16(6): 966–975

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Sustainable method for extracting fenolic compounds from almond hull

Gabriela Cremasco[1*], Adam Sutton[2], Cristiano S. Funari[3], Dario Arrua[2], Emily F. Hilder, Kelly Johana Dussán Medina, Vanderlan S. Bolzani and Daniel Rinaldo[1,4*].

1) Institute of Chemistry University (UNESP - Araraquara);
2) University of South Australia (UniSA);
3) School of Agricultural Sciences (UNESP - Botucatu);
4) School of Sciences (UNESP - Bauru).
e-mail: gabriela.cremasco@unesp.br; daniel.rinaldo@unesp.br

Keywords: *Prunus Dulcis, NADES, Green Chemistry*

ABSTRACT

Based on the UN goals for the 2030 Agenda, the reduction of toxic waste has led researchers to study environmental preservation techniques, such as agricultural residues from *Prunus dulcis* (almonds) because they contain compounds of economic and practical interest. Thus, Deep Eutectic Natural Solvents (NADES) were used as extractor solvent and submitted to the miniaturized microwave-assisted extraction (MAE) technique. Then analyzed by HPLC-DAD. Extraction was optimized using a central composite design (CCD). Using the Analitycal AGREEness (AGREE) metric [5], it was possible to quantify the environmental impact of the developed method and compare it with methods reproduced in the literature.
The developed method resulted in an optimized, efficient and low environmental impact alternative for the extraction of high added value compounds present in the almond shell. NADES lactic acid:glycerol 1:1 (containing 20% water) can be a suitable substitute for frequently used reference solvents.

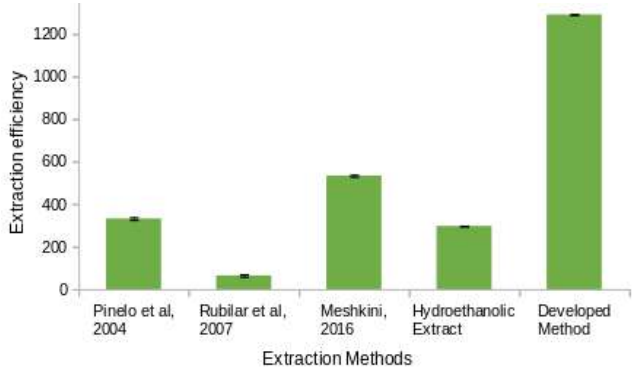


Figure 1: Comparison between extraction methods.

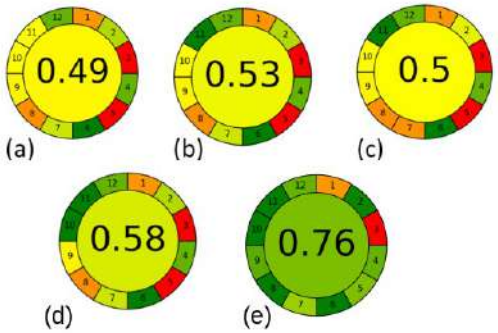


Figure 2: Pictograms AGREE metric (a)[3]; (b)[4]; (c)[5]; (d) hydroethanolic extract and (e) developed method.

ACKNOWLEDGEMENTS

National Council for Scientific and Technological Development (CNPq, Conselho Nacional de Desenvolvimento Científico e Tecnológico), National Institute of Science and Technhology (INCT BioNat – Brazil) [grant # 465637/2014-0]. and the State of São Paulo Research Foundation (FAPESP, Fundação de Amparo à Pesquisa do Estado de São Paulo (2014/50926-0 and 2020/15024-6)).

REFERENCES

[1] ONU. Organização das Nações Unidas. Disponível em: <https://www.un.org/en/>. Access: Mar 2022.
[2] Pena-Pereira, F.; et al. AGREE-Analytical GREEnness Metric Approach and Software. Analytical Chemistry,v. 92, n. 14, p. 10076-10082, 2020.
[3] Pinelo, M. et al. Extraction of antioxidant phenolics from almond hulls (Prunus amygdalus) and pine sawdust (Pinus pinaster). Food Chemistry, v. 85, n. 2, p. 267-273, 2004;
[4] Rubiular, M. et al.. Separation and HPLC-MS Identification of Phenolic Antioxidants from Agricultural Residues: almond hulls and grape pomace. Journal Of Agricultural And Food Chemistry, [s.l.], v. 55, n. 25, p. 10101-10109, dez. 2007.
[5] Meshkini, A. Acetone extract of almond hulls provides protection against oxidative damage and membrane protein degradation. Journal of acupuncture and meridian studies, v. 9, n. 3, p. 134- 142, 2016.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Development of a green chromatography method for the determination of compounds by industrial interest in orange residues

Mirella Thaisa Ferreira Ranzeti,[1*] Gabriela Cremasco,[2] Daniel Rinaldo[3]

Departamento de Química, FC, Universidade Estadual Paulista "Julio de Mesquita Filho", 17033-360

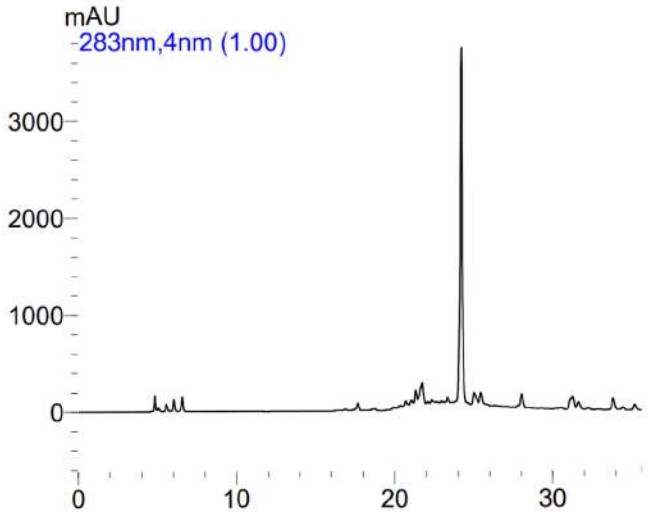
****e-mail: mirella.ferreira@unesp.br***

Keywords: *Citrus sinensis, Green solvents, Chromatography.*

ABSTRACT

Sweet oranges are widely sold in Brazil,[1] where 50% of production is transformed into waste. However, oranges are an extremely important fruit for human health, being rich in vitamin C, β-carotenoids, folic acid and flavonoids. In addition, the fruit has secondary metabolites that bring about its pharmacological effects.[2] For its industrial importance, a green chromatographic method was developed for the analysis. The Fractional Planning $2v^{5-1}$ and Doehlert method were used, where 5 variables were chosen for the analysis, with X1 being the initial % of EtOH, being favorable in 5%, X2 as the final % of EtOH , being favorable at 100%, X3 as temperature, being used at 40ºC, X4 as % of HAc, being favorable at 1,5% and, finally, X5 as flow rate, being used at 0.5 mL/min. Through these factors, it was possible to discard toxic solvents, saving analysis time and energy, as shown in Figure 1.

Figure 1: chromatogram of the developed method.



ACKNOWLEDGEMENTS

The authors gratefully acknowledge financial support from the National Council for Scientific and Technological Development (CNPq, Conselho Nacional de Desenvolvimento Científico e Tecnológico), National Institute of Science and Technology - INCT BioNat, grant # 465637/2014-0, and the State of Sao Paulo Research Foundation (FAPESP, Fundação de Amparo à Pesquisa do Estado de São Paulo), grant # 2014/50926-0, Brazil.

REFERENCES

[1] EMBRAPA, Empresa Brasileira de Pesquisa e Agropecuária. Coleção - 500 perguntas - 500 respostas - CITRUS**.** Embrapa Informação Tecnológica. Brasília - DF, **2005**.

[2] CHIARADIA, M. C. Desenvolvimento, validação e aplicação de métodos para análise multirresidual de agrotóxicos em suco de laranja e tangerina utilizando CLAE-DAD, CL-EM-EM e CLUE-DAD**.** Tese de Doutorado em Ciências apresentado no Instituto de Química da Universidade Estadual de Campinas, Campinas- SP. 23 abr **2009**.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Optimization of the mixture of hydroalcoholic leaves extracts of Cobrina (*Tabernaemontana catharinensis* A.DC), Pau-Brasil (*Paubrasilia echinata* Lam) and Tipuana (*Tipuana Tipu* Benth)

Yasmin Stelle[1*], Thiago Mendanha Cruz[1], Jânio Sousa Santos[2], Daniel Granato[3], Mariza Boscacci Marques[1]

1) Department of Chemistry, State University of Ponta Grossa, 84030-900
2) Department of Pharmacy, Faculdade Integrada Carajás, 68552-735
3) Department of Biological Sciences, Faculty of Science and Engineering, University of Limerick, V94 T9PX
****e-mail: yasminstelle@hotmail.com***

Keywords: *optimization, hydroalcoholic, extracts*

ABSTRACT

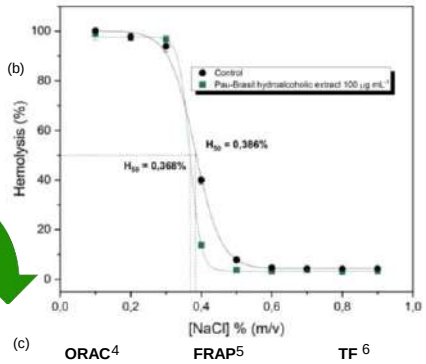
Cobrina, Pau-Brasil and Tipuana are trees native to South America, present in Brazil. Cobrina and Tipuana have more reports in the literature of biological activities than Pau-Brasil, but even so, they are few. In this study, the objective was to optimize the composition of the hydroalcoholic leaves extract, using a simplex-centroid experimental design, obtaining 10 extracts. Through the desirability function, optimizing four parameters simultaneously (total phenolic compounds, DPPH radical inhibition and H_{50} (50% hemolysis) against O+ and O- type erythrocytes in hypotonic conditions), it was obtained that the optimal composition has 100% Pau-Brasil. The optimized extract showed antioxidant activity by the methods of Oxygen Radical Absorbance and ability to reduce Iron III, in addiction to protective action on the erythrocyte membrane of both blood types as can be observed in figure 1.

(a)

MIXTURE	Cob (%)	PB (%)	Tipu (%)	TFC[1] (mgGAE/g)	DPPH[2] (mgAAE/g)	H_{50} O+ (%)*[3]	H_{50} O- (%)*[3]
H1	100,00	0,00	0,00	75,145 ± 1^{g}	41,903 ± 3^{ef}	0,390 ± <0,1^{a}	0,529 ± <0,1^{a}
H2	0,00	100,00	0,00	221,308 ± 5^{a}	540,505 ± 28^{a}	0,368 ± <0,1^{bc}	0,455 ± <0,1^{b}
H3	0,00	0,00	100,00	129,484 ± 1^{cd}	68,468 ± 5^{ef}	0,364 ± <0,1^{cd}	0,467 ± <0,1^{b}
H4	50,00	50,00	0,00	121,182 ± 2de	114,877 ± 1^{cd}	0,360 ± <0,1^{cd}	0,476 ± <0,1^{ab}
H5	0,00	50,00	50,00	144,579 ± 8^{bc}	94,841 ± 9de	0,343 ± <0,1^{d}	0,441 ± <0,1^{b}
H6	50,00	0,00	50,00	83,195 ± 1^{fg}	46,906 ± 2^{f}	0,353 ± <0,1^{c}	0,449 ± <0,1^{b}
H7	33,33	33,33	33,34	113,635 ± 2^{e}	97,908 ± 2^{cd}	0,376 ± <0,1^{ab}	0,432 ± <0,1^{b}
H8	66,66	16,67	16,67	91,748 ± 1^{f}	68,093 ± 3^{e}	0,360 ± <0,1^{cd}	0,436 ± <0,1^{b}
H9	16,67	66,66	16,67	147,094 ± 11^{b}	125,327 ± 2^{c}	0,341 ± <0,1^{d}	0,442 ± <0,1^{b}
H10	16,67	16,67	66,66	111,623 ± <1^{e}	192,522 ± 2^{b}	0,335 ± <0,1^{d}	0,430 ± <0,1^{ab}
p-value (homoscedasticity)				0,236	0,292	0,342	0,079
p-value (ANOVA)				≤0,05	≤0,05	≤0,05	≤0,05

*Control: O+ 0,386^{ab}; O- 0,486^{ab}

(b)



(c)

ORAC[4] (mmolTE/g)	FRAP[5] (mgAAE/g)	TF [6] (mgCE/g)
1,501 ± 0,435	335,523 ± 8,212	120,527 ± 5,605

Figure 1. (a) Composition of the extracts in %, optimized parameters (total phenolic compounds (TFC), DPPH radical inhibition, concentration where 50% of hemolysis occurs for O+ and O- type erythrocytes) and their results, (b) Graph of the hypotonic hemolysis of O+ against the PB hydroalcoholic extract and (c) results of the optimized extract: Oxygen Radical Absorbance, ability to reduce Iron III and total flavonoid content.

ACKNOWLEDGEMENTS

To State University of Ponta Grossa (UEPG), CAPES (88887.688593/2022-00) and CNPq for the structure and financial support. To the Graduate Program in Chemistry at UEPG. To multi-user lab of UEPG (C-Labmu). To the research group QUIMIONAT and LAQUA.

REFERENCES

[1]. MARGRAF, T.; KARNOPP, A. R.; ROSSO, N. D.; GRANATO, D. J. Food. Sci. **2015**, *80*, 2397-2403.
[2]. BRAND-WILLIAMS, W.; CUVELIER, M. E.; BERSET, C. LWT-Food Sci. Technol. **1995**, *28*, 25–30.
[3]. ZHANG, L.; SANTOS, J. S.; CRUZ, T. M.; MARQUES, M. B.; CARMO, M. A. V.; AZEVEDO, L.; WANG, Y.; GRANATO, D. Food Res. Int. **2019**, *125*, 108516.
[4]. DENEV, P.; CIZ, M.; AMBROZOVA, G.; LOJEK, A.; YANAKIEVA, I.; KRATCCHANOVA, M. Food Chem. **2010**, *123*, 1055-1061.
[5]. GRANATO, D.; KARNOPP, A. R.; VAN RUTH, S. M. J. Sci.Food Agric. **2015**, *95*, 1997–2006.
[6]. HERALD, T. J.; GADGIL, P.; TILLEY, M. J. Sci.Food Agric. **2012**, *92*, 2326–2331.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Evaluation of antioxidant activity from *Garcinia cochinchinensis* pulp extracts

Elton Kazmierczak,[1*] Cássia Gonçalves Magalhães,[1] Romaiana Picada Pereira[1]
1) Department of Chemistry, State University of Ponta Grossa, Paraná, Brazil
****e-mail: kazmierczak.elton@gmail.com***

Keywords: *oxidative stress, Clusiaceae, phenolics compounds.*

ABSTRACT

Garcinia cochinchinensis (Clusiaceae) is a fruit native from Vietnam.[1] In folk medicine, the peel of the fruit is used to treat allergies and skin diseases.[2] In addition, fruit extracts show *in vitro* antioxidant activity of acetone extract pulp.[3] There are few studies about this plant grown in Brazil. This work aims to evaluate antioxidant activity of different fractions from pulp fruit extracts of *Garcinia cochinchinensis*. The fruits were subjected ultrasound-assisted extraction (25 kHz, 1 h, H_2O/EtOH 1:1). Liquid-liquid extraction was performed with chloroform (CA, CB). The aqueous phase was adjusted to pH 12 and extracted with ethyl acetate (A12A, A12B), after with pH 8 and 4 (A8A, A8B, A4A, A4B). Antioxidant activity was evaluated against DPPH•, $ABTS^{\bullet+}$, FRAP, Fe^{2+} chelation and used ascorbic acid (AA) as a positive control.

Fractions	DPPH• IC_{50} (ppm)*	$ABTS^{\bullet+}$ IC_{50} (ppm)*	FRAP (mg AA g^{-1})*	Chelation of Fe (II) (%)
CA	366,9±130,6ab	65,08±0,93c	8,52±0,3b	42,7 ± 4cd
A12A	774,3±285,5ab	14,44±0,85a	7,71±0,3b	81,3 ± 2ab
A8A	30,01±0,9c	15,14±1,25a	46,20±0,1b	89 ± 8 a
A4A	24,8±1,4c	33,02±17,81b	5,93±0,3b	83 ± 12 ab
C.B	38,3±3,1c	51,35±8,1c	9,34±0,02b	63,3± 3 abc
A8B	31,6±0,5c	19,27±2,45a	50,3±0,7a	90,6 ± ab
AM8B	43,4±4,1c	55,12±9,77c	4,42±0,01b	91 ± 4 a
A4B	26,6±2,9c	32,01±4,8b	5,48±0,05b	47,7 ± 3 cd
AA	12,46±1,7d	9,96±1,4[a]	-	-

Table 1: Antioxidant activity of extracts from *G. cochinchinensis* pulp.

The highest antioxidant activities were found in ethyl acetate extracts, mainly in pH 8 and 4, so these fractions have potential to be better exploited.

ACKNOWLEDGEMENTS

CLabMu, CAPES (88887.753099/2022-00).

REFERENCES

(1) Kazmierczak, E.; Magalhães, C. G.; Pereira, R. P. Antioxidant Property of Secondary Metabolites from Garcinia Genus: A Short Review. *Eclet. Quim.* **2023**, *48* (1), 41–54. https://doi.org/10.26850/1678-4618eqj.v48.1.2023.p41-54.

(2) Nguyen, H. D.; Trinh, B. T. D.; Nguyen, L. H. D. Guttiferones Q-S, Cytotoxic Polyisoprenylated Benzophenones from the Pericarp of Garcinia Cochinchinensis. *Phytochem. Lett.* **2011**, *4* (2), 129–133. https://doi.org/10.1016/j.phytol.2011.01.001.

(3) Farinazzi-Machado, F. M. V.; Mariano-Nasser, F. A. de C.; Furlaneto, K. A.; Fiorini, A. M. R.; Vieites, R. L. Compostos fenólicos e atividade antioxidante *in vitro* dos frutos e folhas da *Garcinia cochinchinensis* choisy.Pdf. *Rev. Energ. na Agric.* **2017**, *32* (4), 393–400. https://doi.org/https://doi.org/10.17224/EnergAgric.2017v32n4p393-400.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Metabolic fingerprint of *Ocotea diospyrifolia*: A integrated strategy to achieve reliable annotation

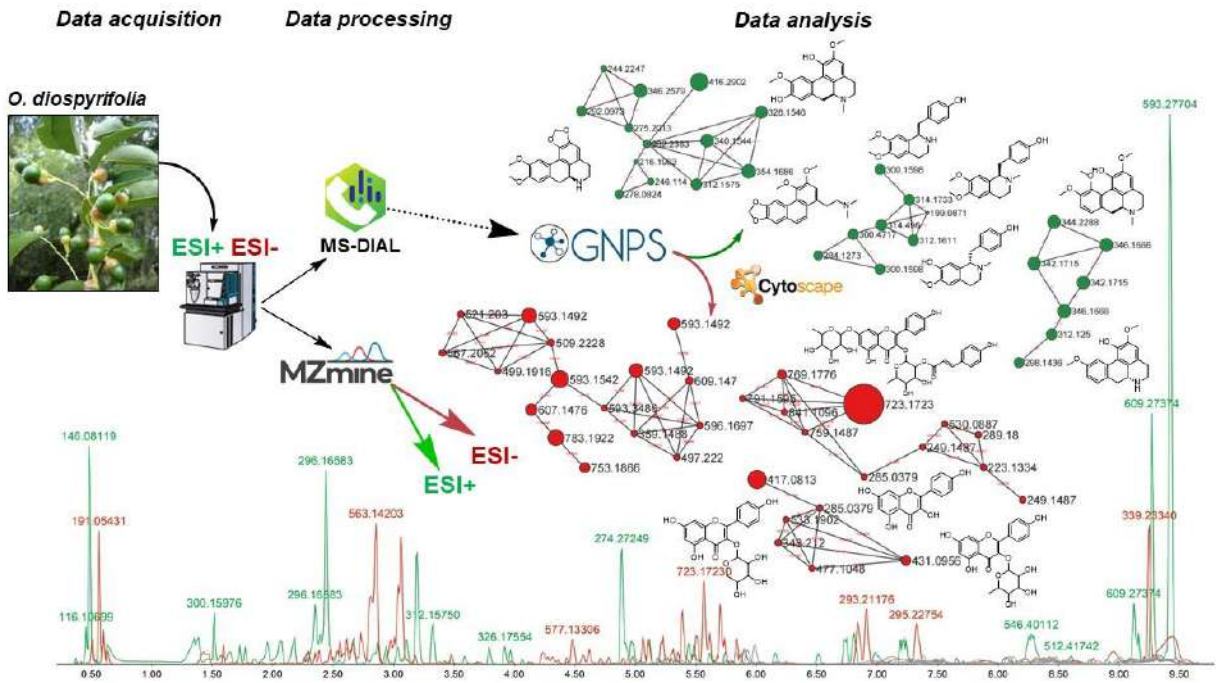
Matheus Fernandes Alves[1*], Albert Katchborian-Neto[1], Michael Murgu[2], Danielle Ferreira Dias[1], Marisi Gomes Soares[1] and Daniela Aparecida Chagas de Paula[1,*]

1) Chemistry Institute, Federal University of Alfenas-MG, 37130-001
2) Waters Corporation, São Paulo, 06455-000
****e-mail: matheus.alves@sou.unifal-mg.edu.br***

Keywords: *Natural products, Liquid Chromatography-Mass Spectrometry, Data-independent acquisition*

ABSTRACT

Bioactivity-guided isolation of natural products (NP) is an effective but laborious process. To rationalize NP research, metabolic profiling and NP dereplication prior isolation using Liquid Chromatography-High Resolution Tandem Mass Spectrometry (LC-HRMS/MS) it's a powerful and suitable strategy[1]. *Ocotea* is a chemically diverse and pharmacologically rich plant genus from Lauraceae that despite great medicinal potential, is still understudied, as the *O. diospyrifolia*[2]. Our goal in this work was to profile the main metabolites of *O. diospyrifolia* by analysing LC-HRMS/MS data using an *in-house* NP database, integrated with molecular networking and gas-phase fragmentations. By this semi-automated approach, we have efficiently annotated 30 alkaloids and 22 flavonoids on confidence level 2 accordingly to the metabolomics standards initiative[3]. This approach enabled us to chemically characterize the *O. diospyrifolia* using a minimal amount of plant material. This strategy proved to be suitable for the study of other endemic and threatened species of the Brazilian flora.



ACKNOWLEDGEMENTS

This work was supported by PIBIC 8/2022, CAPES - Finance Code 001, CNPq (406837/2021-0, 316204/2021-8) and FAPEMIG (APQ-02353-17, APQ 00207-18).

REFERENCES

[1]. Wolfender, JL *et al. Anal Chem* **2019**, 91, 704–742
[2]. Silva, AF *et al*. *Phytochem Let* **2021**, 42, 52-60
[3]. Sumner LW *et al*. *Metabolomics* **2007**, 3, 211-221

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

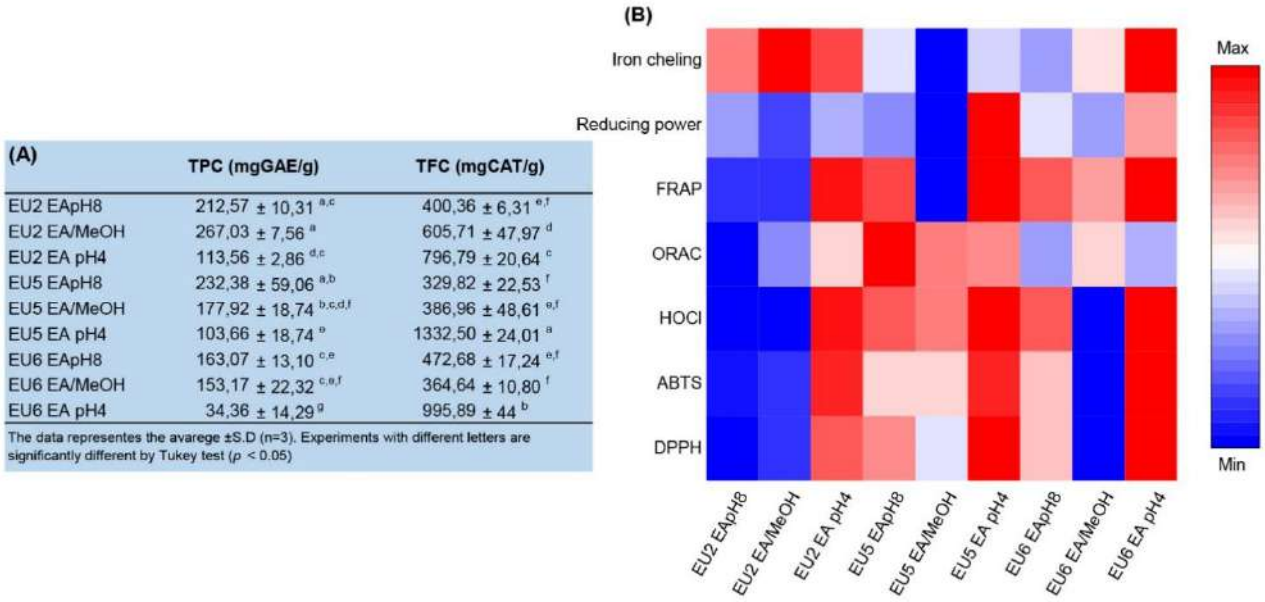
Exploring the antioxidant activity of *Eugenia unflora* L. extracts: A comparative approach by different techniques

Vinicius Monteiro Schaffka,[1*] Romaiana Picada Pereira,[1] Cássia Gonçalves Magalhães[1]
1) Department of Chemistry, Ponta Grossa State University, Ponta Grossa – PR, Brazil
**e-mail: vschaffka@gmail.com*

Keywords: *Eugenia uniflora, antioxidant activity, phenolic compounds*

ABSTRACT

Eugenia uniflora (Myrtaceae), popularly known as pitangueira, is native to Brazil. This plant is recognized as a source of bioactive compounds, moreover polyphenols[1]. Due to the several factors that influence the composition of its extracts, such as genotypic and phenotypic characteristics, assigning antioxidant properties to specimens present in distinct locations under different conditions is of great importance[1,2].



(A)

	TPC (mgGAE/g)	TFC (mgCAT/g)
EU2 EApH8	212,57 ± 10,31 ^{a,c}	400,36 ± 6,31 ^{e,f}
EU2 EA/MeOH	267,03 ± 7,56 ^{a}	605,71 ± 47,97 ^{d}
EU2 EA pH4	113,56 ± 2,86 ^{d,c}	796,79 ± 20,64 ^{c}
EU5 EApH8	232,38 ± 59,06 ^{a,b}	329,82 ± 22,53 ^{f}
EU5 EA/MeOH	177,92 ± 18,74 ^{b,c,d,f}	386,96 ± 48,61 ^{e,f}
EU5 EA pH4	103,66 ± 18,74 ^{e}	1332,50 ± 24,01 ^{a}
EU6 EApH8	163,07 ± 13,10 ^{c,e}	472,68 ± 17,24 ^{e,f}
EU6 EA/MeOH	153,17 ± 22,32 ^{c,e,f}	364,64 ± 10,80 ^{f}
EU6 EA pH4	34,36 ± 14,29 ^{g}	995,89 ± 44 ^{b}

The data representes the avarege ±S.D (n=3). Experiments with different letters are significantly different by Tukey test ($p < 0.05$)

(B)

Iron cheling
Reducing power
FRAP
ORAC
HOCl
ABTS
DPPH

EU2 EApH8
EU2 EA/MeOH
EU2 EA pH4
EU5 EApH8
EU5 EA/MeOH
EU5 EA pH4
EU6 EApH8
EU6 EA/MeOH
EU6 EA pH4

Max
Min

Figure 1: **(A)** Total of phenolic compounds and flavonoids. **(B)** Heat map of the nine samples (X axis) and the antioxidant methods (Y axis). The data are treated by Min-Max scaling.

In this study, the composition (TPC, TFC and HPLC-DAD fingerprint) and antioxidant activity of three different specimens (EU2, EU5 and EU6) were compared. The results indicated that the extracts obtained with ethyl acetate (EA) at pH4 had highest effectiveness, probably due to their high levels of phenolic compounds[3]. Additionally, a massive occurrence of flavonoids in EU5 was observed, as demonstrated by the antioxidant activity of EA at pH8 and EA/MeOH (70:30). Our study on those three specimens contribute to the evaluation on chemical variability and their influence on biological activities.

ACKNOWLEDGEMENTS

CAPES (88887.688634/2022-00), UEPG (Ponta Grossa State University)

REFERENCES

[1] FIDELIS, E. Monteiro; et. al, Arabian Journal Of Chemistry, **2022**, v.15, 1878-5352.
[2] RAMALHO, RRF; et. al, Food Research International, **2019,** v.119, 850-858
[3] GULCIN, I. Archives of Toxicology, **2020,** v.94, 651-715

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Bioprospecting-based untargeted metabolomics identifies alkaloids as potential anti-inflammatory bioactive markers of *Ocotea* species (Lauraceae)

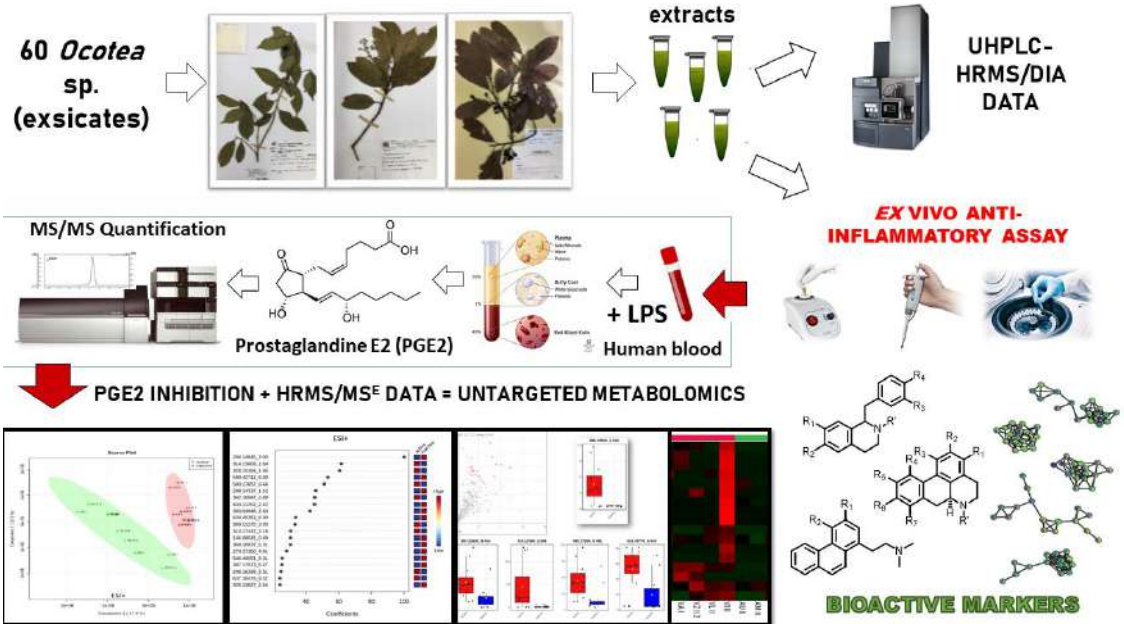
Albert Katchborian-Neto[1*], Karen Jesus Nicácio[2], Jonas Carneiro Cruz[3], Matheus Fernandes Alves[1], Miller Santos Ferreira[1], Michael Murgu[4], Danielle Ferreira Dias[1], Marisi Gomes Soares[1] and Daniela Aparecida Chagas de Paula[1,*]

1) Chemistry Institute, Federal University of Alfenas, Alfenas, 37130-001
2) Department of Chemistry, Federal University of Mato Grosso, Cuiabá, 78060-900
3) Department of Chemistry, University of Sao Paulo, Ribeirão Preto, 14040-901
3) Waters Corporation, São Paulo, 06455-000
****e-mail: albert_katchborian@hotmail.com***

Keywords: *Metabolite Annotation, Liquid Chromatography-Mass Spectrometry, Data-independent acquisition, Alkaloids.*

ABSTRACT

The anti-inflammatory profile of 60 *Ocotea* sp. was investigated employing cutting-edge untargeted metabolomics approaches[1]. Our study employed liquid chromatography coupled with high-resolution mass spectrometry to uncover the bioactive markers present in *Ocotea* species. By the use of MS^E spectra, multivariate and univariate statistical analysis, *in-house* databases, molecular networking and gas-phase fragmentation reactions investigation, we successfully annotated alkaloids, particularly aporphine and benzylisoquinolines, as the primary anti-inflammatory compounds. Remarkably, 50 out of the 60 *Ocotea* species exhibited potent inhibition of prostaglandin E2 (PGE2) release, demonstrating their potential as promising sources for anti-inflammatory drug discovery. Notably, 10 extracts exhibited statistical similarity to the corticosteroid reference drug dexamethasone, underscoring the significance of these natural products. This bioprospecting endeavour, utilizing metabolomics-based techniques and gas-phase fragmentations, expands our understanding of the chemical diversity of the *Ocotea* genus and offers promising avenues for further anti-inflammatory drug discovery studies based on Natural Products sources.



ACKNOWLEDGEMENTS

This work was supported by PIBIC 8/2022, CAPES - Finance Code 001, CNPq (406837/2021-0, 316204/2021-8) and FAPEMIG (APQ-02353-17, APQ 00207-18).

REFERENCES

[1]. Chen, L. *et al.* Metabolite discovery through global annotation of untargeted metabolomics data. *Nat. Methods* **18**, 1377–1385 (2021).

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

PHYTOCHEMSTRY, BIOLOGIC ACTIVITY AND QSAR MODELS OF ENDOPHYTIC FUNGI METABOLITES FROM *Poincianella pluviosa* (SIBIPIRUNA)

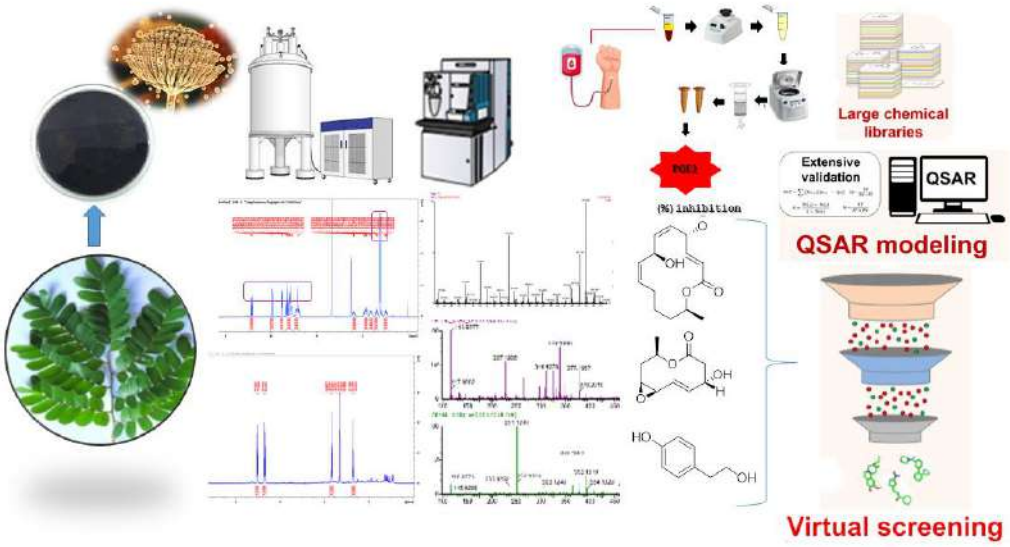
Miller Santos Ferreira[1*], Albert Katchborian-Neto[1], Karen Jesus Nicácio[2], Mario Ferreira C. dos Santos[3], Matheus Fernandes Alves[1], Michael Murgu[4], Danielle Ferreira Dias[1], Daniela Aparecida Chagas de Paula[1] and Marisi Gomes Soares[1*]

1) Chemistry Institute, Federal University of Alfenas-MG, 37130-001
2) Department of Chemistry, Federal University of Mato Grosso, 78060-900
3)Department of Chemistry and Physics, Federal University of Espírito Santo, 29500-000
4) Waters Corporation, São Paulo, 06455-000
****e-mail: millersantosferreira@gmail.com***

Keywords: *Isolation, Metabolite Identification, Anti-inflammatory activity and Machine learning.* .

ABSTRACT

Fungi have a wide variety of specialized metabolites with unique chemical structures and outstanding biological activity, such as anti-inflammatory and antiparasitic properties [1]. Endophytic strains of *Aspergillus* sp. and *Nigrospora* sp. from *Poincianella pluviosa* leaves were isolated and chemically characterized using Mass Spectrometry and Nuclear Magnetic Resonance technics[2]. The latter endophytic strain was identified as *Nigrospora zirmmini* using morphological features and genetic sequencing, and its extract showed *ex vivo* anti-inflammatory activity. By comparing monoisotopic mass data with an Internal Database (IDB), 75 metabolites were putatively identified. Three main compounds isolated from the fungi extract were characterized as the nigrosporolide, tyrosol, and decarestrictin A. However, our systematic review revealed that the *Aspergillus* genus had the highest number of isolated bioactive metabolites for anti-inflammatory activity in the literature. Therefore, QSAR predictive models were constructed to predict the suppression of nitric oxide (NO), an inflammatory mediator, using isolated metabolites from endophytic *Aspergillus* species.



ACKNOWLEDGEMENTS

This work was supported by PIBIC 8/2022, CAPES - Finance Code 001, CNPq (406837/2021-0, 316204/2021-8) and FAPEMIG (APQ-02353-17, APQ 00207-18).

REFERENCES

[1]. Ferreira, MS *et al. Farmacognosia* **2021**, 31, 5
[2]. Huang, L *et al. Arabian Journal of Chemistry* **2023**, 16,5

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Synthesis and investigation of quinoline derivatives as photoinitiators to polymerization of dental resins

Vitor Fernandes Moreno,[1*] Lucas Michelão Martins,[1] Luiz Carlos da Silva Filho[1]

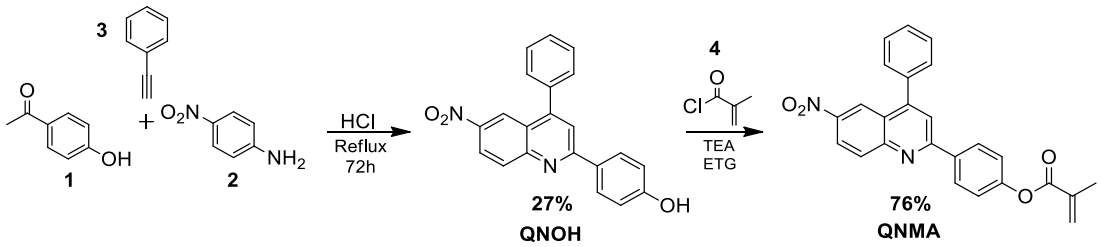
1) Department of Chemistry, São Paulo State University (UNESP), School of Sciences, 17033-360, Bauru, São Paulo, Brazil

****e-mail: vitor.moreno@unesp.com***

Keywords: *quinoline derivatives, photopolymerization, photoinitiator, luminescent polymers, dental restorations*

ABSTRACT

This work sought the synthesis of different quinoline derivatives (Scheme 1) capable of acting as Type II photoinitiators in the reaction of photopolymerization of urethane dimethacrylate monomer (UDMA) (Figure 1) which is widely used in the composition of dental restoration resins.[1-3] Among the objectives, we verified the effect promoted by the different quinoline compounds proposed, including one of them having a methacrylate group like the monomer, which showed promise when reaching more than 60% of conversion degree, result similar to camphorquinone that is used in several composite resins currently. The polymerization times also drew attention, being between 40 and 60 s, and by means of a photolysis investigation we observed the formation of radical species from the first second to the exposure of the photoinitiators to the light of the curing light. In addition, the materials produced have flourescence, which may be interesting for application in the dental field.



Scheme 1. Synthesis of quinoline derivatives

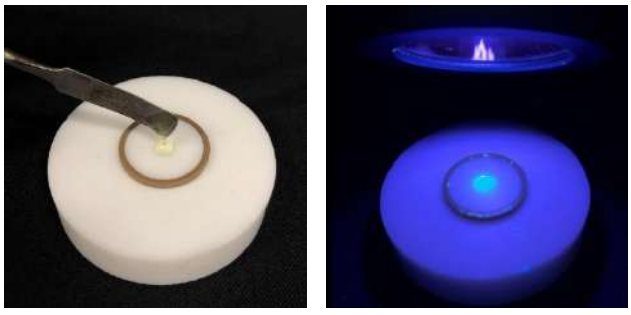


Figure 1. Photopolymerization of UDMA using quinolinic photoinitiators

ACKNOWLEDGEMENTS

The authors would like to thank FAPESP (2018/09235-4 and 2018/14506-7), CAPES (88882.330148/2019-01), and Pró-Reitoria de Pesquisa da UNESP (PROPe-UNESP) for their financial support.

REFERENCES

[1]. Moszner, N.; Völkel, T.; Fischer, U. K.; Klester, A.; Rheinberger, V., *Angew. Makromol. Chem*. 1999, 265 (1), 31–35.
[2]. Alarcon, R. T.; dos Santos, G. C.; de Oliveira, A. R.; da Silva-Filho, L. C.; Bannach, G., *J. Appl. Polym. Sci*. 2019, 136 (19), 47461.
[3]. Fouassier, J. P.; Lalevée, *J. Photoinitiators for Polymer Synthesis*; John Wiley & Sons, 2013.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

New *N*-gluco-nitro-imidazoles, potential bioactive substances

Rayssa de Cássia Alves Iemini[1], Ana Laura Marques Trinca1, Diogo TeixeiraCarvalho[1],Lucas Lopardi Franco [1*]

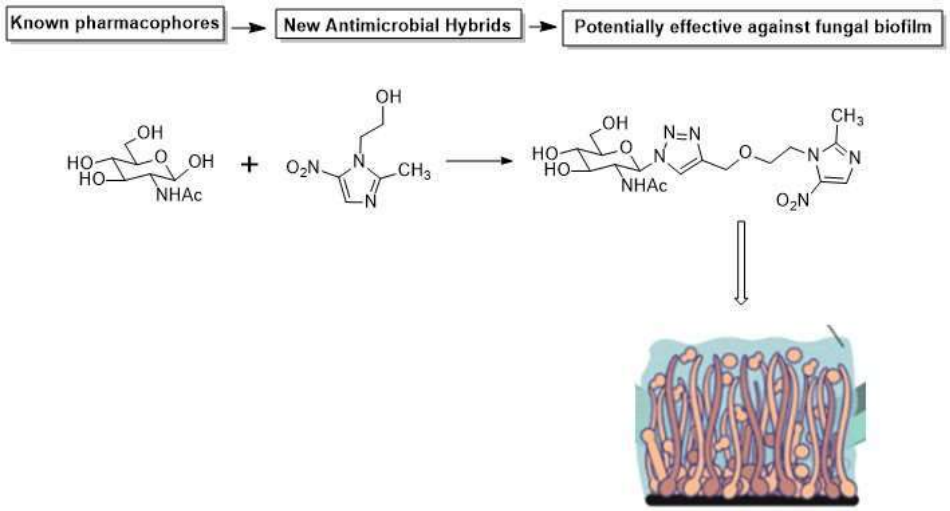
1) Food and Drug Department,* Faculty of Pharmaceutical Sciences*, Federal University of Alfenas, MinasGerais, Brazil

****e-mail: lucas.franco@unifal-mg.edu.br***

Keywords: biofilm, carbohydrates, *N*-gluco-metronidazol

ABSTRACT

The importance of carbohydrates in the proper functioning of the organism have been known for a long time. In medicinal chemistry, they have several applications, as they can be associated with proteins (glycoproteins) and lipids (glycolipids). Thus, the field of research of glycol-compounds as enzyme inhibitors or transporters has been growing significantly, as the development of carbohydrate derivatives can therapeutically interfere with the metabolic processes of an individual in a pathological state. Another important therapeutic class is the nitro-nitroimidazoles, with 5-nitroimidazoles being responsible for its greatest therapeutic success, having several bioactive compounds, such as antiparasitic and antimicrobial. Therefore, it seemed interesting to us to prepare glyco-compounds containing a 5-nitroimidazole unit, to investigate their biological properties, such as against fungal biofilm. In this work, we performed the synthesis and characterization of *N*-gluco-metronidazole, obtained by non-classical glycosylation, performed bya click chemistry reaction, to evaluate its properties against fungal biofilms.



We will report herein the synthesis of a new gluco-metronidazole as a potential bioactive compound.

ACKNOWLEDGEMENTS

Thanks to FAPEMIG, CAPES, CNPq and UNIFAL-MG

REFERENCES

(1) Moreth, M.; Ornelas, D.; Gomes, C. R. B.; Souza, M. V. N. de. Nitroimidazoles - a Promising Class of Compounds for the Treatment of Tuberculosis. *Revista Virtual de Química* **2010**, *2* (2). https://doi.org/10.5935/1984-6835.20100010.

(2) Barbosa, T. P.; Sousa, S. C. O.; Amorim, F. M.; Rodrigues, Y. K. S.; de Assis, P. A. C.; Caldas, J. P. A.; Oliveira, M. R.; Vasconcellos, M. L. A. A. Design, Synthesis and Antileishmanial in Vitro Activity of New Series of Chalcones-like Compounds: A Molecular Hybridization Approach. *Bioorganic and Medicinal Chemistry* **2011**, *19* (14), 4250–4256. https://doi.org/10.1016/j.bmc.2011.05.055.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Preparation of 4-aminoquinazolines with potential antitumor activity

Gabriel de P. Bueno,[1*] Giuliano C. Clososki.[2]

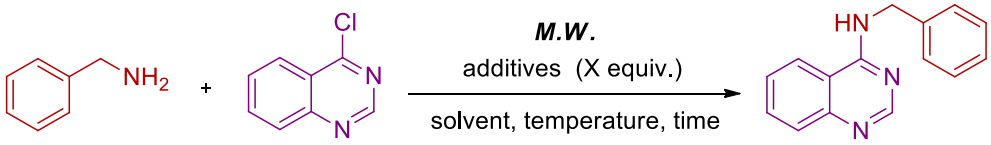
1) Research Center for Natural and Synthetic Products, Faculty of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Av. do Café S/N, Ribeirão Preto, SP 14.040-903, Brazil.

****e-mail: gabriel_bueno@usp.br***

Keywords: *4-aminoquinazolines, EGFR, Theranostics.*

ABSTRACT

Quinazolines are important molecules with biological potential, and are representative of a wide class of *N*-aromatic heterocycles. It is worth mentioning that 4-aminoquinazoline derivatives are highly desired by the pharmaceutical industry, in which it is present in many molecules and drugs, like *erlotinib*, *gefitinib*, *afatinib* and *prazosin* being highlighted, as well as other EGFR epidermal growth factor receptor inhibitors.[1-3] In view of the importance of this class of compounds, synthetic studies were developed for the synthesis of 4-aminoquinazolines of medicinal interest from nucleophilic aromatic substitution reactions (S_NAr), (Scheme 1),[4-7] in strategic positions of the quinazoline ring, with potential antitumor activity and future applications in functional supramolecular nanosystems (Figure 1), for the development of new drugs with theranostic properties.[1-4]



Scheme 1. Study of the reaction condition.

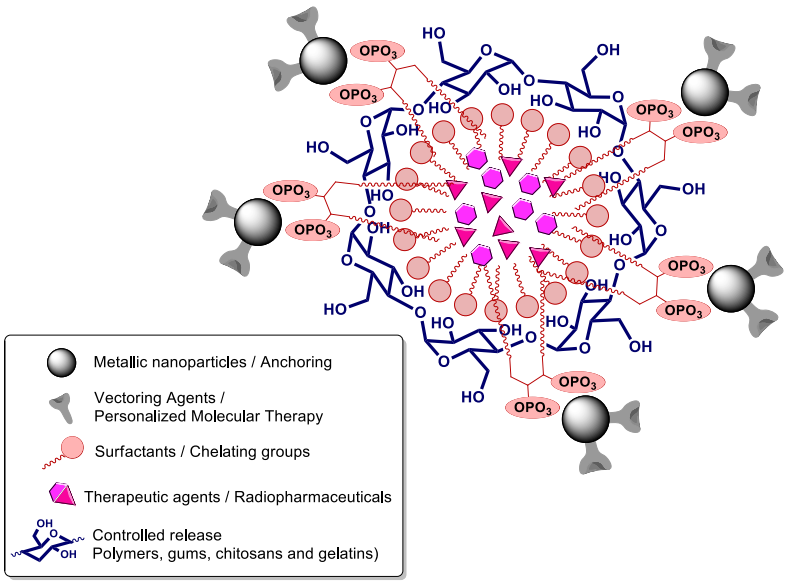


Figure 1. Supramolecular Nanosystems.

ACKNOWLEDGEMENTS

University of São Paulo (USP), CAPES and CNPq (163350/2021-3).

REFERENCES

[1]. *Nanoparticle Therapeutics: An Emerging Treatment Modality for Cancer*. **2008**, *7*, 771–782. [2]. *Eur. J. Med. Chem*. **2021**, *211*, 113016. [3]. *J. Org. Chem*. **2018**, *83*(2), 871–880. [4]. *Beilstein J. Org. Chem*. **2021**, *17*, 2968–2975. [5]. *Org. Lett*. **2021**, *23*(19), 7396–7400. [6]. *Eur. J. Med. Chem*. **2019**, *161*, 506–525. [7]. *Bioorganic Med. Chem*. **2011**, *19*(2), 939–950.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Temperature-Controlled Mechanochemistry for the Nickel-Catalysed Suzuki–Miyaura-Type Coupling of Aryl Chlorides via Ball Milling

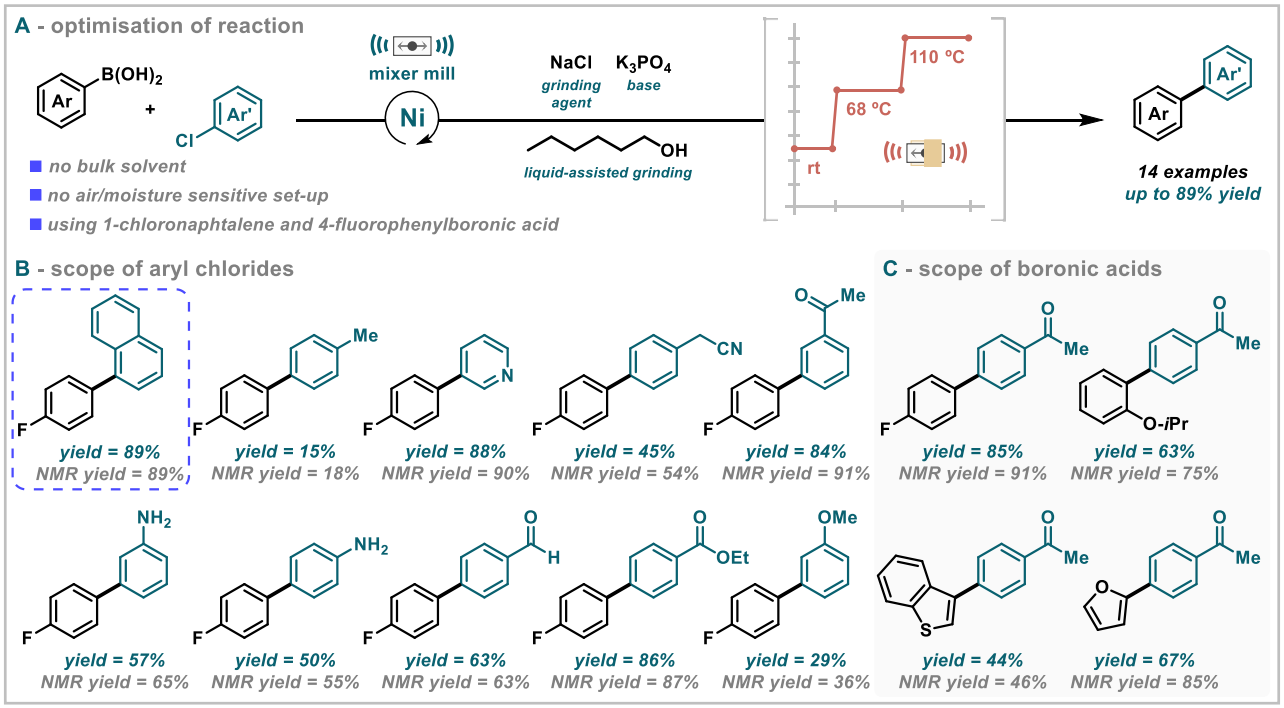
Renan Rodini Mattioli,[1,2] Robert R. A. Bolt,[2] Sarah E. Raby-Buck,[2] Julio Cezar Pastre,[1*] and Duncan L. Browne[2*]

1) First affiliation: Institute of Chemistry, University of Campinas (UNICAMP), 13083-970, Campinas, SP, Brazil
2) Second affiliation: School of Pharmacy, University College London (UCL), WC1N 1AX, London, UK
****e-mail: jpastre@unicamp.br, duncan.browne@ucl.ac.uk***

Keywords: *Ball milling, cross-coupling, nickel catalysis, aryl chlorides.*

ABSTRACT

Research interests in mechanochemistry have been growing in recent years. Due to its retrosynthetic disconnections importance, Suzuki–Miyaura chemistry has also been one of the main targets in the development of mechanochemical cross-coupling protocols.[1] Due to its reliable and robust nature, the cross coupling protocol is one of the most dependable transformations used in industrial settings.[2] Inspired on previous sulfamate-based coupling, we showcase Suzuki–Miyaura cross-coupling reaction by milling using an earth-abundant nickel catalyst and aryl chlorides (Scheme 1).[3] Optimised results were achieved between 1-chloronaphtalene and 4-fluorophenylboronic acid yielding 89% by NMR analysis. Preliminary and diverse scope ensured 14 successful examples in up to 89% isolated yield. Phenol, isocyanate, alcohol and alkyl halide groups installed in aryl chlorides showed intolerance, as well as high melting point aryl chlorides (generally above 70 ºC). Further aryl chlorides and boronic acids are still under investigation.



Scheme 1. Temperature-controlled nickel catalysed Suzuki–Miyaura reaction by ball milling.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge financial support from the São Paulo Research Foundation – FAPESP (RRM, 2022/03872-8; JCP, 2021/06661-5) and Prof. Dr. Duncan Leonard Browne for laboratory resources and supervision at University College London (UCL).

REFERENCES

[1] K. Kubota, H. Ito, *Trends Chem.* **2020**, *2*, 1066–1081; [2] W. P. Walters, J. Green, J. R. Weiss, M. A. Murcko, *J. Med. Chem.* **2011**, *54*, 6405–6416; [3] R. R. A. Bolt, S. E. Raby-Buck, K. Ingram, J. A. Leitch, D. L. Browne, *Angew. Chem., Int. Ed.* **2022**, *61*, e202210508.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

The Second Generation of the In-tandem Enantioselective Heck-Matsuda Arylations of Unactivated Olefins Directly from Anilines and Nitroarenes

Luiz P. M. O. Leão (PG),[1*] Valdeir C. Oliveira (PG),[1] Tomaz Henrique Duarte Chorro,[1] Carlos R. D. Correia (PQ).[1*]

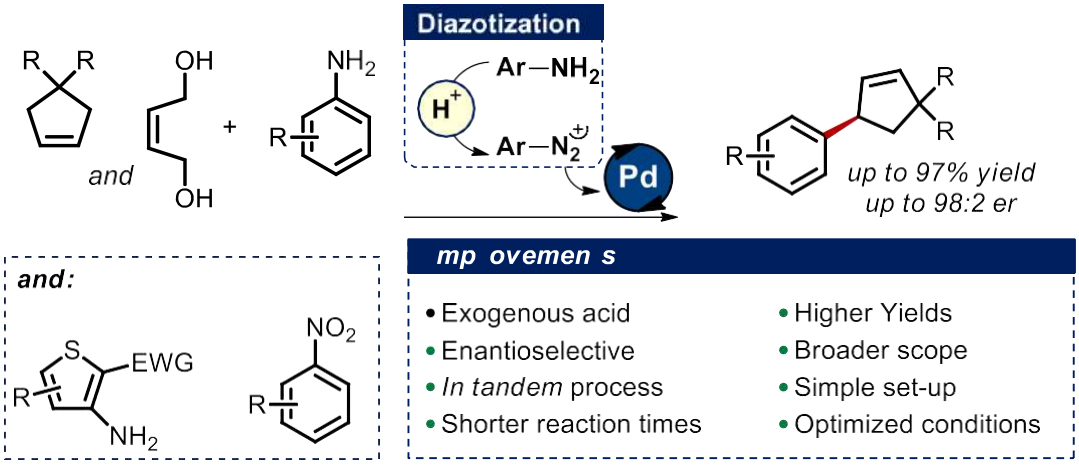
1) [1]Instituto de Química, Unicamp, 13083-970

l264637@dac.unicamp.br, *roque@iqm.unicamp.br

Keywords: *Enantioselective Catalysis, In Tandem Reaction, In Situ Diazotization*.

ABSTRACT

A much improved second generation of the sequential one-pot enantioselective Heck-Matsuda reaction directly from aniline derivatives has been developed.[1,2] This new, simple, and effective arylation method relies on the *in-situ* diazotization of the electronically diverse anilines and, aminothiophenes, followed by the enantioselective Heck-Matsuda reaction under mildly acidic conditions, skipping the need for the preparation of unstable arenediazonium salts.[3] This effective and very practical protocol was used to perform, among other processes, the desymmetrization of unactivated olefins leading to the synthesis of enantioenriched cyclopentenes and *β*-aryl-*γ*-lactones in high yields (up to 99%) and *er* (up to 99:1). Importantly, the protocol was also applied in the formal total synthesis of the biologically active compound VPC01091, a drug candidate for multiple sclerosis with excellent yield (94%), in 97:3 *er* and >20:1 *dr*. The method is amenable to multigram-scale reactions. A first approach using nitroarenes in a reduction-diazotization-Heck reaction step is presented.



Scheme 1. In-tandem enantioselective Heck-Matsuda reaction directly from anilines and nitroarenes.

ACKNOWLEDGEMENTS

We acknowledge the financial support of FAPESP (2014/25770-6), the Coordination for the Improvement of Higher Education Personnel (CAPES) for the fellowship to L.P.M.O.L. (88887.486174/2020-00), and CNPq for the fellowship to V.C.O. (140326/2019-7)

REFERENCES

1. a) Xie, J-Q., Liang, J-X., Jia, Y-X. *Chin. J. Chem*. **2021**, *39*, 710-728; b) Oliveira, C.C., Roque, C. R. D. *Chem. Rec*. **2021**, *21*, 2688–2701;
2. Herrera, C. L., Santiago, J. V., Pastre, J. C., Correia, C. R. D. *Adv. Synth. Catal*. **2022**, *364*, 1863–1872;
3. Firth, J. D., Fairlamb, J. S. *Org. Lett*. **2020**, *22*, 18, 7057–7059.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Synthesis of enantioenriched helical complexes

Lucas S. Cunha,[1] Caio C. Oliveira[1,*]

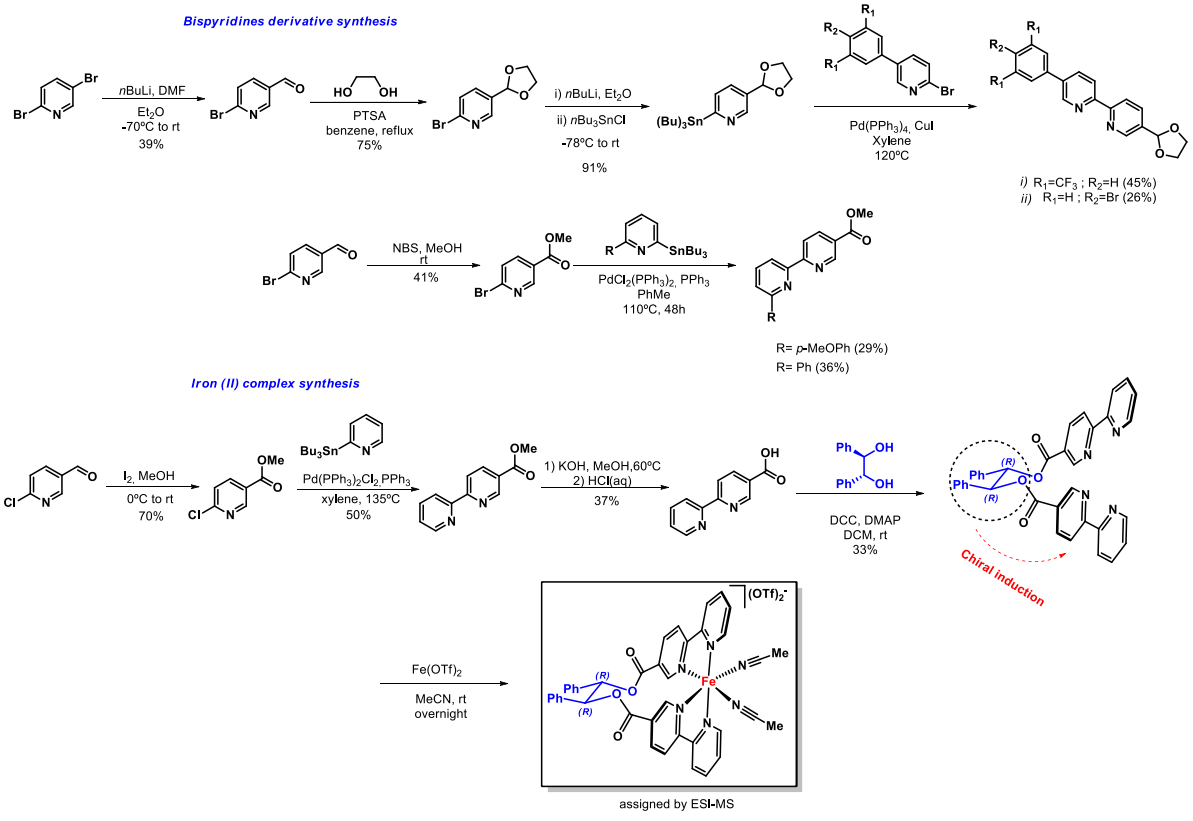
1) Department of Organic Chemistry, State University of Campinas, Rua Monteiro Lobato 270, 13083-862, Campinas, SP, Brazil

e-mail: l262829@dac.unicamp.br, caio.oliveira@unicamp.br

Keywords: Chiral-at-metal complexes, Helical, Asymmetric catalysis

ABSTRACT

Bipyridines and their derivatives are commonly used in catalysis and metal complexes synthesis.[1,2] In this way, this work focus on the synthesis of bisbypiridines, by introducing chiral backbone to yield helical enantioenriched complexes. The synthetic of the bipyridines was achieved by cross-coupling reactions such as Negishi, Suzuki and Stille as well deprotonative reaction and the chiral diol backbone was attached by Steglich reaction. Series of new ligands was obtained by this strategy and synthesis of metal ruthenium(II) complexes are ongoing just as catalytic studies. A new iron(II) complex was obtained using this strategy.



Scheme 1. Synthetic Route of bispyridine derivatives and formation of iron (II) complex.

ACKNOWLEDGEMENTS

(Process Number: 2019/15883-1)

REFERENCES

[1]. E. C. Constable,C.E.Housecroft, *Molecules* **2019**, 24,3951.
[2]. Cook, X. A. F.; de Gombert, A.; McKnight, J.; Pantaine, L. R. E.; Willis, M. C., *Angew.Chem.Int.Ed.***2021**,60,11068–11091.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

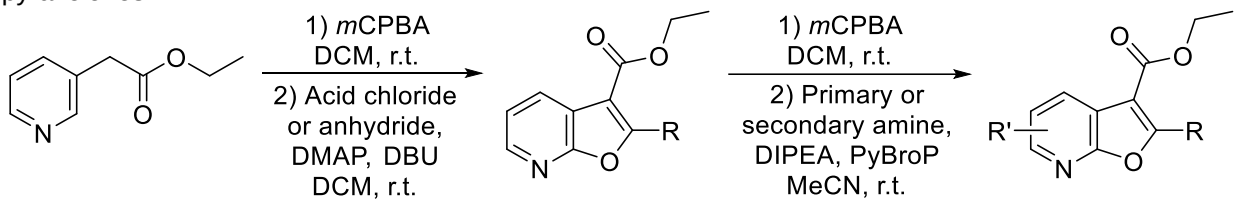
Exploring a fast and simple method for the synthesis of 4,5-substituted 3-pyrazolones via 2,3-substituted furo[2,3-*b*]pyridine ring opening

Rodrigues, V. L. T.,[1*] Emery, F. S.,[1]
1) Faculdade de Ciências Farmacêuticas de Ribeirão Preto, USP
****e-mail: tarouq@usp.br***

Keywords: *Pyrazolone, Heterocycle, Synthesis.*

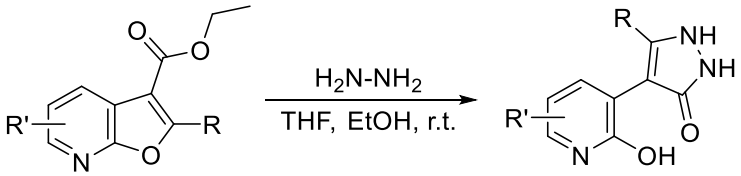
ABSTRACT

Pyrazolones are five-membered heterocycles derived from the pyrazole that have a wide range of commercial use, as this moiety is found in dyes, agrochemical and pharmaceutical molecules.[1] Some recent studies also reported its potential anticancer activity,[2, 3] therefore increasing the interest in new pyrazlone derivates. Still, the synthesis of these substituted pyrazolones demands various steps.[3, 4] Since substituted furo[2,3-*b*]pyridines can be easily synthetized by the cyclization of substituted pyridine and further easily functionalized,[5] the use of this heterocycle might be an interesting approach for the synthesis of functionalized 3-pyrazolones.



Scheme 1. Synthesis of 2,3-substituted furo[2,3-*b*]pyridines.

A simple method for the preparation of substituted 3-pyrazolones through ring opening of furo[2,3-b]pyridines was recently first described,[5] so this work explores more deeply the chemistry that involves this ring opening and how to make the 3-pyrazolone synthesis more effective.



Scheme 2. Ring opening of the 2,3-substituted furo[2,3-b]pyridine.

ACKNOWLEDGEMENTS

CAPES PROEX (88887.696480/2022-00).

REFERENCES

[1]. Kornis, G. I. Pyrazoles, Pyrazolines, and Pyrazolones, *ECT 2nd ed.* **2000**, *v. 16*, 763-779.
[2]. Kshatriya, R. *et al.* Synthesis and Evaluation of Anticancer Activity of Pyrazolone Appended Triarylmethanes (TRAMs), *ChemistrySelect*. **2021**, v. 6, issue 24, 6230-6239.
[3]. Burja, B. *et al.* Pyrazolone-fused combretastatins and their precursors: synthesis, cytotoxicity, antitubulin activity and molecular modeling studies, *Bioorg. & Med. Chem*. **2010**, v. 18, issue 7, 2375-2387.
[4]. Burja, B. *et al.* A simple approach to pyrazol-3-ones via diazenes, *Tetrahedron*. **2009**, v. 65, 8690-8696.
[5]. Fumagalli, F., Emery, F. S. Charting the Chemical Reactivity Space of 2,3-Substituted Furo[2,3-*b*]pyridines Synthesized via the Heterocyclization of Pyridine-N-oxide Derivatives, *J. Org. Chem.* **2016**, v. 81, issue 21, 10339-10347.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

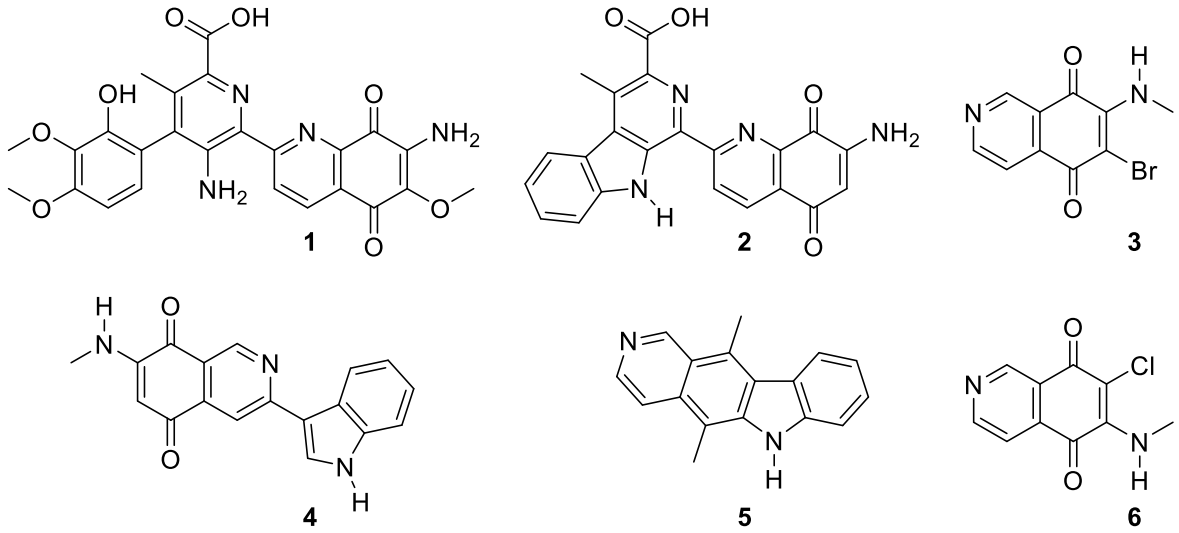
Regiochemical Switching in Oxidative Amination of Azanaphthoquinones

Caio M. Porto,[1] Joaquim A. M. Castro,[2] Alan R. S. Davide,[2]
Lucas C. Santana,[1] Nelson H. Morgon,[1] Paulo C. M. L. Miranda.[2,*]
1) Department of Physical Chemistry, Institute of Chemistry, UNICAMP
2) Department of Organic Chemistry, Institute of Chemistry, UNICAMP
****e-mail: pmiranda@unicamp.br***

Keywords: *Oxidative Amination, Alkaloids, Regiochemical Switching.*

ABSTRACT

Oxidative amination is a reaction sequence thoroughly used in total syntheses involving the nucleophilic attack of an amine at a quinone scaffold followed by an in-situ oxidation step. It has been used in the total syntheses of several azanaphthoquinone alkaloids such as streptonigrin (**1**), lavendamycin (**2**), caulibugulone B (**3**), and mansouramycin D (**4**). The major drawback of this approach is the regiochemistry selectivity, which is generally driven by the nitrogen atom at the heterocyclic ring and can't be easily switched in the case of isoquinolinediones. In this work, we describe the structural effects controlling the regiochemistry of the oxidative amination of quinolinediones and isoquinolinediones and how to switch the usual outcome of each compound to synthesize alkaloids such as ellipticine (**5**) and isocaulibugulone C (**6**).[1-4] Using DFT calculations, we will show that this usual tendency is not necessarily driven by the Parr functions of concurrent sites of the electrophile and the implications in all cases.



Scheme 1. Synthesized alkaloids using the usual regiochemical outcome of the oxidative amination: streptonigrin (**1**), lavendamycin (**2**), caulibugulone B (**3**), and mansouramycin D (**4**); and the switched outcome: ellipticine (**5**) and isocaulibugulone C (**6**).

ACKNOWLEDGEMENTS

CENAPAD-SP at UNICAMP and the Center for Computational Engineering and Sciences (CEPID/CCES)
FINEP; Grant # 01.11.0100.00
FAPESP grants 14/25770-6, 16/10498-4, and 2021/11039-1

REFERENCES

[1]. Castro, J. A. M.; Serikava, B. K.; Maior, C. R. S.; Naciuk, F. F.; Rocco, S. A.; Ligiéro, C. B. P.; Morgon, N. H.; Miranda, P. C. M. L. *J. Org. Chem.* **2022**, *87*, 7610-7617.
[2]. Castro, J. A. M.; Serikava, B. K.; Naciuk, F. F.; Ligiéro, C. B. P.; Morgon, N. H.; Miranda, P. C. M. L., *ChemistrySelect* **2023**, *8*, e202300347.
[3]. Naciuk, F. F.; Milan, J. C.; Andreão, A.; Miranda, P. C. M. L. *J. Org. Chem.* **2013**, *78*, 5026-5030.
[4]. Naciuk, F. F.; Castro, J. A. M.; Serikava, Miranda, P. C. M. L., *ChemistrySelect* **2018**, *3*, 436-439.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

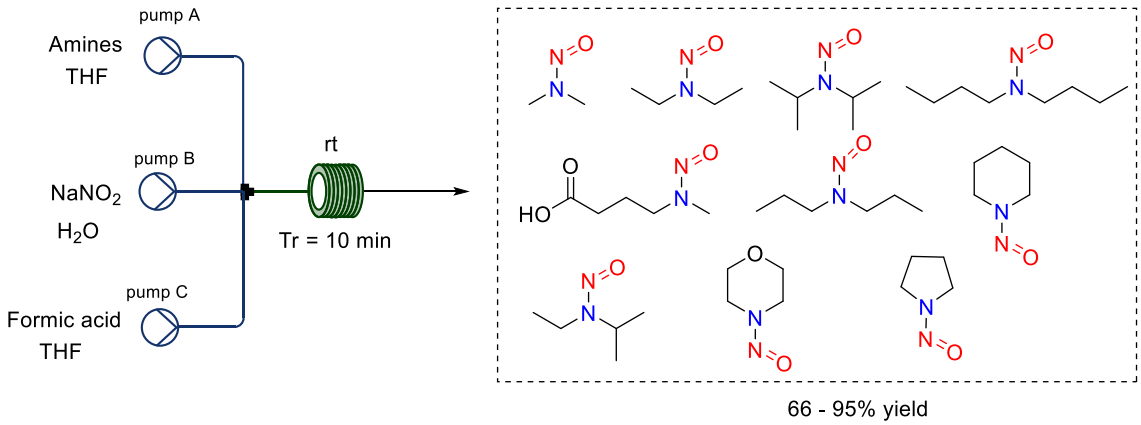
DEVELOPMENT OF A PLATFORM FOR SYNTHESIS AND ANALYTICAL CERTIFICATION OF NITROSAMINES OF PHARMACEUTICAL INTEREST

Leandro A. Bozzini,[1*] João Luiz C. Lopes,[1,2] and Giuliano C. Clososki[2]
1) Avita Produtos Químicos Farmacêuticos Ltda, 14056-680 Ribeirão Preto – SP, Brazil
2) Department of Biomolecular Sciences, FCFRP, University of Sao Paulo, 14040-903 Ribeirão Preto -SP, Brazil
****e-mail: leandrobozzini@yahoo.com.br***

Keywords: *Nitrosamines, continuous flow, pharmaceutical impurities.*

ABSTRACT

Nitrosamines are a class of chemical compounds that have been classified as probable human carcinogens based on animal studies. In recent years, there has been significant concern over the presence of nitrosamine impurities in drugs, as several commonly used medications were found to have unexpectedly high levels of these compounds.[1] Consequently, pharmaceutical companies and regulatory agencies have made extensive efforts to prevent, detect, and control nitrosamine impurities. In this work, we have successfully devised an efficient and innovative method for synthesizing pharmaceutical-grade nitrosamines using continuous flow technology. The utilization of continuous flow processes has gained considerable attention due to their inherent advantages such as improved safety, faster reaction kinetics, scalability, cost-effectiveness, and enhanced atom economy.[2] Our developed process demonstrates remarkable advantages, allowing for the rapid synthesis of various nitrosamines of pharmaceutical relevance in 10-minute residence time under mild reaction conditions. Furthermore, we have achieved the isolation of these compounds with high purity levels and moderate to high yields. This breakthrough has significant implications for the pharmaceutical industry and can contributed with the preparation of certificated standards necessary for nitrosamine control in pharmaceutical products.



Scheme 1. Continuous flow synthesis of nitrosamines.

ACKNOWLEDGEMENTS

CAPES, CNPq (No. 35166/2022-5) and Fapesp (No. 2022/05327-7)

REFERENCES

[1] a) Sörgel, F.; Kinzig, M.; Abdel-Tawab, M.; Bidmon, C.; Schreiber, A.; Ermel, S.; Wohlfarte, J.; Besa, A.; Scherf-Clavel, O.; Holzgrabee, U. *Journal of Pharmaceutical and Biomedical Analysis*, **2019**, 172, 395-405; b) Parr, M. K.; Josehp, J. F. *Journal of Pharmaceutical and Biomedical Analysis*, **2019**, 164, 536-549; c) Loeppky, R. N.; Bao, Y. T.; Bae, J.; Yu, L. Shevlin, G. ACS Symposium Series, Chapter 5, Whashington DC, **1994**.
[2] a) Movsisyan, M.; Delbeke, E. I. P.; Berton, J. K. I. T.; Barttilocchio, C.; Ley S. V.; Stevens, C. V. *Chemical Society Reviews*, **2016**, *45*, 4892–4928. b) Porta, R.; Benaglia, M.; Puglisi, A. *Organic Process Research & Development*, **2016**, 20, 2–25. c) Britton, J.; Raston, C. L. *Chemical Society Reviews*, **2017**, *46*, 1250–1271.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Synthesis of Novel Chiral Ruthenium Complexes and Evaluation in Asymmetric Catalysis

Erick M. C. Pinheiro (PG), Pablo A. S. Silva (IC), and Caio C. Oliveira (PQ).

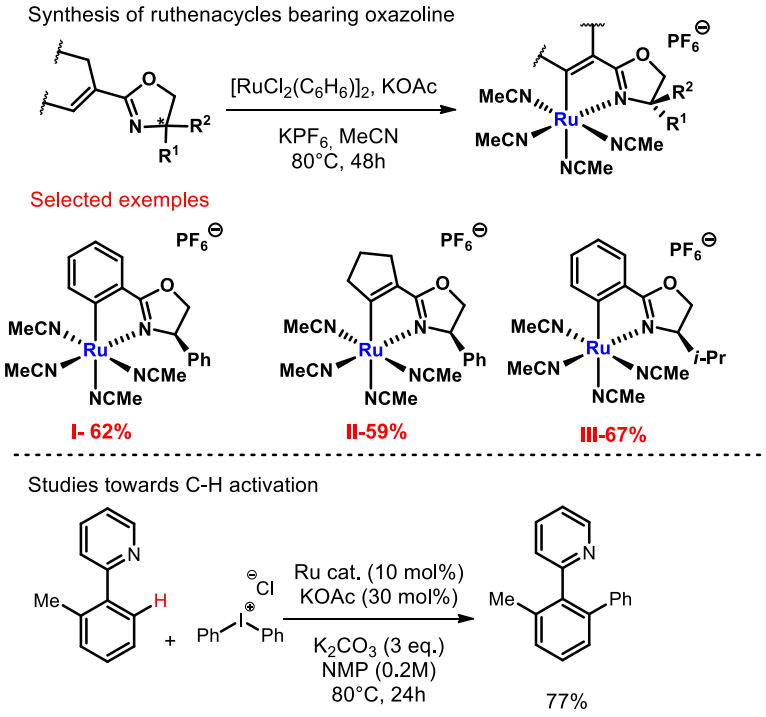
Institute of Chemistry, University of Campinas (UNICAMP), 13083-970, Campinas, SP, Brazil

caio.oliveira@unicamp.br

Keywords: Asymmetric catalysis, Chiral complexes, Ruthenium.

ABSTRACT

p-Cymene ruthenium complex is the most employed ruthenium catalyst in C-H functionalizations.[1] Recently, Larossa's group reported that ruthenacycles are efficient catalysts for alkylation and arylation reactions under mild conditions.[2,3] Herein, we report an operationally simple synthesis of bench-stable chiral ruthenacycles **I**, **II** and **III** that were able to catalyze arylation of 2-aryl-pyridine derivatives.



Scheme 1. Synthesis and evaluation of ruthenacycles in C-H activation.

ACKNOWLEDGEMENTS

FAPESP (Process number: 2020/12435-5)

REFERENCES

1. Liang, H.; Guo, W.; Li, J.; Jiang J.; Wang J. *Angew, Chem In. Ed. 2022*, *61*, e202204926.
2. Wang,G.; Wheatley, M.; Simonetti, M.; Cannas, M.D.; Larrosa, I. *Chem* 2020, 6, 1459-1468.
3. Simonetti, M.; Cannas,M.D.; Just-Baringo, X.; Vitorica-Yrezabal, J.I.; Larrosa, I *Nature Chemistry* 2018, 10, 724-731.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

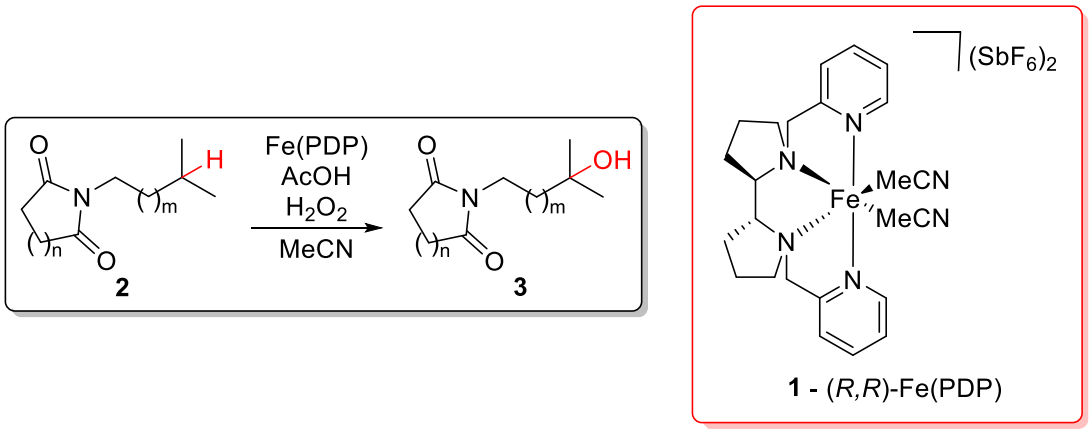
Investigating tertiary alcohol synthesis employing oxidation of aliphatic C—H bonds

Felipe Akio Saito,[1*] Kelita Angelo de Paula,[1] and Emilio Carlos de Lucca Júnior.[1*]
1) Institute of Chemistry, University of Campinas, 13083-970, Campinas, São Paulo, Brazil
****e-mail: f196657@dac.unicamp.br; eluccajr@unicamp.br***

Keywords*: C-H oxidation, Organic Synthesis, tertiary alcohol.*

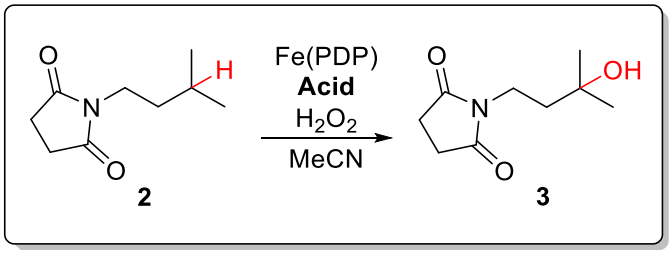
ABSTRACT

In recent decades, many advances have been made regarding the activation of inert C—H bonds as a viable tool for organic synthesis. In the mid-2000s, White and collaborators developed the $[Fe(II)(PDP)(MeCN)_2](SbF_6)_2$, also known as Fe(PDP) (**1**), an iron-based catalyst capable of oxidizing tertiary C-H bonds with a high level of selectivity without the need for pre-existing directing groups.[1] In 2015, the use of Fe(PDP) to oxidate remote tertiary C—H bonds in molecules containing imide groups was also demonstrated.[2]



Scheme 1. C-H oxidation in imide-containing molecules employing Fe(PDP).

Thus, our research group decided to reinvestigate the original reaction conditions by varying the employed carboxylic acid. With this, we desire to better understand the effects of the carboxylic acid on the reaction under which the C—H oxidation catalyzed by Fe(PDP) occurs.



Acid	Yields
Acetic acid	65%
Propionic acid	61%
Isobutyric acid	64%
Pivalic acid	40%
Chloroacetic acid	30%
Trifluoroacetic acid	9%

Scheme 2. Fe(PDP) catalyzed oxidation, employing varied carboxylic acids.

ACKNOWLEDGEMENTS

CNPq (Process Number 131703/2022-6)
FAPESP (Process Number 2018/04837-6 and 2020/11568-1)

REFERENCES

(1) Chen, M. S.; White, M. C. A Predictably Selective Aliphatic C–H Oxidation Reaction for Complex Molecule Synthesis. *Science* **2007**, *318* (5851), 783–787. https://doi.org/10.1126/science.1148597.
(2) Howell, J. M.; Feng, K.; Clark, J. R.; Trzepkowski, L. J.; White, M. C. Remote Oxidation of Aliphatic C–H Bonds in Nitrogen-Containing Molecules. *J. Am. Chem. Soc.* **2015**, *137* (46), 14590–14593. https://doi.org/10.1021/jacs.5b10299.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Selective late-stage oxidation of C—H bonds in the synthesis of complex natural diterpenes

Victor C. S. Santana,[1] Emmanoel V. Costa,[2] and Emilio C. de Lucca Júnior[1*]

1) Institute of Chemistry, University of Campinas, 13083-970, Campinas, SP, Brazil

2) Department of Chemistry, Federal University of Amazonas, 69067-005, Manaus, AM, Brazil

****e-mail: eluccajr@unicamp.br***

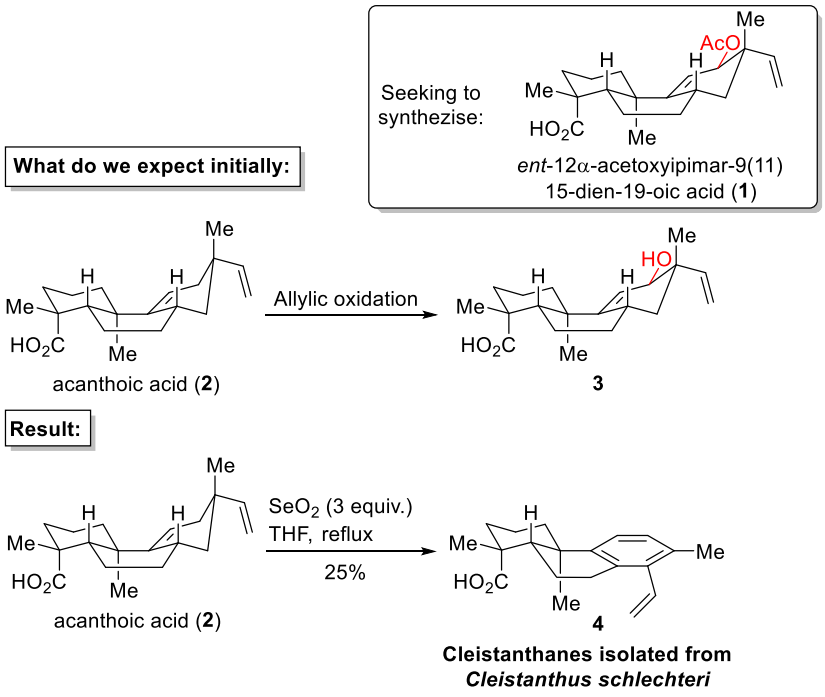
Keywords: *Diterpenes, Late-stage functionalization, Oxidation*

ABSTRACT

One of the main challenges in the area of C—H bond oxidation is the development of selective reactions due to the ubiquity of this type of bond in organic molecules and its low reactivity. In the case of transformations applied at a late-stage, obtaining chemoselectivity is of great interest. In this sense, our main goal is to use complex natural diterpenes as platforms to perform selective C—H oxidations in the synthesis of other natural products in a higher oxidative level.

In order to synthesize the natural product **1**, we envisioned that the *ent*-pimarane acanthoic acid (**2**)[1] could be converted to the allylic alcohol **3**. However, the allylic oxidation of compound **2** with three equivalents of SeO_2 in THF at reflux furnished the aromatic compound **4** in 25% yield (Scheme 1).

This result enabled us to access the cleistanthanes class of natural products[2] in a biomimetic way.



Scheme 1. Allylic oxidation of acanthoic acid with SeO_2

ACKNOWLEDGEMENTS

We are grateful to São Paulo Research Foundation (FAPESP) for the support for this work (grant 2018/048376 and fellowships 2019/27528-1 and 2023/03033-9).

REFERENCES

[1] Pinheiro, M. L. B.; Xavier, C. M.; de Souza, A. D. L.; Rabelo, D. M.; Batista, C. L.; Batista, R. L.; Costa, E. V.; Campos, F. R.; Barison, A.; Valdez, R. H.; Ueda-Nakamura, T.; Nakamura, C. V. *J. Braz. Chem. Soc.* **2009**, *20*, 1095–1102.

[2] a) Pinto, A. C.; Zocher, D. H. T.; Queiroz, P. S.; Kelecom, A. *Phytochemistry* **1987**, *26*, 2409–2411. b) Pinto, A. C.; Antunes, O. A. C.; Rezende, C. M.; Correia, C. R. D. *Phytochemistry* **1995**, *38*, 1269–1271.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

The use of iron complexes to mask olefins in the oxidation of C–H bonds

Milena Cristina Vieira Fernandes,[1*] Victor Camargo Stork Santana[1] and Emilio C. de Lucca Jr[1*]

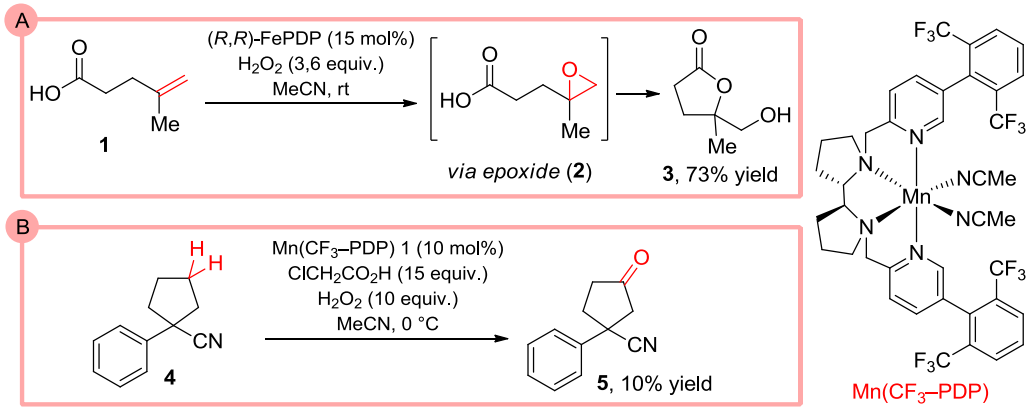
1) Institute of Chemistry, University of Campinas, CEP. 13083-970, Campinas, São Paulo, Brazil

****e-mail: eluccajr@unicamp.br***

Keywords: *functionalization, iron organometallics, olefins*

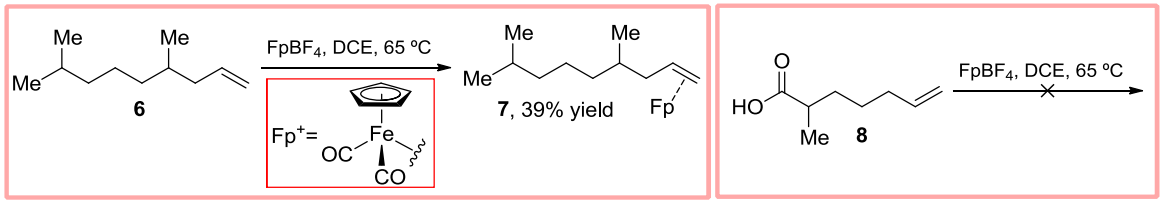
ABSTRACT

A prominent problem in the functionalization of C–H bonds is the presence of πC–C bonds in the substrates, as they are oxidized to epoxides.[1-3] The use uf systems such as FePDP leads to the major formation of epoxides and quinones (Scheme 1). In the diagram below, in (A) the treatment of **1** with FePDP and H_2O_2 as a terminal oxidant led to the formation of **3** via **2** and in (B) the low yield and selectivity of **5** is due to the formation of quinone byproducts.[4,5]



Scheme 1. Oxidations of substrates (A) with olefins and (B) aromatic rings.

To circumvent this limitation, we propose the complexation of terminal olefins with an iron complex (Scheme 2). In this way, it will be possible to mask the reactivity of the double bond against the C–H bonds and favor the oxidation of remote C–H bonds.



Scheme 2. Complexation of terminal olefins with iron.

ACKNOWLEDGEMENTS

FAPESP (Grants 2021/07167-4, 2019/27528-1 and 2018/04837-6), CNPq and Capes for financial support.

REFERENCES

[1] Chen, M. White, M., *Sci.* **2010**, 327 (5965), 566-571.
[2] Chen, M. S.; White, M. C., *Sci.* **2007**, 318 (5851), 783-787.
[3] Gormisky, P.; White, M., *J. Am. Chem. Soc.* **2013**, 135 (38), 14052-14055.
[4] Zhao, J.; Nanjo, T.; de Lucca, E. C.; White, M. C., *Nat. Chem.* **2019**, 11 (3), 213-221.
[5] Bigi, M. A.; Reed, S. A.; White, M. C., *Nat. Chem.* **2011**, 3 (3), 216-222.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Synthesis of tetraaryl-1,4-dihydropyrrolo[3,2-*b*]pyrrole and application as a photoinitiator from 3D priting

Maria Laura Gallerani Linheira,[1*] Lucas Michelão Martins,[2] Vitor Fernandes Moreno and [3]Luiz Carlos da Silva Filho.

1) Departament of Chemistry, São Paulo State University (UNESP), School of Sciences, 17033-360, Bauru, São Paulo, Brazil

e-mail: maria.gallerani@unesp.br

Keywords: *Photoinitiator, photopolymerization, polymer.*

ABSTRACT

Photopolymerization is a technique that uses light energy to produce polymers; macromolecules formed from monomers. For the reaction to occur, the presence of a photoinitiator that absorbs a certain wavelength is necessary, producing radicals that initiate polymerization. This work developed the synthesis of derivatives of tetraaryl-1,4-dihydropyrrolo[3,2-b]pyrrole to use them as photoinitiators, in the polymerization of monomers widely used in dental restorations. capable of producing materials in very short time intervals. The following were tested: urethane dimethacrylate (UDMA), dimethacrylatetriethyleneglycol (TEG-DMA), and dimethacrylateglycerol (BIS-GMA), in addition to mixtures of these monomers (Figure 01), in order to simulate the use of the photoinitiator in dental resins. Promising results were observed with the mixture of BIS-GMA with TEG-DMA, with good polymer rigidity in less than 100 seconds of resin exposure to ultraviolet light irradiation.

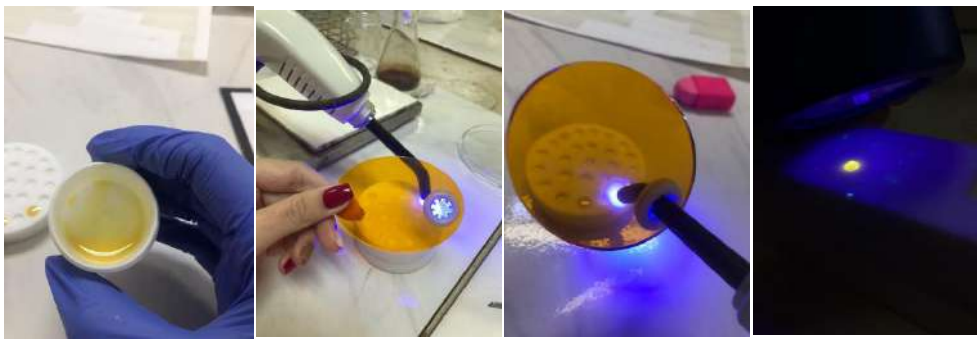


Figure 01. Photopolymerization using pyrrole-pyrroles and UDMA, BIS-DMA and TEG-DMA.

ACKNOWLEDGEMENTS

The authors acknowledge financial support from the CNPq (Process 134060/2022-9).

REFERENCES

1 Xu, Y.; Chen, Y.; Liu, X.; Xue, S. ACS Omega. 2021, 6, 20902.
2 Martins, L.M.; Vieira, S. F.; Baldacim, G.B.; Bregadiolli, B.A.; Caraschi, J.C.; Batagin-Neto, A.; Silva-Filho, L. C. Dyes Pigm. 2018, 148, 81.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Synthesis of New Aromatic Compounds Derived from Renewable Sources

Bruna Butke de Souza,[1] Pedro Dominguez Branco,[1] Camila Souza Santos[1] and Julio Cezar Pastre.[1*]

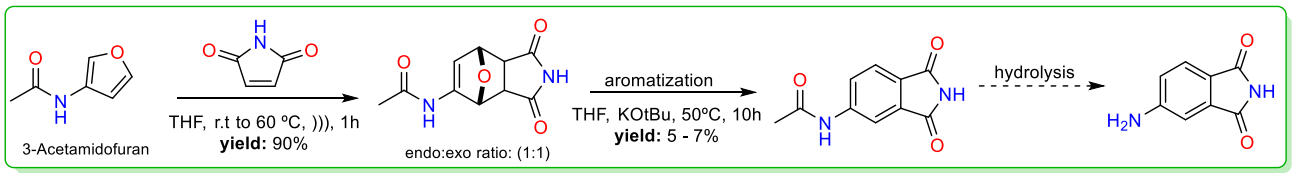
1) Institute of Chemistry (IQ), University of Campinas – UNICAMP, 13083-970, Campinas, SP – Brazil

****e-mail: jpastre@unicamp.br***

Keywords: *Aromatic Compounds, Renewable Sources, Chitin.*

ABSTRACT

Since the beginning of the chemical industry, aromatic compounds have played a crucial role in the production of high added-value chemicals. Currently, fossil carbon sources are still the predominant starting materials for the synthesis of aromatic compounds.[1] In this sense, our goal is to provide the preparation of aromatic compounds from renewable sources. Chitin biomass is a rich renewable resource that widely exists in crustacean shells. Chitin has the potential for obtaining nitrogen-containing derivatives, such as *N*-acetyl-glucosamine (**NAG**).[1,2] 3-Acetamidofuran (**3AF**) is obtained from **NAG** and has a wide application prospect, because the acetyl-protected amine can be easily transformed.[3] Bearing this in mind, the application of the furan derivative (**3AF**) in sequential Diels-Alder and aromatization reactions can inspire a new environmentally-safe approach to obtain nitrogenated aromatic compounds, as shown in **Scheme 1**.



Scheme 1. Synthetic route for the production of nitrogenated aromatic compounds from the chitin-derived furan **3AF**.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge financial support from São Paulo Research Foundation, FAPESP (Awards N.: BBS, 2023/01238-2; PDB, 2023/01232-4; CSS, 2022/00774-5; JCP, 2021/06661-5) and the Brazilian National Council for Scientific and Technological Development, CNPq.

REFERENCES

[**1**] Santos, C. S., Matiolli, R. R.; Baptista, J. S.; Silva, V. H. M.; Browne, D. L.; Pastre, J. C. *Green Chem.*, **2023**, Advance Article. DOI: https://doi.org/10.1039/D3GC00272A

[**2**] Zhou D., Shen D., Lu W., Song T., Wang M., Feng H., Shentu J., Long Y. Molecules, 2020, 25, 541.

[**3**] Lin, C., Yang, H., Gao, X., Zhuang, Y., Feng, C., Wu, H., Gan, H., Cao, F., Wei, P., Ouyang, P. ChemSusChem, **2023**, e202300133.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

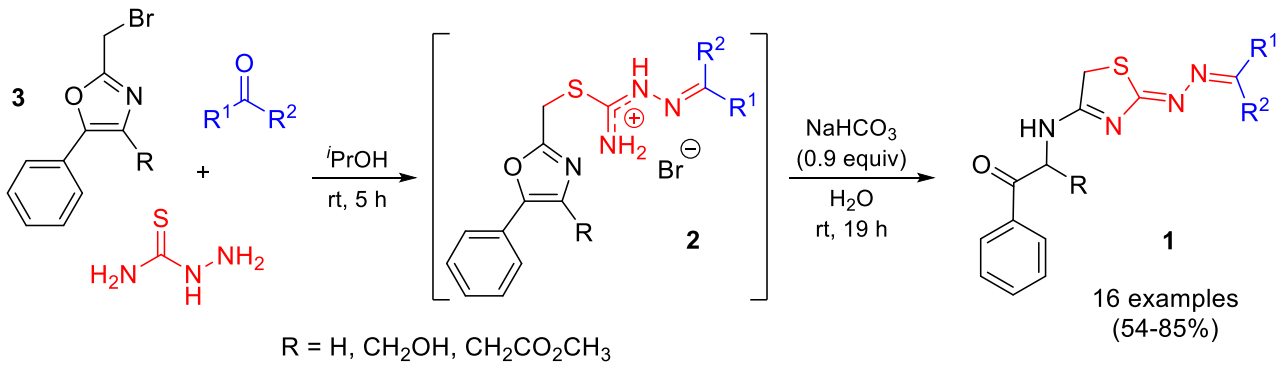
Synthesis of 2-hydrazono-3-thiazolines through a novel one-pot multicomponent/rearrangement process from 2-substituted oxazoles

Giovana da S. Ramos,* Thaís A. Rossa, Marcus M. Sá
Laboratório de Metodologia e Síntese Orgânica (MESOLab)
Departamento de Química, Universidade Federal de Santa Catarina, Florianópolis-SC 88040-900
****e-mail: ramos.d.s.giovana@gmail.com***

Keywords: *azoles, multicomponent synthesis, rearrangement of oxazoles*

ABSTRACT

2-Hydrazino-substituted thiazoles are known to have antioxidant[1,2] and antifungal[3,4] activities. During our ongoing studies dealing with the preparation of 2-(isothioureidomethyl)oxazoles **2** and analogues of biological relevance,[5] we observed an unexpected acid-catalyzed oxazole ring opening with subsequent cyclization to give functionalized 2-hydrazono-3-thiazolines **1** (Scheme). This new rearrangement of oxazoles poses an interesting discovery on the electrophilicity of the oxazolic C-2.[6] The reaction was investigated in more detail and was further optimized to give the corresponding thiazolines **1** as the main product in good to moderate yields (85-54%) from 2-(bromomethyl)oxazole **3**. The transformation was best conducted through two consecutive steps. First, oxazole **3**[7] was treated with thiosemicarbazide and a carbonyl compound to furnish the multicomponent adduct **2**. Then, the addition of a mild aqueous base in sub-equivalent quantities allowed a smooth self-catalyzed ring-opening/ring-closure process to 2-hydrazono-3-thiazolines **1**. This one-pot multicomponent/rearrangement process tolerates a wide range of substitution patterns and different functional groups to give a set of 16 thiazolines **1** as stable crystalline solids.



R = H, CH_2OH, $CH_2CO_2CH_3$
R^1 = C_6H_5, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 2-BrC_6H_4, 4-$NO_2C_6H_4$, (*E*)-C_6H_5CH=CH, CH_3
R^2 = H, CH_3

Scheme. Synthesis of 2-hydrazono-3-thiazolines **1** from the rearrangement of oxazoles **2**.

ACKNOWLEDGEMENTS

CNPq, CAPES, FAPESC, INCT-Catálise

REFERENCES

[1] Resende, M. F.; Lino, C. I.; Souza-Fagundes, E. M.; Rettore, J. V. P.; Oliveira, R. B.; Labanca, R. A. *Braz. J. Pharm. Sci.* **2019**, *55*, e18218.
[2] Shih, M.-H.; Su, Y.-S.; Wu, C.-L. *Chem. Pharm. Bull.* **2007**, *55*, 1126-1135.
[3] Lv, Q.-Z.; Ni, T.-J.-H.; Li, L.-P.; Li, T.; Zhang, D.-Z.; Jiang, Y.-Y. *Front. Cell. Infect. Microbiol.* **2020**, *10*, 578956.
[4] Carradori, S.; Secci, D.; Bolasco, A.; Rivanera, D.; Mari, E.; Zicari, A. Lotti, L. V.; Bizzarri, B. *Eur. J. Med. Chem.* **2013**, *65*, 102-111.
[5] Assunção, L. S.; Kretzer, I. F.; Restrepo, J. A. S.; Mello Jr, L. J.; Silva, A. H.; Oliveira, E. M.; Ferreira, M.; Sá, M. M.; Creczynski-Pasa, T. B. *Biochim. Biophys. Acta – Gen. Subj.* **2019**, *1863*, 1332-1342.
[6] LaMattina, J. L.; Mularski, C. J. *Tetrahedron Lett.* **1984**, *25*, 2957-2960.
[7] Rossa, T. A.; Suveges, N. S.; Sá, M. M.; Cantillo, D.; Kappe, C. O. *Beilstein J. Org. Chem.* **2018**, *14*, 506-514.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Synthesis of cinnamic acid derivatives with potential application as myotoxin inhibitors.

Letícia Santos Bezerra,[1*] **Lucas Michelão Martins**,[1] **Vitor Fernandes Moreno**,[1] **Luiz Carlos da Silva Filho**[1,]

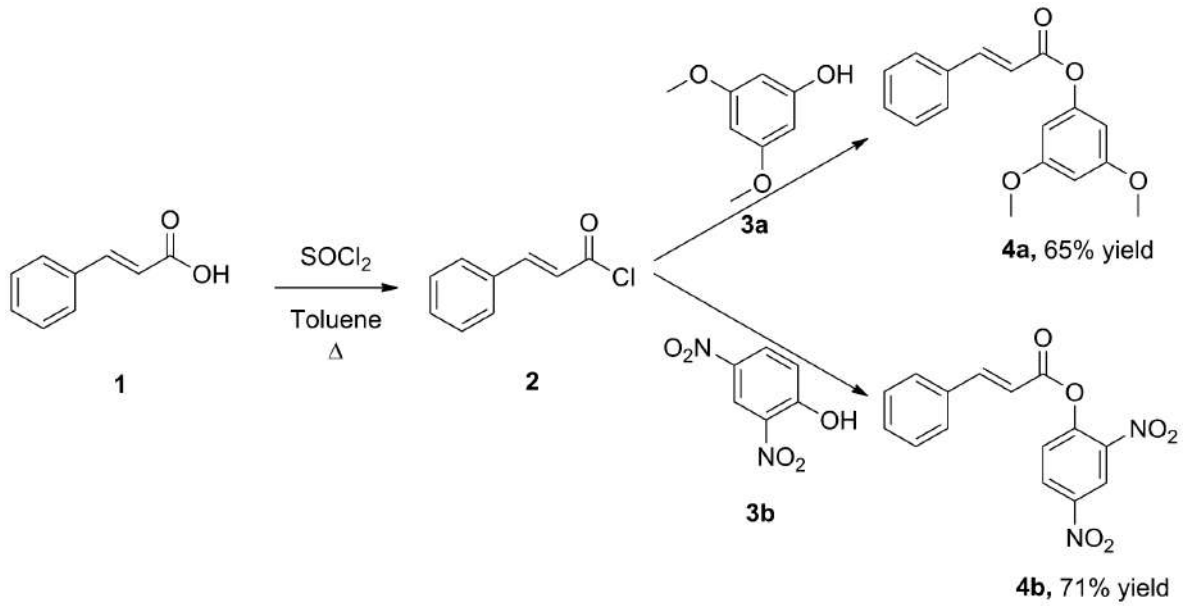
1) Department of Chemistry, São Paulo State University (UNESP), School of Sciences, 17033-360, Bauru, São Paulo, Brazil

****e-mail: leticia.s.bezerra@unesp.br***

Keywords: *derivatives cinnamic acid, myotoxin inhibitors.*

ABSTRACT

This work aimed to synthesize derivatives of cinnamic acid, a natural product obtained from cinnamon oil and coca leaves, that belongs to the group of auxins, vegetables responsible for regulating cell growth and differentiation, and some of its derivatives play an important role in the defense of plants against the attack of microorganisms and insects.[1] It can be used as myotoxin inhibitors of snakes poisoning, which is quite prevalent in Brazil and results in amputation cases. The main objective of this work was to synthesize new derivatives of cinnamic acid that have polar groups in their structure that can increase solubility in the application of biological potential as inhibitors of botropic myotoxins (scheme 1).[2-3]



Scheme 1. Synthesis of derivatives of Cinnamic acid

The reactions yielded solid products which were recrystallized and the melting point was performed to confirm their nature. These samples will be tested for biological activity.

ACKNOWLEDGEMENTS

The authors would like to thank Fapesp (20/10143-7), CNPq and FEPAF for their financial support.

REFERENCES

[1] THIMANN, K. V. The Auxins. IN: WILKINS, M. B. Physiology of plant growth and development. McGraw-Hill, London, **1969,** p. 2-45.
[2] DE LIMA, L. F. G.; BORGES, R. J.; VIVIESCAS, M. A.; FERNANDES, C. A. H.; FONTES, M. R. M. Structural studies with BnSP-7 reveal an atypical oligomeric conformation compared to phospholipases A2-like toxins. Biochimie, **2017**, v. 142, p. 11-21.
[3] FERNANDES, C. A. H.; CARDOSO, F. F.; CAVALCANTE, W. G. L.; SOARES, A. M.; DAL-PAI, M.; GALLACI, M.; FONTES, M. R. M. Structural Basis for the Inhibition of a Phospholipase A2-Like Toxin by Caffeic and Aristolochic Acids. PLoS ONE, **2015** v. 10, p. 1-19.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Desymmetrization of olefins catalyzed by Ni(0).

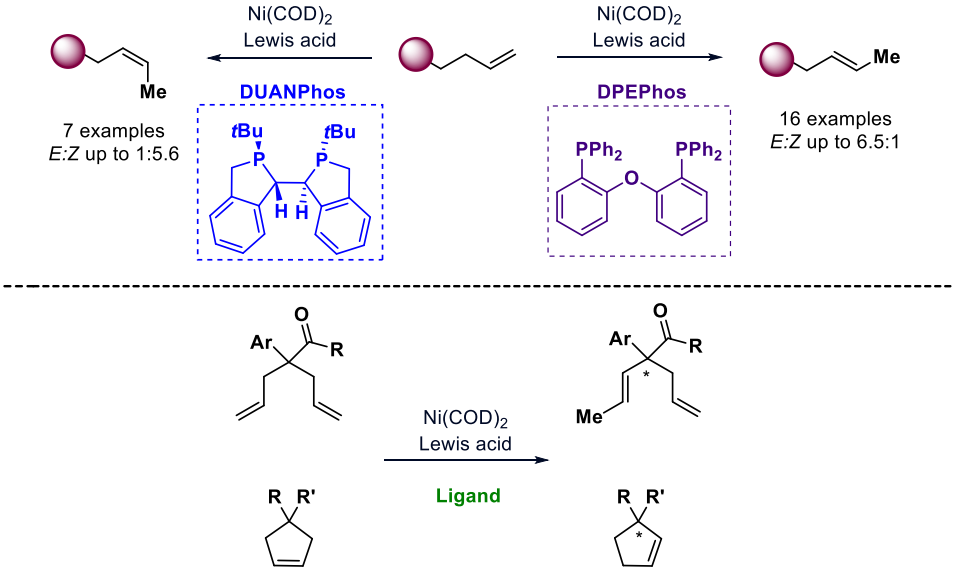
Eduardo J.C. Junior (PG),[1] Henrique S. Almeida (IC),[1] Caio C. Oliveira (PQ).[1]

[1]Institute of Chemistry, University of Campinas (UNICAMP)
e230035@dac.unicamp.br; h172265@dac.unicamp.br; caio.oliveira@unicamp.br

Keywords: *Catalysis, Olefin Isomerization, Nickel, Lewis Acid.*

ABSTRACT

The combination of Ni(0) and Lewis Acid (LA) successfully allowed the transposition of terminal double bonds to yield 1,2-alkenes. Interestingly, only one migration was observed, even when further migrations would lead to a more stable, conjugated isomer.[1] Careful ligand choice allowed the stereocontrol for these reactions. While DPEPhos produce *E*-products, DUANPhos produce *Z* isomers. The success of this method inspired the development of a desymmetrization protocol in route to more complex olefins. Bisallylic and cyclic substrates were successfully isomerized and its enantioselective version is ongoing.



Scheme 1. Stereoselective monotransposition of double bonds.

ACKNOWLEDGEMENTS

FAPESP (2019/00080-0)

REFERENCES

(1) Carvalho-Junior, E. J.; Oliveira, C. Nickel-Catalyzed Double Bond Transposition under Kinetic Control. ChemRxiv November 25, 2022. https://doi.org/10.26434/chemrxiv-2022-w9n02.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Three Component Arylsulfonylation of 2,3-dihydrofuran and Vinyl Esters Via Ni/Photoredox Dual Catalysis

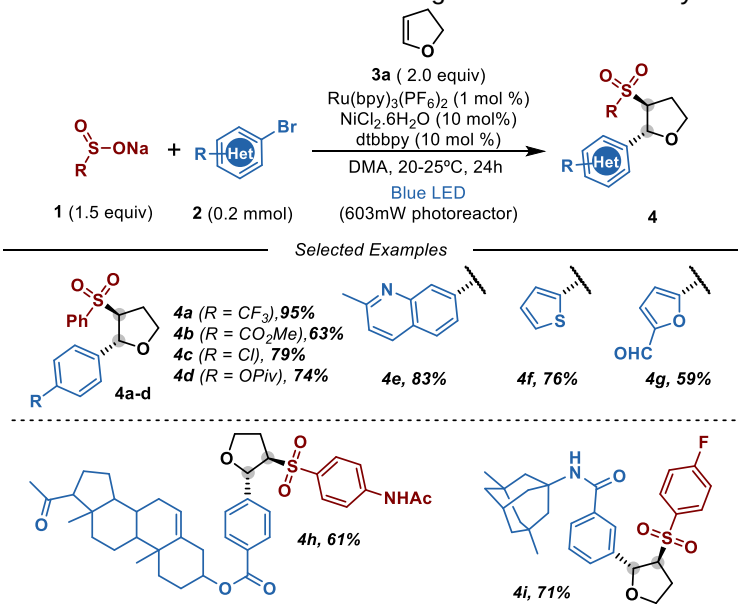
Lucas V. B. L. Pugnal,[1]* Kimberly B. Vega,[1] Emanuele F. Pissinati,[1] José Tiago M. Correia,[1] Julio Zukerman-Schpector,[1] Ruben Martin,[2] and Márcio W. Paixão[1]*

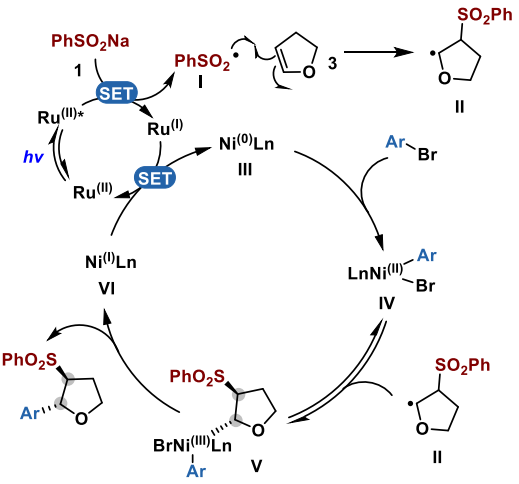
1) First affiliation: Department of Chemistry, Federal University of São Carlos, UFSCar, 13565-905
2) Second affiliation*: Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, *43007

e-mail: lucasloss96@gmail.com; mwpaixao@ufscar.br
Keywords: *arylsulfonylation, metallaphotoredox, 1,2-difunctionalyzation, dual catalysis*

ABSTRACT

Development of novel cross-coupling protocols has remained in the academia focus since seminal reports in this field, which rendered the 2010 chemistry Nobel prize for Heck, Negishi and Suzuki. In the past few years, many research groups worked in order to combine different types of catalysis, which led to development of systems we now call metallaphotoredox, in which transition metal and photocatalysis are conveniently merged.[1] Such combination is highly interesting once it can merge both catalytical cycles in a synergistic way, mitigating their main individual disadvantages as well as paving the way for new reactivities, unreachable by both methodologies alone.[1] Among its numerous applications, intermolecular alkene difunctionalization has been widely explored in recent years.[2] In this context, a dual photocatalytic arylsulfonylation of electron-rich alkenes is described. By combining sulfinate salts, (hetero)-aryl-bromides and 2,3-dihydrofuran under Ru and Ni dual catalysis, over 35 examples of aryl-sulfonylated scaffolds could be obtained in good to excellent yields, under mild reaction conditions and high diastereoselectivity.





ACKNOWLEDGEMENTS

We are grateful to the Brazilian funding agencies CNPq (INCT Catálise, 444061/ 2018-5, the Universal Project 405052/2021-9) and FAPESP (2021/06099-5 for MWP; 2020/09353-7 for LVBLP). This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - code 001.

REFERENCES

[1] Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. *Nat. Rev. Chem.* **2017**, 52, 1-18.
[2] a) Zhu, C.; Yue, H.; Chu, L.; Rueping, M. *Chem. Sci.* **2020**,11, 4051-4064; b) Badri, S. O.; Molander, G. A. *Chem*. **2020**, 6, 1327–1339.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Shining Light on Peptide Modification: Photocatalytic Difluoroacetylation and Difluoroamidation of Tryptophan-Containing Peptides

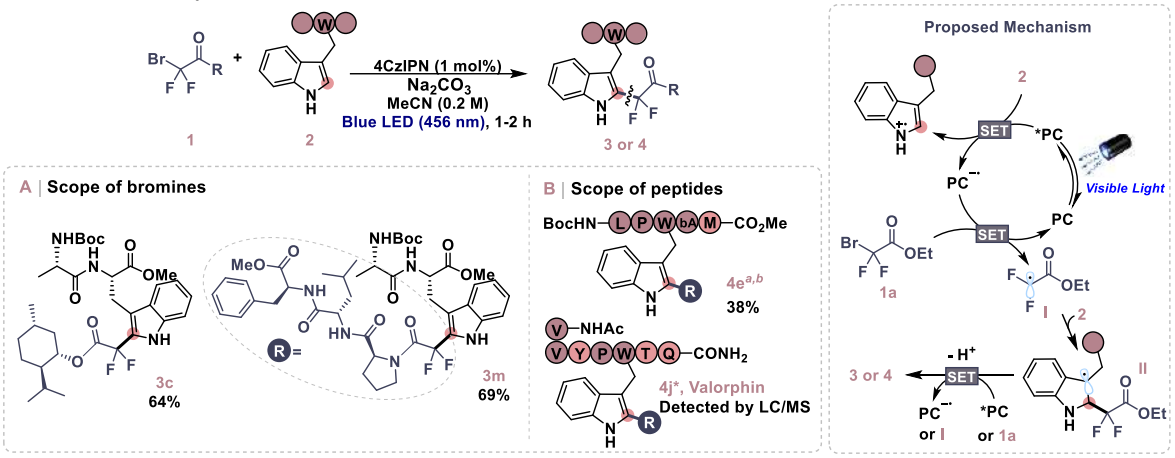
Emanuele F. Pissinati,[1]* Lucas V. B. L. Pugnal,[1] Iva S. de Jesus,[1] Rafaely N. Lima,[1] José A. C. Delgado,[1] Roberto G. S. Berlinck,[2] and Márcio W. Paixão[1]*

1) First affiliation: Laboratory for Sustainable Organic Synthesis and Catalysis, Department of Chemistry, Federal University of São Carlos, UFSCar, 13565-905
2) Second affiliation: Institute of Chemistry of São Carlos, University of São Paulo, USP, 13560-970

e-mail: ferrariemanuelep@gmail.com; mwpaixao@ufscar.br
Keywords: *α-gemdifluoro radicals, Tryptophan, Peptides, Photocatalysis*

ABSTRACT

Modifications on tryptophan (Trp) residues became an attractive alternative to peptide or protein functionalization due to its unique reactivity and low abundance in living system enabling chemoselective transformations.[1] The Trp core has been commonly functionalized using polar protocols.[2] More recently, selective photocatalytic C-H functionalization methods have also been reported.[3] Considering the distinctive properties and applications of fluorine-containing scaffolds in medicinal and agrochemistry, Chen,[4] Chiang[5] have developed the insertion of fluoroalkyl or perfluoroalkyl radicals into the indole ring of Trp. Building upon the foundation laid by previous research and recognizing the significance of fluorine-containing compounds, we present herein a novel protocol for the incorporation of α-gemdifluoro radicals into Trp-containing peptides. The reduction of bromodifluoroacetates and bromodifluoroamides generate the desired α-gemdifluoro radicals, followed by insertion into the indole ring. α-gemdifluoroamide radical derived from a tripeptide could be coupled with peptides containing reactive deprotected side chains, and a wide range of fluorinated compounds could be obtained with this protocol.



ACKNOWLEDGEMENTS

We are grateful to the Brazilian funding agencies CNPq (INCT Catálise, 444061/2018-5, the Universal Project 405052/2021-9) and FAPESP (2021/06099-5 for MWP; 2022/04597-0 for EFP). This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - code 001.

REFERENCES

[1] Bottecchia, C.; Noël, T. *Chem. Eur. J.* **2019**, 25, 26-42.
[2] (a) Wang, W.; Lorion, M.M.; Shah, J.; Kapdi, A.R.; Ackermann, L. *Angew. Chem. Int. Ed.* **2018**, 57, 14700-14717; (b) Antos, J.M.;McFarland, J.M.; Ivarone, A.T.; Francis, M. B. *J. Am. Chem. Soc.* **2009**, 131, 6301-6308; (c) Petersen, J.; Christensen, K.E.; Nielsen, M.T.; Mortensen, K.T.; Komnatnyy, V.V.; Nielsen, T.E.; Qvortrup, K. *ACS. Comb. Sci.* **2018**, 20, 344-349
[3] (a) Laroche, B.; Tang, X.; Archer, G.; Di Sanza, R.; Melchiorre, P. *Org. Lett.* **2021**, 23, 285-289; (b) Lima, R. N.; Delgado, J. A. C.; Bernardi, D. I.; Berlinck, R. G. S.; Kaplaneris, N.; Ackermann, L.; Paixão, M. *Chem. Commun.*, **2021**, *57*, 5758-5761.
[4] Wang, Y.; Wang, J.; Li, GX.; He, G.; Chen, G. *Org. Lett.* **2017**, 19, 1442-1445.
[5] Ding, B.; Weng, Y.; Liu, Y.; Song, C.; Yin, L.; Yuan, J.; Ren, Y.; Lei, A.; Chiang, CW. *Eur. J. Org. Chem.* **2019**, 7596–7605.
[6] Rahimidashaghoul, K.; Klimánková, I.; Hubálek, M.; Matoušek, V.; Filgas, J.; Slavíček, P.; Slanina, T.; Beier, P. *ChemPhotoChem* **2021**, 5, 43-50.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

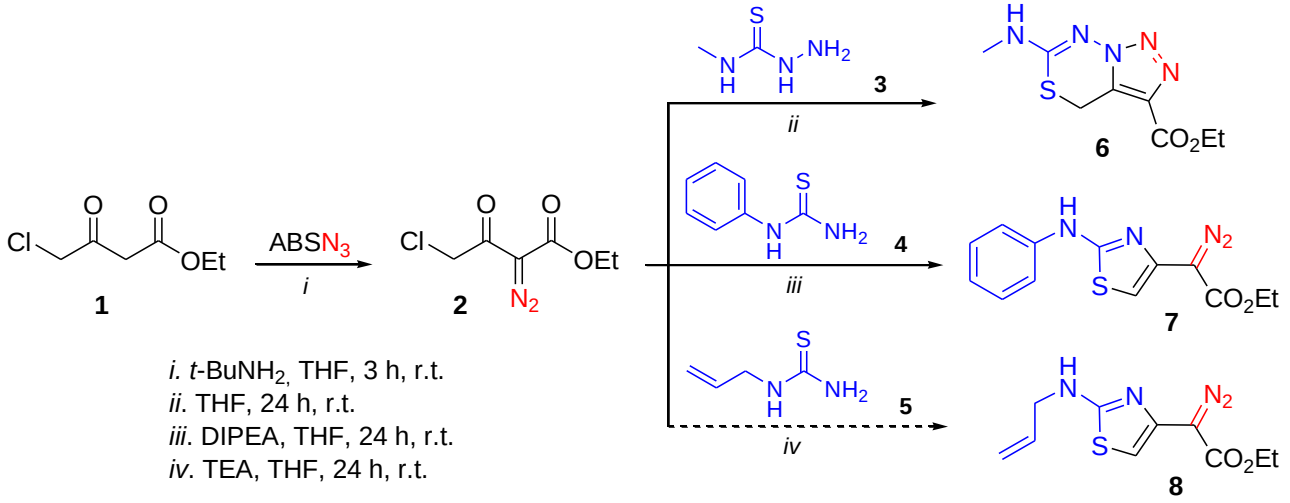
Preparation of diazo thiazoles through the reaction between a γ-chloro-α-diazo-β-ketoester and substituted thioureas

Cinara T. Avila, Marcus M. Sá
Laboratório de Metodologia e Síntese Orgânica (MESOLab)
Departamento de Química, Universidade Federal de Santa Catarina, Florianópolis-SC 88040-900
****e-mail: cinara.t.avila@hotmail.com***

Keywords: *α-Diazo esters, Thioureas, Thiazoles*

ABSTRACT

2-Aminothiazoles are related to a variety of biological activities.[1-3] While α-diazo carbonyl compounds are widely recognized as versatile building blocks,[4] studies dealing with the synthesis and reactivity of thiazoles bearing α-diazo carbonyl group are limited.[5] Herein, we report our achievements through the synthesis of α-diazo-α-thiazolyl esters from thioureas and α-diazoesters. The strategy involves the reaction between a substituted thiourea (**3-5**) and γ-chloro-α-diazo-β-ketoester **2**, readily obtained from **1** through our recently developed method[6,7] (Scheme). The use of the substituted thiosemicarbazide **3** led to the triazolo-thiadiazine **6**, which is in line with related reports.[8] However, treatment of **2** with phenylthiourea (**4**) and base led to the formation of diazo-substituted 2-aminothiazole **7**. Similar results were observed for allylthiourea (**5**), but the attempts to purify the expected diazo thiazole **8** were not successful. This study demonstrates the divergent reactivity of γ-chloro-α-diazo-β-ketoester **2** with substituted thioureas to give either bicyclic triazole **6** or diazo thiazoles **7,8**.



Scheme. Reaction of γ-chloro-α-diazo-β-ketoester **2** with thiourea derivatives (**3**, **4** and **5**).

ACKNOWLEDGEMENTS

CNPq, CAPES, FAPESC, INCT-Catálise

REFERENCES

[1] Jakopin, S. *Chem.-Biol. Interact.* **2020**, *330*, 109244.
[2] Pathania, S.; Narang, R. K.; Rawal, R. K. *Eur. J. Med. Chem.* **2019**, *180*, 486-508.
[3] Santana, T. I.; Barbosa, M. O.; Gomes, P. A. T. M.; Cruz, A. C. N.; Silva, T. G.; Leite, A. C. L. *Eur. J. Med. Chem.* **2018**, *144*, 874-886.
[4] Wang, J. *Tetrahedron Lett.* **2022**, *108*, 154135.
[5] Padwa, A.; Sá, M. M.; Weingarten, M. D. *Tetrahedron* **1997**, *53*, 2371-2386
[6] Costin, T. A.; Dutra, L. G.; Bortoluzzi, A. J.; Sá, M. M. *Tetrahedron* **2017**, *73*, 4549-4559.
[7] Fantinel, M.; Valiati, N.; Moro, P. A. M.; Sá, M. M. *Tetrahedron* **2021**, *86*, 132081.
[8] Dar'in, D.; Khoroshilova, O.; Kantin, G.; Krasavin, M. *Synthesis* **2020**, *52*, 1266-1272.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Microwave Assisted Synthesis of 3-Acetamidofuran, a Chitin-Derived Platform Molecule

Pedro Dominguez Branco,[1] Bruna Butke de Souza,[1] Camila Souza Santos[1] and Julio Cezar Pastre[1,*]

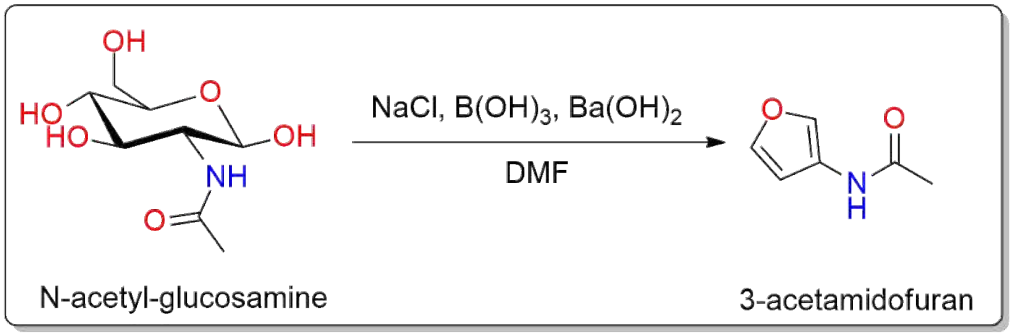
1) Institute of Chemistry (IQ), University of Campinas - UNICAMP, 13083-970, Campinas, SP - Brazil

****e-mail: jpastre@unicamp.br***

Keywords: *green chemistry, platform molecules, enabling technologies, 3-acetamidofuran.*

ABSTRACT

Renewable biomass can replace fossil resources to produce chemicals and materials using greener technologies. In this context, our research group has already identified that enabling technologies, such as continuous flow chemistry and microwave irradiation, are mandatory for the valorization of such materials. Indeed, many of the principles of Green Chemistry and Sustainability can be achieved by adopting new technologies that are inherently cleaner when compared to the current *status quo*. Chitin is the most abundant aminopolysaccharide polymer found in nature, serving as the primary structural component of the exoskeletons of crustaceans and insects.[1, 2] Chitin derivatives, such as *N*-acetyl-glucosamine (**NAG**)[3] can be used to prepare new platform molecules containing nitrogen atoms, like 3-acetamidofuran (**3AF**), which can be later used in a new, environmentally safe approach for the synthesis of nitrogenated aromatic compounds.[4]



Entry	NAG:NaCl:$B(OH)_3$:$Ba(OH)_2$	Concentration (mol L^{-1})	Temperature (ºC)	Time (min)	Conditions	Yield (%)
1	(1 : 2 : 1 : 0.15)	0,20	180	120	Sealed tube	**26**
2	(1 : 2 : 1 : 0.30)	0,20	180	20	Sealed tube	**30**
3	(1 : 2 : 1 : 0.15)	0,45	200	20	MW	**19**
4	(1 : 2 : 1 : 0.15)	0,40	180	20	MW	**36**
5	(1 : 2 : 1 : 0.30)	0,20	180	20	MW	**30**

Figure 1: Conversion of NAG into 3AF.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge financial support from São Paulo Research Foundation, FAPESP (Awards N.: PDB, 2023/01232-4; BBS, 2023/01238-2; CSS, 2022/00774-5; JCP, 2021/06661-5) and the Brazilian National Council for Scientific and Technological Development, CNPq.

REFERENCES

[1] Elieh-Ali-Komi, D.; Hamblin, M. R. Int. J. Adv. Res. (Indore) 2016, 4, 411. [2] Chen, X.; Chew, S. L.; Kerton, F. M.; Yan, N. Green Chem. 2014, 16, 2204. [3] Santos, C. S., Mattioli, R. R., Baptista, J. S., da Silva, V. H. M., Browne, D. L., & Pastre, J. C. (2023). *Green Chem.* doi.org/10.1039/D3GC00272A [4] Lin, C., et al. *ChemSusChem* **2023**, e202300133.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Synthesis of α-difluoroglycosil bromides via visible-light photoredox 1,2-difunctionalization

Pedro A. M. Moro,[1] Kimberly B. Vega,[1] Emanuele F. Pissinati,[1]
Pedro H. R. Oliveira,[1] Márcio W. Paixão[1*]

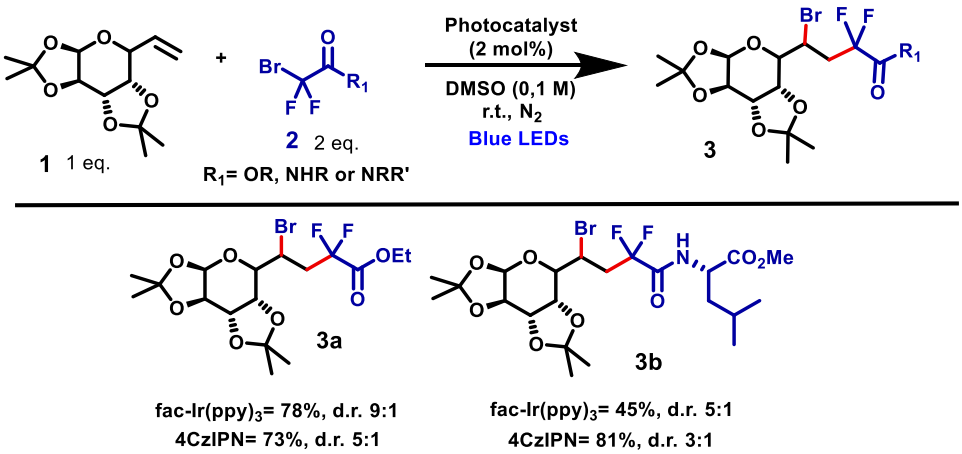
1) Laboratory for Sustainable Organic Synthesis and Catalysis, Department of Chemistry, Federal University of São Carlos – UFSCar, São Carlos, São Paulo, Brazil.

****e-mail:*** mwpaixao@ufscar.br

Keywords: photocatalysis, glycosyl olefins, 1,2-bromo-difluorofunctionalization

ABSTRACT

Photocatalytic alkene difunctionalization has emerged as a powerful synthetic strategy for building molecular complexity.[1] Regarding styrenes and acrylates, such reactions have been extensively explored.[2] Meanwhile, the chemical space of glycosyl olefins, that hold significant potential as valuable synthons remains elusive. Considering the biological appeal of saccharides[3] and the medicinal chemistry value of fluorinated molecules,[4] we herein present our preliminary results on the 1,2-bromo-difluorolkylation of glycol olefins, in a mild, metalfree and redox neutral manner. Under the optimized reaction conditions (Scheme 1), we successfully obtained the desired product in high yields with moderate stereoselectivity. Currently, our focus lies on exploring the generality of this transformation by examining different difluoro esters and difluoro amides, including drugs, natural products, and amino acids derivatives. Through these efforts, we anticipate the development of a powerful and efficient method for the synthesis of α-brominated-β-difluorinated glycosides, opening doors to novel possibilities in drug discovery and chemical synthesis.



Scheme 1. Synthesis of α-difluoroglycosil bromides.

ACKNOWLEDGEMENTS

We are grateful to the Brazilian funding agencies CNPq (INCT Catálise, Grants No 444061/ 2018-5 and Universal Project 405052/2021-9) and FAPESP (2021/06099-5 for MWP). This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil CAPES - Financial code 001.

REFERENCES

[1] Merino, E.; Nevado, C. Addition of CF_3 across unsaturated moieties: a powerful functionalization tool. *Chem. Soc. Rev.*, **2014**, *43*, 6598–6608.
[2] Cao, M.; Ren, X. Lu, Z. Olefin difunctionalizations via visible light photocatalysis. *Tetrahedron Letters,* **2015**, *56, 24,* 3732-3742.
[3] Shivatare, S. S.; Shivatare, V. S.; Wong, C. Glycoconjugates: Synthesis, Functional Studies, and Therapeutic Developments. *Chemical Reviews* **2022**, *122, 20*, 15603-15671.
[4] Johnson, B. M.; Shu, Y.; Zhuo, X.; Meanwell, N. A. Metabolic and Pharmaceutical Aspects of Fluorinated Compounds. *J. Med. Chem.* **2020**, *63, 12*, 6315–6386.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Cross Coupling Reactions: challenges in the orotate chemistry

Bruna F. Godoi[1,3], Jyoti Chauhan[2], Lori Ferrins[2] and Flavio da S. Emery[1,3]

1) Laboratory of Heterocyclic and Medicinal Chemistry (QHETEM), School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo (FCFRP/ USP), Brazil

2)* Laboratory of Neglected Tropical Diseases, Department of Chemistry and Chemical Biology, Northeastern University, *Boston, USA

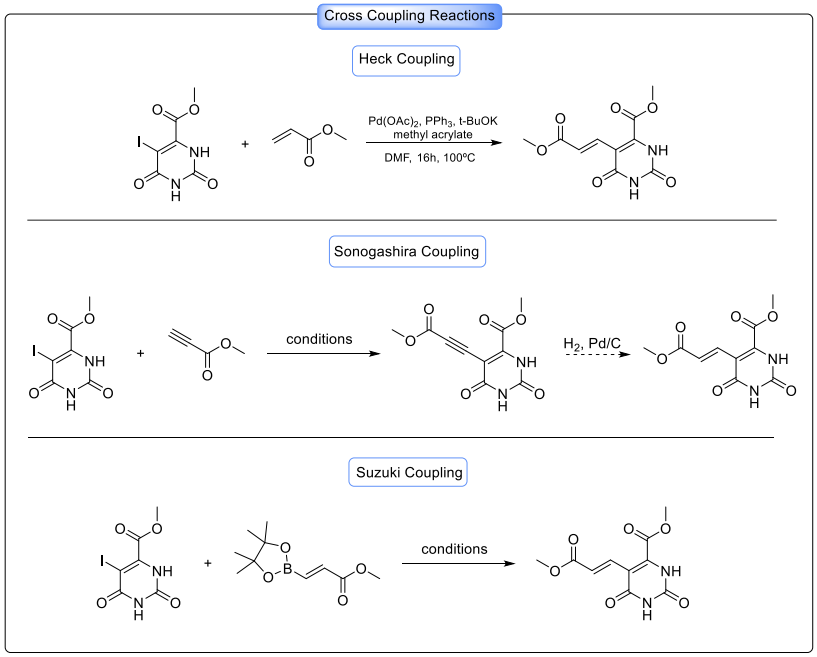
3) Center for the Research and Advancement of Fragments and Molecular Targets (CRAFT), FCFRP/USP, Brazil

****e-mail: bruna.fleck@usp.br***

Keywords: *Sonogashira, Heck, Orotate*

ABSTRACT

Three different cross coupling reactions were tested in order to achieve 5-substituted orotate analogs from the reaction between 5-iodo-methyl-orotate and methyl acrylate, methyl propiolate or methyl acrylate boronic acid (pinacol ester), respectively: Heck[1], Sonogashira[2], and Suzuki[3]. After several attempts changing conditions[4] as catalysts, ligands, bases, time, temperature and solvents, the best condition found was the Heck coupling using palladium acetate, triphenylphosphine, potassium tert-butoxide and dimethylformamide, for 16 hours at 100ºC. The reaction was monitored by LCMS (liquid chromatography-mass spectra), which showed 30% conversion to product. However, besides the challenges during the synthesis, the purification step proved to be even more difficult. Chromatographic columns with normal and reverse phase silica, basic silica (KP-NH®) and basic alumina were tested and none of them worked. The product got stuck inside the cartridge and nothing came out of the column. Because of negative results in the orotate synthesis and purification, no compound was isolated, and we are still trying a method to purify the analog.



Scheme 1. Different cross coupling reactions tested with orotate scaffold

ACKNOWLEDGEMENTS

FAPESP (processes numbers 2021/10084-3 and 2022/06007-6).

REFERENCES

[1] Heck R. *J. Am. Chem. Soc*.**1969**, 91 (24): 6707–6714.; [2] Sonogashira, K.; Tohda, Y.; Hagihara, N, *Tetrahedron Lett*., **1975**, 16 (50): 4467–4470.; [3] Miyaura, N.; Yamada, K. Suzuki, A. **1979**, *Tetrahedron Lett*., 20 (36): 3437–3440.; [4] Inaoka et al. *Bioorg Med Chem* **2017**. *V. 25(4)*: p. 1465-1470.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Synthesis, spectroscopic characterization by NMR, antioxidant activity, pharmacokinetic properties and ADME *in silico* of Azachalcones and Furanochalcones derivatives

Kerek, A. L[*]; **Antonichen, M. R; Guaringue, R. P; Kozan, L; Protachevicz, E; Sens, L; Fiorin, B. C**
Chemistry Department, State University of Ponta Grossa, 84030-900
e-mail: andre_kerek@hotmail.com

Keywords: *Synthesis, Chalcone, NMR.*

ABSTRACT

Chalcones are very important compounds in nature, being considered precursors of several flavonoids in the biosynthetic route.(1) In addition, obtaining these compounds by synthetic routes allows several modifications to be made in their structures to enhance biological activity. The presence of hydroxyl groups and the modification of an aromatic ring with the nitrogen or oxygen atom can increase several biological activities, such as antitumor, anti-inflammatory, antioxidant and antibacterial.(2) The objective of this work was the synthesis, spectroscopic characterization by Nuclear Magnetic Resonance (NMR), antioxidant activity, pharmacokinetic properties and ADME *in silico* of Azachalcones and Furanochalcones derivatives, containing hydroxyl or not and with an aromatic ring replaced by a ring with nitrogen or oxigen. The methodology used for the synthesis of the chalcones of interest and the results for yield, melting point, ADME *in silico* and DPPH are depicted in Figure 1.

Compound	Results
CHAL1	**Yield:** 63.0%. **m.p:** 152.0 – 155.2 °C. **Physicochemical properties *in silico*:** MW (208.26), NRBs (3), NHBAs (1), NHBDs (0), TPSA (17.07), Consensus Log $P_{o/w}$ (3.29), Water Solubility (Moderately Soluble). **ADME *in silico*:** GI (High), BBB (Yes), P-gp substrate (No), CYP1A2 (No), CYP2C19 (Yes), CYP2C9 (No), CYP2D6 (No), CYP3A4 (No), Log K_p (-5.38). **IC_{50} DPPH Inhibition (%):** 3483.13 mM.
CHAL2	**Yield:** 35.6%. **m.p:** 85.4 – 87.2 °C. **Physicochemical properties *in silico*:** MW (224.25), NRBs (3), NHBAs (2), NHBDs (1), TPSA (37.30), Consensus Log $P_{o/w}$ (3.13), Water Solubility (Moderately Soluble). **ADME *in silico*:** GI (High), BBB (Yes), P-gp substrate (No), CYP1A2 (No), CYP2C19 (Yes), CYP2C9 (Yes), CYP2D6 (No), CYP3A4 (No), Log K_p (-4.91). **IC_{50} DPPH Inhibition (%):** 593.32 mM.
CHAL3	**Yield:** 28.7%. **m.p:** 52.8 – 54.3 °C. **Physicochemical properties *in silico*:** MW (209.24), NRBs (3), NHBAs (2), NHBDs (0), TPSA (29.96), Consensus Log $P_{o/w}$ (2.58), Water Solubility (Moderately Soluble). **ADME *in silico*:** GI (High), BBB (Yes), P-gp substrate (No), CYP1A2 (Yes), CYP2C19 (Yes), CYP2C9 (No), CYP2D6 (No), CYP3A4 (No), Log K_p (-5.69). **IC_{50} DPPH Inhibition (%):** 772.28 mM.
CHAL4	**Yield:** 23.1%. **m.p:** 94.4 – 95.1 °C. **Physicochemical properties *in silico*:** MW (225.24), NRBs (3), NHBAs (3), NHBDs (1), TPSA (50.19), Consensus Log $P_{o/w}$ (2.38), Water Solubility (Soluble). **ADME *in silico*:** GI (High), BBB (Yes), P-gp substrate (No), CYP1A2 (Yes), CYP2C19 (Yes), CYP2C9 (No), CYP2D6 (No), CYP3A4 (No), Log K_p (-5.65). **IC_{50} DPPH Inhibition (%):** 56.04 mM.
CHAL5	**Yield:** 83.0%. **m.p:** 198.7 – 200.5°C. **Physicochemical properties *in silico*:** MW (209.24), NRBs (3), NHBAs (2), NHBDs (0), TPSA (29.96), Consensus Log $P_{o/w}$ (2.60), Water Solubility (Moderately Soluble). **ADME *in silico*:** GI (High), BBB (Yes), P-gp substrate (No), CYP1A2 (Yes), CYP2C19 (Yes), CYP2C9 (No), CYP2D6 (No), CYP3A4 (No), Log K_p (-5.48). **IC_{50} DPPH Inhibition (%):** 526.88 mM.
CHAL6	**Yield:** 29.4%. **m.p:** 101.5 – 102.3 °C. **Physicochemical properties *in silico*:** MW (214.22), NRBs (3), NHBAs (3), NHBDs (1), TPSA (50.44), Consensus Log $P_{o/w}$ (2.36), Water Solubility (Soluble). **ADME *in silico*:** GI (High), BBB (Yes), P-gp substrate (No), CYP1A2 (Yes), CYP2C19 (Yes), CYP2C9 (No), CYP2D6 (No), CYP3A4 (No), Log K_p (-5.48). **IC_{50} DPPH Inhibition (%):** 74.71 mM.
CHAL7	**Yield:** 75.3%. **m.p:** 111.5 – 112.9 °C. **Physicochemical properties *in silico*:** MW (199.21), NRBs (3), NHBAs (3), NHBDs (0), TPSA (43.10), Consensus Log $P_{o/w}$ (1.90), Water Solubility (Soluble). **ADME *in silico*:** GI (High), BBB (Yes), P-gp substrate (No), CYP1A2 (Yes), CYP2C19 (Yes), CYP2C9 (No), CYP2D6 (No), CYP3A4 (No), Log K_p (-6.06). **IC_{50} DPPH Inhibition (%):** 85.07 mM.

Figure 1. Reaction scheme and results for yield, melting point, ADME *in silico* and DPPH for Azachalcone and Furanochalcone derivatives.

ACKNOWLEDGEMENTS

The authors are thankful to CNPq and CAPES for research funding and C-LABMU and UEPG for all the structure made available.

REFERENCES

(1) Zhuang, C. et al. Chalcone: A Privileged Structure in Medicinal Chemistry. *Chem Rev* **2017**, *117* (12), 7762–7810.
(2) Karki, R. et al. Topoisomerase I and II Inhibitory Activity, Cytotoxicity, and Structure-Activity Relationship Study of Dihydroxylated 2,6-Diphenyl-4-Aryl Pyridines. *Bioorg Med Chem* **2015**, *23* (13), 3638–3654.
(3) Pereira, V. R. D. et al. In Vitro and in Vivo Antischistosomal Activities of Chalcones. *Chem Biodivers* **2018**, *15* (12), cbdv.201800398.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Comparison of synthesis methods and antioxidant evaluation of substituted *o*-furanochalcones

Eduardo Protachevicz*, **André Luis Kerek, Raphaela Pereira Guaringue, Magno Roger Antonichen, Larissa Kozan, Barbara Celânia Fiorin**

Chemistry Department, State University of Ponta Grossa, 84030-900

****e-mail: eduardo.protachevicz@yahoo.com***

Keywords: *Furanochalcone, ultrasound, synthesis*

ABSTRACT

Chalcones are compounds that have an α,β-unsaturated carbonyl system between two benzene rings (Figure 1)[1]. Compounds analogous to chalcones are the furanochalcones, in which one of the benzene rings is replaced by a furan ring (Figure 2)[2].

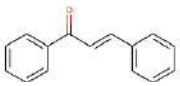


Figure 1. Chalcone

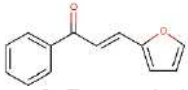
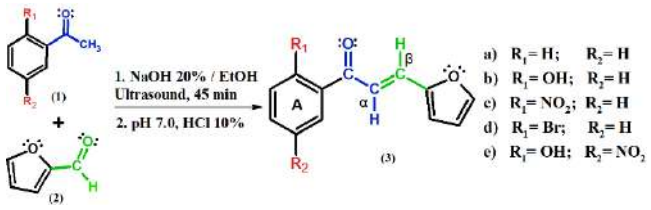


Figure 2. Furanochalcone

Sonochemistry can bring benefits to chemical reactions, such as: decreasing the time and number of reagents needed, increase yield and selectivity[3]. The objective of this work was to synthesize a series of ortho-substituted furanochalcones according to the Claisen Schmidt reaction[4] using two different procedures. At one moment, conventional magnetic stirrer was used, and at the other, an ultrasound probe (Scheme 1). Ultrasound syntheses were more effective.



	Ultrasound	Magnetic stirrer
Reaction time	40 minutes	24 hours
Yield	85-92%	49-58%
Extraction with organic solvent	No	Yes
Purity (NMR)	↑	↓

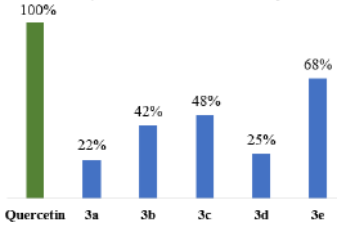
Scheme 1. Reaction Conditions

NMR spectra (^1H,^{13}C, DEPT90, HMBC and HMQC) were acquired. A study of the antioxidant activity against the DPPH methodology (Table 1) and reduction of the phosphomolybdenum complex (Figure 3) were carried out. The compound with the highest antioxidant capacity were 3e, furanochalcone with OH and NO_2 groups.

Table 1. Results IC_{50} DPPH method

Sample	IC_{50} ($mmol.L^{-1}$)
Quercetin	3.31
3a	35.44
3b	28.85
3c	20.48
3d	32.21
3e	16.06

Figure 3. Results (%inhibition) of the phosphomolybdenum complex reduction analysis



ACKNOWLEDGEMENTS

CAPES, CNPQ, UEPG, C-LabMu/UEPG, LEsCaM.

REFERENCES

[1] GARCIA, E. et al. Medicinal Chemistry Research, **2019**, 28(4), p. 608–622.
[2] Mishra, R.; et al. Der Pharma Chemica, **2011** p. 38-54.
[3] Davidson, R. S., T. S., Ed.; The Royal Society of Chemistry; Cambridge, **1990**; 6, p. 69.
[4] SIVAKUMAR, P. M. et al. **2011**, Medicinal Chemistry Research, v.20, p. 482-492.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Silver-catalyzed stereoselective Meyer-Schuster-type rearrangement: Synthesis of densely substituted α-iodo, α, β-unsaturated thioesters

José L. Lopes,[1,*] Lucas L. Baldassari[1] and Diogo S. Lüdtke[1]

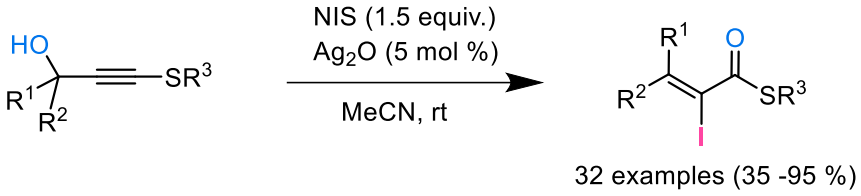
[1]***Instituto de Química, Universidade Federal do Rio Grande do Sul, UFRGS, Av. Bento Gonçalves 9500, 91501-970, Porto Alegre, RS, Brazil.***

*** Corresponding Author: joselopes8226@gmail.com**

Keywords: *α-iodo-α, β -unsaturated thioesters, Meyer-Schuster-type rearrangement, synthesis.*

ABSTRACT

α, β-unsaturated thioesters steadily gaining strong attention in organic synthesis as building block for new bond formation.[1] Given its high importance, numerous methods for their preparation were developed, such as aldol reactions[2] and thiocarbonylation of alkynes.[3] However, many of these methods present regioselectivity problems and form complex mixture of products. In this context, Meyer-Schuster rearrangement became valuable alternative, as it favors the formation of α, β-unsaturated carbonyl compound.[4] Recently, our research group applied the Meyer-Schuster rearrangement to transform propargyl thioalkyne in α-selanyl-α, β-unsaturated thioesters in presence of an electrophilic selenium species.[5] Herein, we developed new approach of Meyer-Schuster rearrangement for access α-iodo-α, β-unsaturated thioesters from propargyl thioalkyne using silver catalyst, *N*-iodosuccinimide as electrophilic iodine source in acetonitrile, at room temperature. The (*Z*)-α-iodo α, β-unsaturated thioester was isolated as the major product with moderate to excellent yields (35 – 95 %).



Scheme 1. Reaction scope

ACKNOWLEDGEMENTS

UFRGS, CAPES, LAMOCA, INCT Catálise

REFERENCES

[1] Rittner, A.; Joppe, M.; Schmidt, J. J.; Mayer, L. M.; Reiners, S.; Heid, E.; Grininger, M. *Nat. Chem.* **2022**, *14*, 1000-1006.

[2] Boateng, A.; Harada, T.; Ashikari, Y.; Nakajima, M.; Sugiura, M. *Tetrahedron Lett.* **2020**, *61*, 152280.

[3] Ai, H. J.; Lu, W.; Wu, X. F. *Angew. Chem. Int. Ed.* **2021**, *60*, 17178-17184.

[4] Yoshimatsu, M.; Naito, M.; Kawahigashi, M.; Shimizu, H.; Kataoka, T. *J. Org. Chem*. **1995**, *60*, 4798-4802.

[5] Baldassari, L. L., Mantovani, A. C., Jardim, M., Maryasin, B., and Lüdtke, D. S. *Chem. Commun.*, **2021,** *57(1),* 117-120.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Synthesis of reduced graphene oxide conjugates with quinoline derivatives for application in solar cells

José Henrique Lazaro de Carvalho,[1*] Lucas Michelão Martins[1], Luiz Carlos da Silva Filho[1]

1) Departamento de Química, Faculdade de Ciências (FC) Universidade Estadual Paulista (UNESP), Campus Bauru

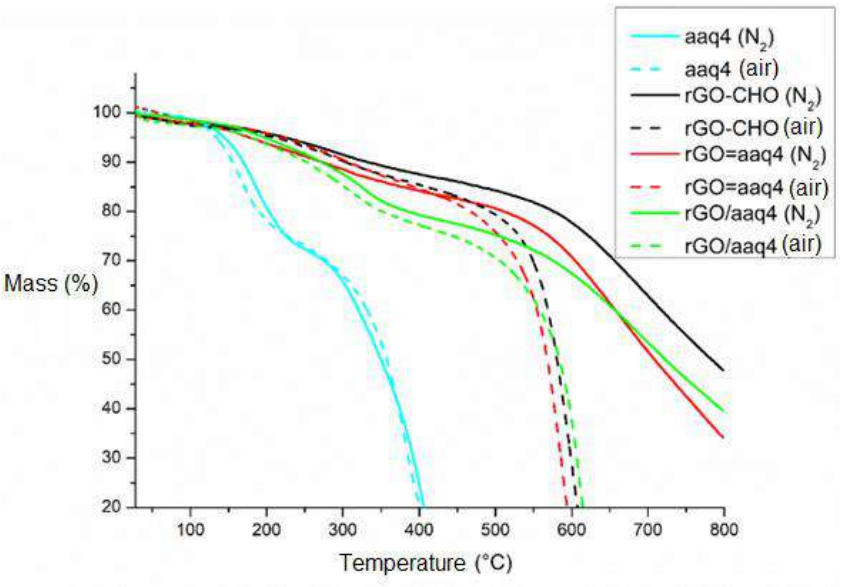
****e-mail: jose.h.carvalho@gmail.com***

Keywords: *quinoline, graphene oxide, solar cells*

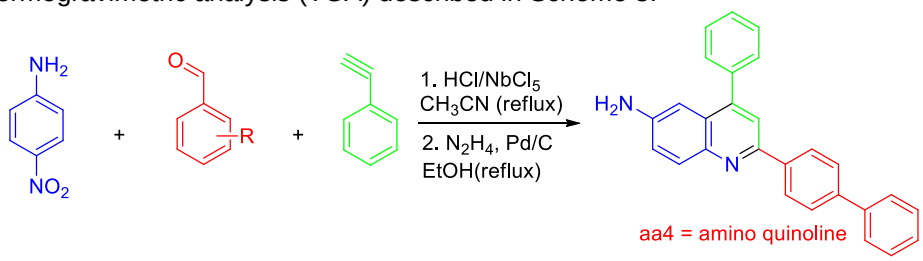
ABSTRACT

The global growing demand for clean, cheap, and efficient energy sources unequivocally make researchers look for better photovoltaic cell architectures[1,2]. This work proposes an organic photovoltaic cell (OPVs) based on reduced graphene oxide (rGO)[3] conjugates with quinoline derivatives. This will potentially join the π-donor-acceptor character of the azacompound with the thermal, and electric conductivity, and stability of the rGO creating in theory a good hole transfer material (HTM) for solar cell devices.

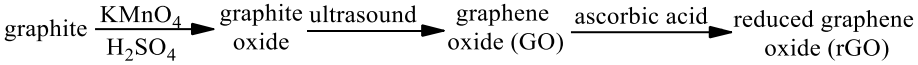
The quinoline derivatives were synthesized as described in Scheme 1. The rGO was prepared following the Scheme 2. Amino quinoline derivatives were then merged to create the conjugated. To ensure that the process work effectively, both chemical and physical preparations of the conjugated were submitted to thermogravimetric analysis (TGA) described in Scheme 3.



Scheme 3: Comparative thermogram of the compounds aaq4, rGO-CHO, rGO-CHO=aaq4 and rGO-CHO/aaq4.



Scheme 1: General reaction for production of amino-aryl-quinoline derivatives



Scheme 2: Procedure of synthesis of reduced graphene oxide using graphite as precursor[3].

ACKNOWLEDGEMENTS

We want to thank Capes, CNPq, FAPESP and FEPAF for financial support.

REFERENCES

[1] Cao, W. and J. Xue, Energy & Environmental Science, **2014**. 7(7): p. 2123-2144.
[2] Agency, K.W.E.S.d.I.E. http://www.iea.org/textbase/nppdf/free/2008/key_stats_2008.pdf
[3] Abdolhosseinzadeh, S., Asgharzadeh, H., & Seop Kim, H. Scientific Reports, **2015**, 5(1)

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

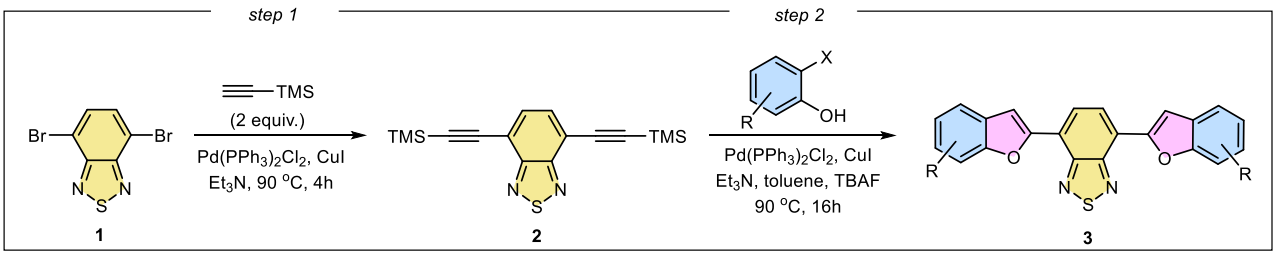
Synthesis of fluorescent functionalized benzothiadiazoles bearing benzofuranes

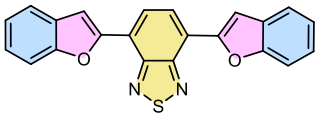
Hamilton Castigo Zimba* **and Angélica Venturini Moro**
Instituto de Química, universidade Federal do Rio Grande do Sul, UFRGS, CEP 91501-970
e-mail: hamiltonzimba@gmail.com

Keywords: fluorescent, benzothiadiazoles, *Sonogashira coupling, cyclization.*

ABSTRACT

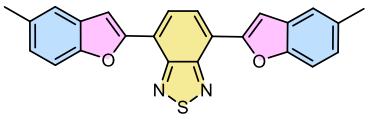
Herein we report the synthesis of fluorescent benzothiadiazoles functionalized with benzofurans. Initially, a Sonogashira coupling reaction was performed between dibrominated benzothiadiazole **1** and TMS-alkyne to obtain compound **2**.[1] After simple filtration, step 2 was performed with the initial addition of TBAF, to remove the TMS group. In addition to the Sonogashira coupling, forming a new C-C bond, cyclization also occurs with the formation of a new C-O bond and benzofuran **3a** with 95% yield. Attempts to perform both steps in a one-pot process have failed. Despite having several advantages, such as reducing the number of elementary operations and reducing the amount of solvent used, the one-pot process is challenging because unreacted materials and by-products remain in the reaction medium and might interfere or prevent the subsequent reaction.[2] Currently, the methodology is being expanded to obtain compounds with different substitution patterns. It was observed that the use of bromo-phenols instead of iodo-phenols resulted in a decrease in the isolated yields.





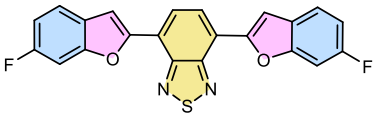
3a

95% yield (2 steps)
when X = I



3b

20% yield (2 steps)
when X = Br



3c

30% yield (2 steps)
when X = Br

ACKNOWLEDGEMENTS

We are grateful to CNPq, CAPES and INCT- Catálise for financial support.

REFERENCES

[1] Moro, A. V.; Ferreira, P. C.; Migowiski, P.; Rodembusch, F. S.; Dupont, J.; Ludtke, D. S. *Tetrahedron* **2013**, *69*, 201.
[2] (a) Broadwater, S. J.; Roth, S. L.; Price, K. E.; Kobaslija, M.; McQuade, D. T. *Org. Biomol. Chem.* **2005**, *3*, 2899. (b) Ajamian, A.; Gleason, J. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 3754.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

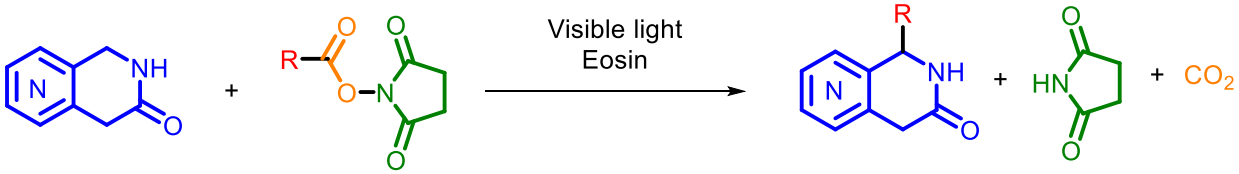
Decarboxylative alkylation of C(sp^3)−H bond in Naphthyridinones via photocatalysis

Temitayo .O. Alegbejo Price[1], Raul M. Novais,[1] Thiago dos Santos[1], Flavio da Silva Emery[1]
1) Department of Pharmaceutical Sciences, School of Pharmaceutical Sciences of Ribeirão Preto – FCFRP-USP, São Paulo, Brazil
e-mail: tayoalegbejo@usp.br

Keywords: *C(sp^3)−H bonds, Napthyridonone, visible-light.*

ABSTRACT

In recent years, numerous molecules that made it to preclinical candidacy failed during clinical trials due to ADME and pharmacokinetic problems such as solubility, bioavailability, and toxicity.[1] One important related motive accounts for the presence of more unsaturated rings giving the compounds a flat conformation, less flexibility, and, consequently, poor solubility besides the reduced ability to adopt an optimal configuration within the target receptors.[2] Currently, there is a need to transition from entirely flat unsaturated systems by incorporating partially unsaturated systems. To achieve so, visible light can be of great help to drive C(sp^3)−H selective functionalizations by decarboxylative alkylations. [3,4,5,6] This approach enables the direct modification of typically unreactive C−H bonds, using visible light as a gentle and environmentally friendly energy source.[7] Therefore, we intend to employ a sensitized dye and a semiconductor in the presence of visible light, to functionalize C(sp^3)−H bonds in Napthyridinones, an underexplored heterocyclic system (**Scheme 1**).



Scheme 1: The proposed synthetic route for the alkylation of Napthyridinones.

ACKNOWLEDGEMENTS

TWAS-CNPq-163813/2018, FAPESP, QHETEM, for the assistance, collaborations and scholarships granted.

REFERENCES

1. Kola, I and Landis, J. *Nat. Rev. Drug Discovery*, **2004**, 3, 711–716.
2. Lovering, F. *MedChemComm* **2013**, *4* (3), 515.
3. Fagnoni, M.; Dondi, D.; Ravelli, D.; Albini, A. *Chem. Rev*.**2007**, 107, 2725.
4. Xi, Y.; Yi, H.; Lei, A. *Org. Biomol. Chem*. **2013**,11, 2387.
5. Tellis, J. C.; Primer, D. N.; Molander, G. *A. Science* **2014**, 345, 433.
6. Balzani, V.; Bergamini, G.; Ceroni, P. *Angew. Chem., Int.Ed*. **2015**, 54, 11320.
7. Ren, L and Cong, H. *Org. Lett*. **2018**, 20, 3225−3228

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Conformational behavior and synthesis of chalcones derived from vanillin

Raphaela Pereira Guaringue,* **André Luis Kerek, Eduardo Protachevicz, Magno Roger Antonichen, Larissa Kozan, Barbara Celânia Fiorin**

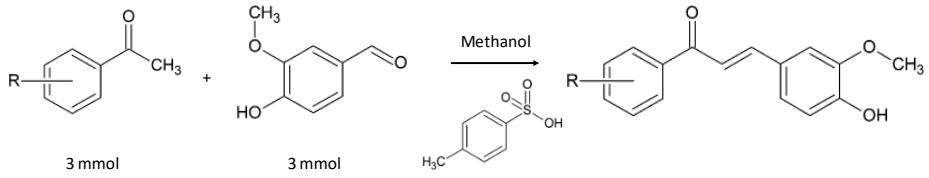
Chemistry Department, State University of Ponta Grossa, 84030-900

e-mail: raphaelaguaringue@outlook.com

Keywords: *Chalcone, Vanillin, NMR*

ABSTRACT

The antioxidant property of flavonoids and chalcones might present an expressive increase in the presence of hydroxyl groups in their structural aromatic rings. Such antioxidant potential is associated to a reduction in oxidative stress related to several diseases, including cancer[1]. In addition since some nitroaromatic compounds have cytotoxic, antibacterial and antifungal activities[2]. For these reasons, in this work we report the synthesis and conformational analysis of the chalcones shown in Figure 1. The compounds were synthesized and characterized by NMR spectroscopy. The presence of vinylic hydrogens doublets confirms the formation of chalcones. With theoretical calculations (GAUSSIAN 09 and NBO 5.9 programs) it was possible to determine the geometries involved in the equilibrium of these chalcones. The *s-cis* conformations were the most stable at equilibrium for both chalcones (Figure 2). These investigations are important, mainly because we select groups on aromatic rings that are potentially known to have pronounced biological activity.



Compoud	R	Yield (%)
Chal 1	4'NO_2	78
Chal 2	2'OH 5'NO_2	46

Figure 1. General reaction to obtain chalcones and yield obtained.

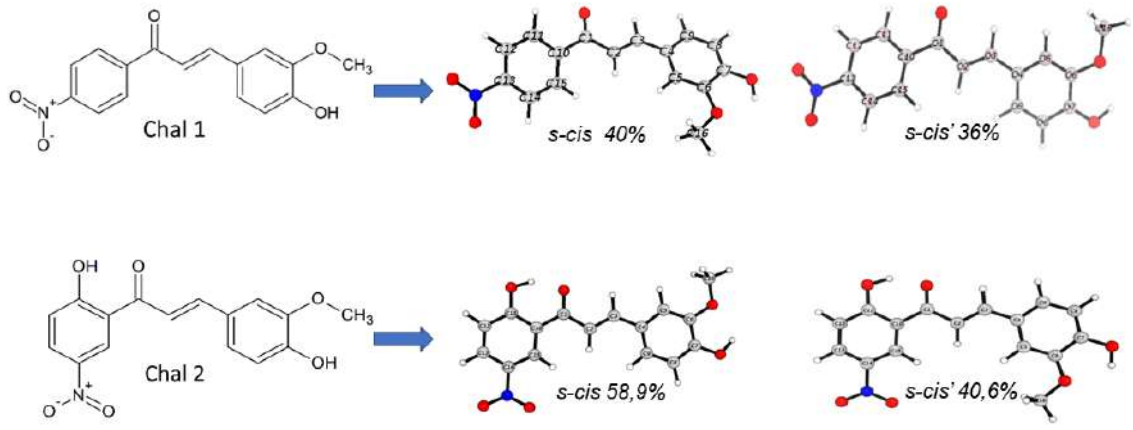


Figure 2. More stable conformations of chalcones.

ACKNOWLEDGEMENTS

CAPES, CNPQ, UEPG, C-LabMu UEPG

REFERENCES

[1] Kumar, S.; Pandey, A. K. Sci. World J. 2013, 16, 1.
[2] Ju, K.; Parales, R. E. *J. Clin. Microbiol*. 2010, *74*, 250.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

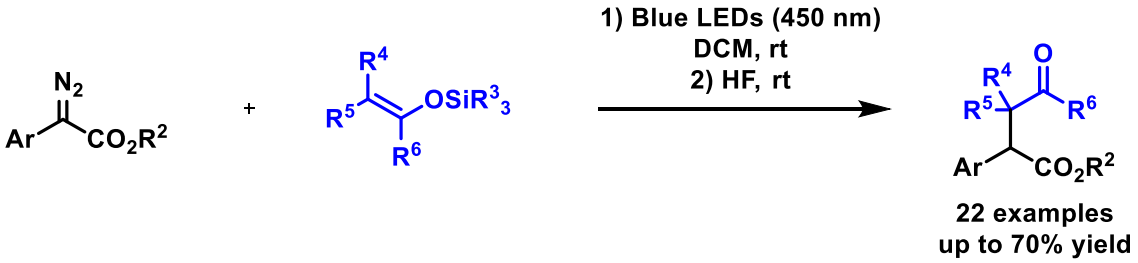
A Visible Light-Mediated Strategy for the Formal C-Alkylation of Silyl Enol Ethers with Aryldiazoacetates

Cariello, Guilherme[1*]; Gallo, Rafael D. C.[1]; Cormanich, Rodrigo A.[1]; Jurberg, Igor D.[1]
1) Institute of Chemistry, University of Campinas, Campinas, SP, Brazil.
****e-mail: g262805@dac.unicamp.br***

Keywords: Diazo Compounds, *C-C Bond Formation, Photochemistry*

ABSTRACT

Diazo compounds have been known to undergo UV light-mediated photolysis for several decades. However, recently, an especial class of donor-acceptor diazo compounds, aryldiazoacetates, have been uncovered to also absorb in the visible region of the electromagnetic spectrum. Therefore, upon visible light irradiation (typically employing blue light, ca. 440-485 nm), they undergo photolysis leading to highly reactive free carbene intermediates, which can be trapped with several reacting partners in productive organic transformations.[1-5] In this context, continuing our studies in this area, we became interested in investigating visible light-mediated C-C bond forming events between electron-rich olefins and aryldiazoacetates. In the current work, we report the synthesis of 18 examples of products derived from the formal α-alkylation of aldehydes, ketones, and esters using the corresponding parent silyl enol ethers. In addition, 4 examples of formal [4+1]-cycloaddition products could be also accessed from the use of Danishefsky's diene. Experimental, theoretical, and kinetics studies are being performed in order to gain more insights into the reaction mechanisms involved in these transformations.



ACKNOWLEDGEMENTS

The authors thank the funding agencies FAPESP for research grants to I. D. J. (2022/01104-3 and 2019/17721-9); and Capes for a PhD Fellowship to G. C. (88887.669179/2022-00).

REFERENCES

[1].Gallo, R. D. C; Cariello, G; Goulart, Tales A. C; Jurberg, I. D. *Chem. Commun.,* **2023**, *59*, 7356-7360.
[2] Durka, J.; Turkowska, J.; Gryko, D. *ACS Sustain. Chem. Eng.* **2021**, *9*, 8895–8918.
[3] Yang, Z.; Stivanin, M. L.; Jurberg, I. D.; Koenigs, R. M. *Chem. Soc. Rev.,* **2020**, *49*, 6833–6847.
[4] Jurberg, I. D.; Davies, H. M. L. *Chem. Sci.* **2018**, *9*, 5112–5118.
[5] Xiao, T.; Mei, M.; He, Y.; Zhou, L. *Chem. Commun.* **2018**, *54,* 8865– 8868.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Building a molecular library with heterocycles of the future: The synthesis of unprecedented nitrogen-containing [5,5]-fused rings

Raul Marques Novais,[1*] **Thiago dos Santos,** [1] **Flávio da Silva Emery.** [1*]

Department of Pharmaceutical Sciences, School of Pharmaceutical Sciences of Ribeirão Preto – FCFRP-USP, São Paulo, Brazil

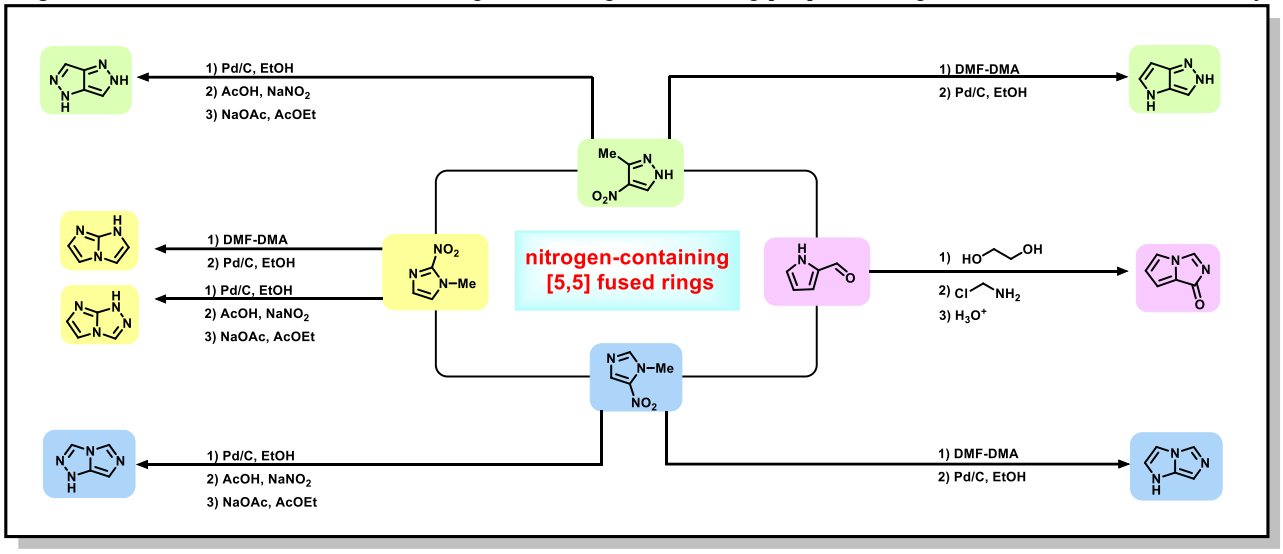
****e-mail: rmnovais@usp.br***

Keywords: *Molecular library, fragments, nitrogen-containing rings, heterocycles of the future.*

ABSTRACT

Heterocyclic rings are fundamental in the pharmaceutical industry. Statistical surveys show that about 72% of the drugs released annually by the FDA have some heterocycle moiety in their structure, of which one-third is considered unprecedented,[1,2] fitting the concept of heterocycles of the future, i.e., those underexplored or never explored before.[3,4] In this sense, nitrogen-containing [5,5]-fused rings as fragments were planned and are already being synthesized. Through known reactions, different routes have been tested in order to obtain the non-substituted heterocycles of our interest, overcoming the synthetic challenges throughout the process (**Figure 1**). The research, planning, and synthesis of new heterocyclic entities are essential so that strategies such as fragment-based drug discovery can be applied in order to explore the potential of these rings for different biological targets.[5]

Figure 1. General scheme to obtain the fragments nitrogen-containing [5,5]-fused rings to increase a molecular library.



ACKNOWLEDGEMENTS

To Capes, CNPQ, FAPESP, NIH, and CRAFT, for the assistance, collaborations, and granted scholarships.

REFERENCES

[1] Jampilek, J. *Molecules*, **v. 24** (21), p. 1–4. 2019.
[2] Taylor, R. D.; Maccoss, M.; Lawson, A. D. G. *J. Med. Chem*., **v. 57** (14), p. 5845–5859, 2014.
[3] Pitt, W. R.; Parry, D. M.; Perry, B. G.; Groom, C. R. *J. Med. Chem*., **v. 52** (9), p. 2952–2963, 2009.
[4] Passador, K.; Thorimbert, S.; Botuha, C. *Synthesis,* **v. 51** (2), p. 384–398, 2019.
[5] Shi, Y.; Itzstein, M. *Molecules,* **v. 24**, p. 1 – 10, 2019.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Indium-Catalyzed 1,6-addition of Indolizines to *para*-Quinone Methides

Ana Júlia S. Senna[1], Manoel T. Rodrigues Jr. [1*], Hugo Santos[1], Ralph C. Gomes[1], Fernando Coelho[1*]

1) Laboratório de Síntese de Produtos Naturais e Fármacos, Instituto de Química, Universidade Estadual de Campinas, UNICAMP, CP 6154

****e-mail:* facoelho@unicamp.br**

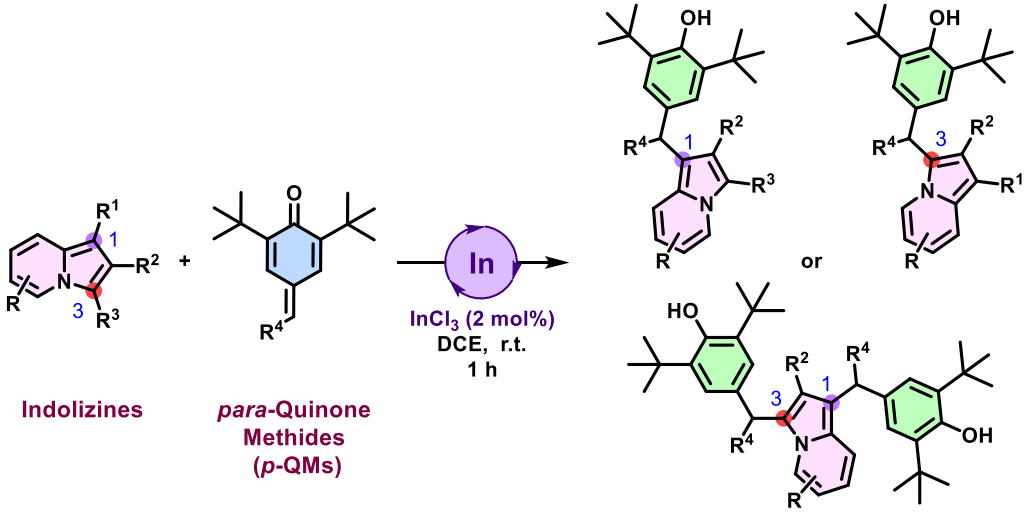
****e-mail: mtrjquim@yahoo.com.br***

Keywords: *Catalysis, Indium Chloride, p-quinone methides, indolizines.*

ABSTRACT

para-Quinone methides (p-QMs) are a variety of compounds that have been extensively studied in the organic synthesis field over the past few years.[1] They can be characterized as reactive intermediates containing an electrophilic site[2] and can be used as 1,6- Michael acceptors in the presence of Lewis acids as catalyst.[3] In this work we explored the use of $InCl_3$ as catalyst (2 mol%) to enhance the reaction between *p*-QM's and indolizines. The method successfully allows the regioselective addition of indolizines at positions 1 and/or 3 to p-quinone methides, leading to the formation of 23 analogues in excellent yields in most cases (up to 99%) under mild conditions and in short reaction time **(Figure 1)**.

Figure 1. reaction between p-QM's and indolizines with indium chloride as catalyst.



ACKNOWLEDGEMENTS

CNPq (301330/2018-2), CAPES (Finance Code 001 to A.J.S.S), FAPESP (2013/07600-3), PROEX/CAPES (IQ-Unicamp).

REFERENCES

(1) (a) Lafzi, F.; Kilic, H. Metal- and Additive-Free C3-Functionalization of Imidazo[1,2-a]Pyridines with Para Quinone Methides. *Asian J. Org. Chem*. **2021,** *10*, 1814–1821. (b) Zhou, J.-Y.; Ma, C.; Zhang, Y.-Z.; Wu, Q.; Shi, F. Catalyst-Free [4 + 2] Cyclization of Para-Quinone Methide Derivatives with Homophthalic Anhydrides. *Org. Biomol. Chem* **2018**, *16*, 9382–9389. (c) Zhang, Z.-P.; Dong, N.; Li, X. Bismuth-Catalyzed Allylation of Para-Quinone Methides. *Chem. Commun*. **2017**, *53*, 1301–1304. (d) Zanarotti, A. Synthesis and Reactivity of Vinyl Quinone Methides. *J. Org. Chem*. **1985**, *50*, 941−945. (e) Filar, L. J.; Winstein, S. Preparation and Behavior of Simple Quinone Methides. *Tetrahedron Lett*. **1960**, *1,* 9−16.

(2) (a) Richter, D.; Hampel, N.; Singer, T.; Ofial, A. R.; Mayr, H. Synthesis and Characterization of Novel Quinone Methides: Reference Electrophiles for the Construction of Nucleophilicity Scales. *Eur. J. Org. Chem*. **2009**, *2009*, 3203–3211. (b) Eitzinger, A.; Mayer, R. J.; Hampel, N.; Mayer, P.; Waser, M.; Ofial, A. R. Electrophilic Reactivities of Vinyl P-Quinone Methides. *Org. Lett.* **2020**, *22*, 2182–2186.

(3) (a) Sun, Z.; Sun, B.; Kumagai, N.; Shibasaki, M. Direct Catalytic Asymmetric 1,6-Conjugate Addition of Amides to p-Quinone Methides. *Org. Lett.* **2018**, *20*, 3070–3073. (b) Yang, B.; Yao, W.; Xia, X. -F.; Wang, D. Mn-Catalyzed 1,6-conjugate addition/aromatization of para-quinone methides. *Org. Biomol. Chem*. **2018**, *16*, 4547–4557. (c) Liu, X.; Liu, B.; Shi, Z.; Tan, C.; Fan, R.; Li, Z.; Tan, J. Hf(OTf)4-Catalyzed 1,6-Conjugate Addition of 2-Alkyl-azaarenes to para-Quinone Methides. *J. Org. Chem*. **2021**, *86*, 3615–3624.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Development of an asymmetric version of the Morita-Baylis-Hillman reaction using vinyl-1,2,4-oxadiazoles as nucleofilic partners

Thaynan A. B. Chagas,[1*] Fábio S. Fernandes,[1] Nicola L. Rocha,[2] Rodrigo A. Cormanich[2] and Fernando Coelho[1]

1) Laboratory of Synthesis of Natural Products and Drugs, Institute of Chemistry, University of Campinas – UNICAMP, postal code 6154, Campinas, SP, Brazil, 13083-970

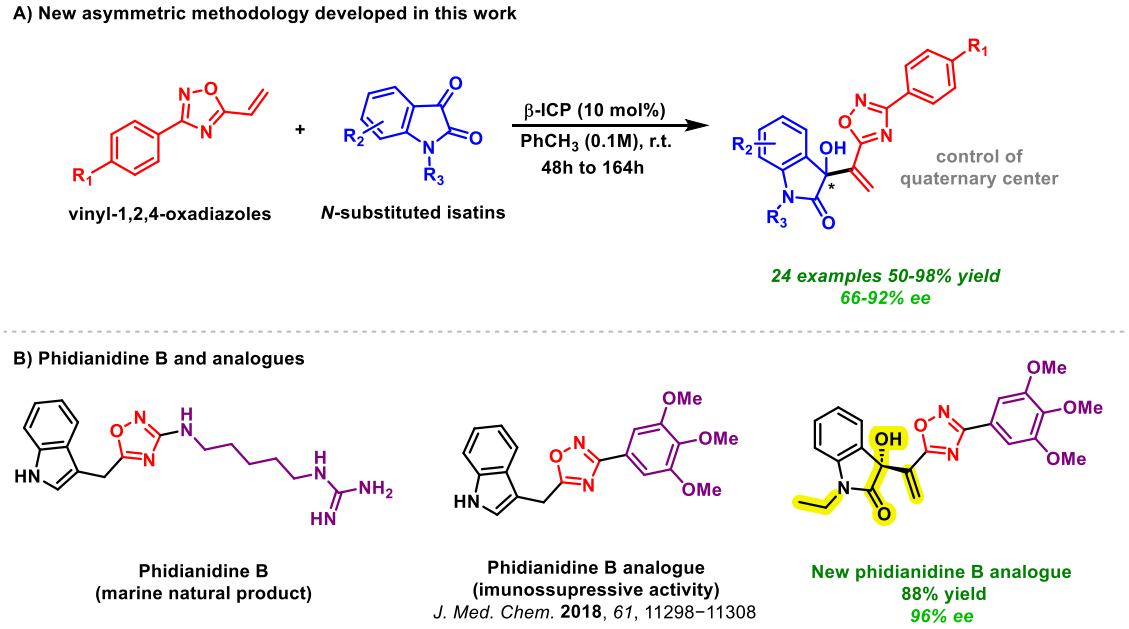
2) Laboratory of Experimental and Theoretical Organic Chemistry, Institute of Chemistry, University of Campinas – UNICAMP, postal code 6154, Campinas, SP, Brazil, 13083-970

****e-mail: t216279@dac.unicamp.br***

Keywords: *Asymmetric synthesis, Vinyl-1,2,4-oxadiazole, Morita-Baylis-Hillman reaction.*

ABSTRACT

The development of new substrates for asymmetric Morita-Baylis-Hillman (MBH) reactions has been a challenge in the last decades.[1] Due to the great potential of the products for further transformation and the superior mild reaction conditions, the development of a suitable asymmetric version of this reaction has attracted considerable interest in recent years[2] and, so far, there is no report on the use of vinyl heterocyclics able to realize asymmetric MBH reactions. Recently, we discovered a novel class of antiparasitic agents bearing two heterocyclic scaffolds (1,2,4-oxadiazole and 3-oxindol) prepared by a MBH reaction.[3] In this work we developed a new efficient method for the asymmetric construction of these chiral MBH adducts (Scheme 1A). This methodology allowed us to obtain a new analogue of natural compound “phidianidine B” (Scheme 1B). Theoretical studies are being conducted to understand the factors that influence enantiomeric excesses.



Scheme 1. New asymmetric methodology of MBH reaction.

ACKNOWLEDGEMENTS

We thank FAPESP (grant 2021/13544-5 and 2003/07600-3), CNPq (grant 151763/2022-4 and 301330/2018-2) and CAPES for scholarships and financial support.

REFERENCES

[1] (a) Liu, T. Y.; Xie, M.; Chen, Y. C. *Chem. Soc. Rev.*, **2012**, *41*, 4101–4112; (b) Basavaiah D.; Veeraraghavaiah, G. *Chem. Soc. Rev.*, **2012**, *41*, 68–78; (c) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.*, **2010**, *110*, 5447–5674.
[2] Fei, Y.; Shi, M.; *Chem. Rev.*, **2013**, *113*, 6659-6690.
[3] Fernandes, F.; S.; Rocha, S.; L.; Santos, H.; Conti, C.; Rodrigues Jr, M. T.; Zeoly, L. A.; Ferreira, L; L; G.; Krogh, R.; Andricopulo, A.; D.; Coelho, F. *Eur. J. Med. Chem.* **2020**, *200*, 112418-112465.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Studies on the oxidation of aliphatic C—H bonds using Fe-PHI

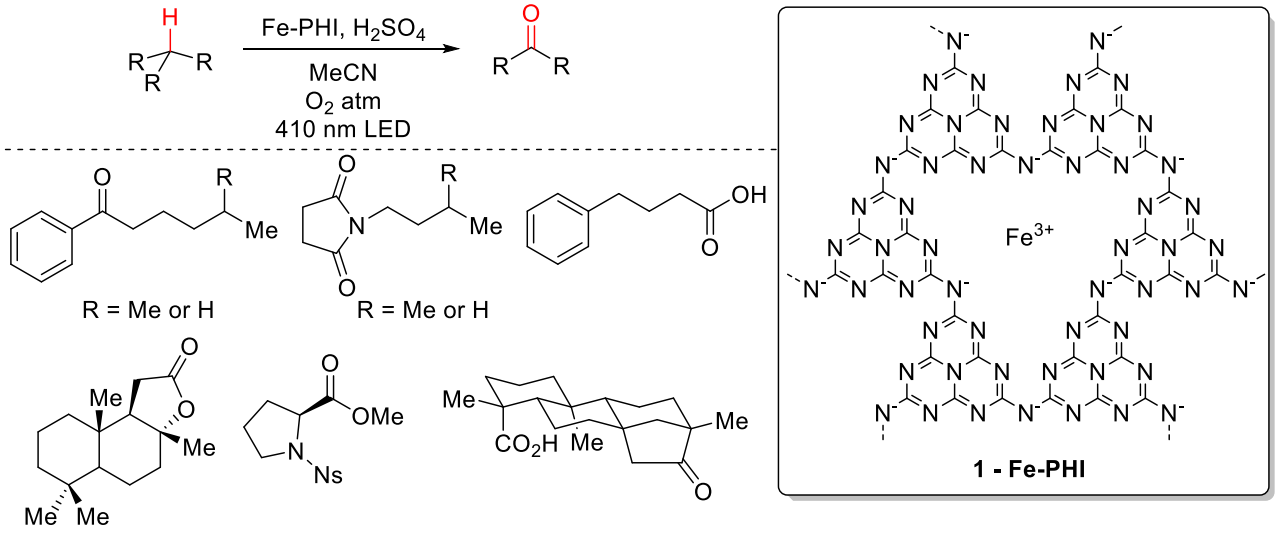
César Augusto Denadai Zaragoza,[1*] Marcos A. R. da Silva,[2] Ivo F. Teixeira,[2] Emilio Carlos de Lucca Júnior.[1*]

1) Institute of Chemistry, University of Campinas, 13083-970, Campinas, São Paulo, Brazil
2) Chemistry Department, University of São Carlos, 13565-905, São Carlos, São Paulo, Brazil
e-mail: c214536@dac.unicamp.br, eluccajr@unicamo.br

Keywords: *C—H Oxidation, Organic Synthesis, Photocatalysis.*

ABSTRACT

Teixeira and coworkers successfully developed a single-atom photocatalyst for the oxidation of C—H bonds in a heterogeneous system, known as Fe-poly(heptazine imide) (**1**), or Fe-PHI. They achieved the conversion of methylenes to their corresponding ketones by utilizing O_2 as the terminal oxidant and 410 nm LEDs for electronic excitation of the catalyst. The catalyst works by the *in situ* generation of H_2O_2, which leads to the formation of the iron-oxo sites that promote the C—H bond oxidation.[1]



Scheme 1. Substrates proposed for the study of C—H oxidation employing Fe-PHI.

We propose a study in which we aim to optimize the reaction conditions and explore the range of substrates compatible with this catalyst.

ACKNOWLEDGEMENTS

CNPq (130749/2023-0)
FAPESP (2018/04837-6)

REFERENCES

[1] da Silva, M. A. R.; Silva, I. F.; Xue, Q.; Lo, B. T. W.; Tarakina, N. V.; Nunes, B. N.; Adler, P.; Sahoo, S. K.; Bahnemann, D. W.; López-Salas, N.; Savateev, A.; Ribeiro, C.; Kühne, T. D.; Antonietti, M.; Teixeira, I. F. Sustainable Oxidation Catalysis Supported by Light: Fe-Poly (Heptazine Imide) as a Heterogeneous Single-Atom Photocatalyst. *Appl. Catal. B Environ.* **2022**, *304*, 120965. https://doi.org/10.1016/j.apcatb.2021.120965.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Synthesis of new heterocycles arrangements from Morita-Baylis-Hillman adducts

João Arantes[1], Manoel T. Rodrigues Jr.[1] and Fernando Coelho[1,*]

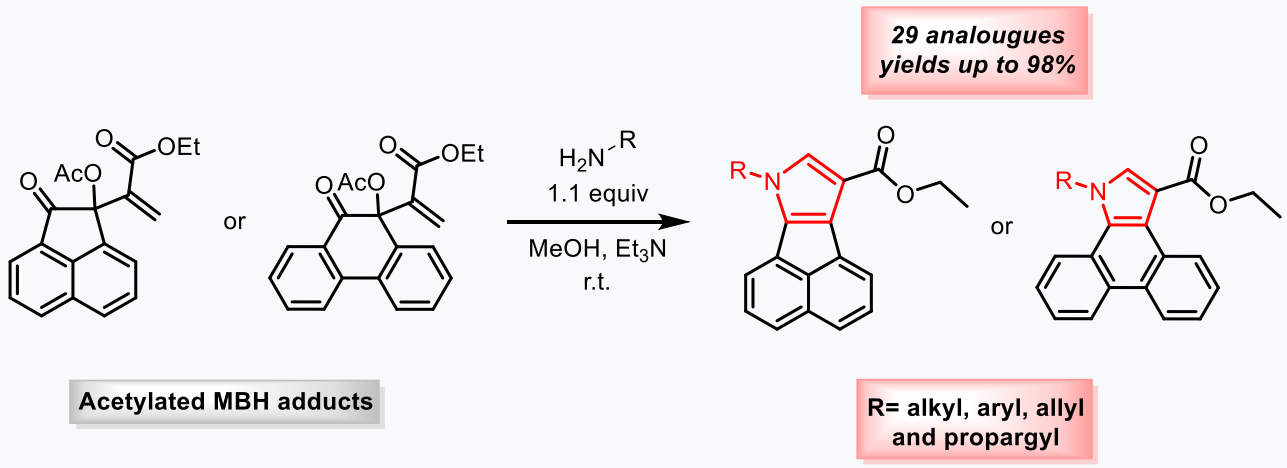
1) Chemistry Institute, University of Campinas (UNICAMP) – PO Box 6154 – 13083-970 – Campinas, São Paulo, Brazil.
****e-mail: facoelho@unicamp.br***

Keywords: *Morita Baylis Hillman, Heterocycles.*

ABSTRACT

In this work, starting with dicarbonilic compounds, different MBH adducts where synthetized[1] followed by acetylation[2]. The last synthetic step is the addition of a primary amine in the presence of tryethilamine to give new acenaphto[1,2-b]pyrroles and 1H-dibenzo-[e,g]-indoles (scheme 1). These classes of polycyclic N-substituted heterocycles are novel molecules readily accessible.

Scheme 1 – Synthesis of polycyclic N-heterocycles.



ACKNOWLEDGEMENTS

CNPq (301330/2018-2), CAPES (Finance Code 001 to J.P.A.C.), FAPESP (2013/07600-3), (IQ-Unicamp).

REFERENCES

[1]. Camilo, N. et al. *Eur. J. Org. Chem*. 2022, 9.
[2]. Batchu, H. and Batra, S. *Eur. J. Org. Chem*. 2012, 2935-2944.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Synthetc Studies Towards the Total Synthesis of Dimataíresinol

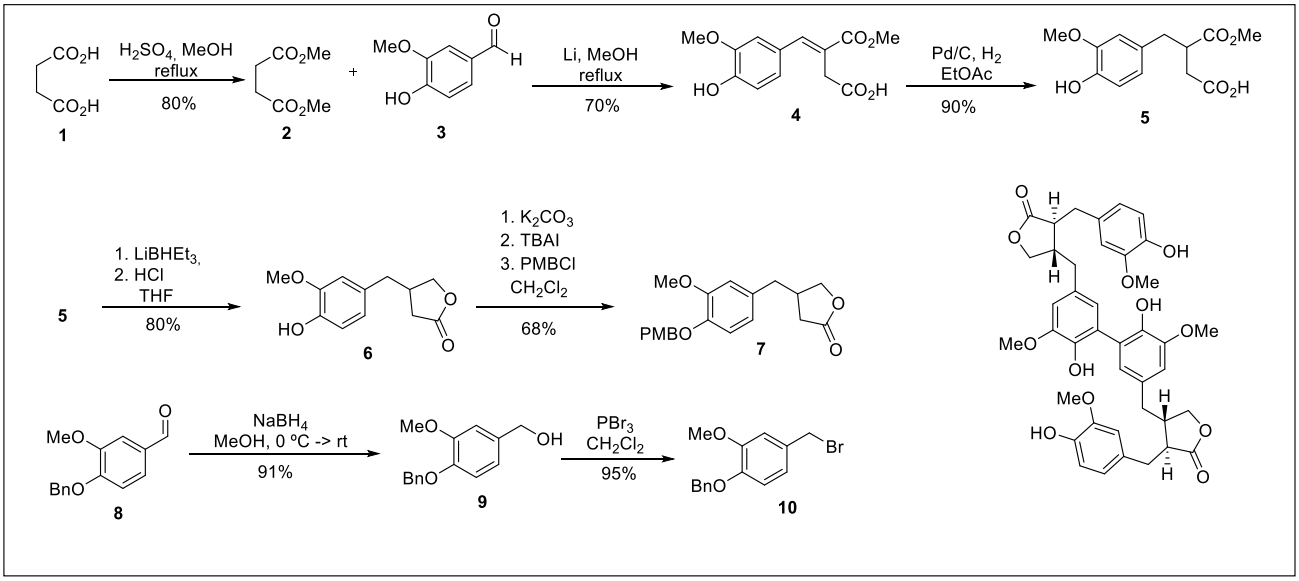
Pedro Henrique Marques da Silva,[1*] Ana Carolina Gonzales Richieri,[1] Marcio Hayashi,[1] and Emilio C. de Lucca Jr[1]

Institute of Chemistry, University of Campinas, CEP 13083-970, Campinas, São Paulo, Brazil
Email: eluccajr@unicamp.br

Keywords: *natural products, C-H bond functionalization*

ABSTRACT

After Yang and coworkers isolated several dimers of lignans, extracted from the dried roots of an Asian plant, new paths and ideas were opened for the synthesis of these compounds, of which the focus of this work is dimataíresinol, a dimer of matairesinol.[1,] Our proposal for the synthesis of this dimer is through the oxidative coupling of phenols, which is a C—H bond functionalization of the, an extremely versatile type of strategy.[2] Following this logic, it is possible to visualize the synthesis of dimataíresinol from vanillin, a commercially available compound.[3] Starting from succinic acid forming product 7 in good yields and generating product 10 from vanillin protected with BN, the next step is to carry out an alkylation with these two compounds.



Scheme 1. Studies towards the synthesis of dimataíresinol

ACKNOWLEDGEMENTS

Fapesp (2018/04837-6), Capes (88887.694204/2022-00), and CNPq for financial Suport

REFERENCES

[1] Harworth, R. D. *J. Chem. Soc.* **1942**, 448.
[2] Huh, J.; Song, J. H.; Kim, S. R.; Cho, H. M.; Ko, H-J.; Yang, H.; Sung, S. H. *J. Nat. Prod.* **2019**, 82, 232.
[3] Godula, K.; Sames, D. *Science* **2006**, *312*, 67

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Ecofriendly synthesis of 4-acyl-1,2,3-triazoles as precursors for novel p.Phe508del-CFTR traffic correctors

Camilla D. Buarque (PQ)[1]*, Guilherme Caleffi (PQ)[2], Marcelo Folhadella M. F. Azevedo (PG)[1], Samuel B. Ribeiro (PG)[1], David C. Zeitune (IC)[1],

[1]*DDepartamento de Química, PUC-Rio*

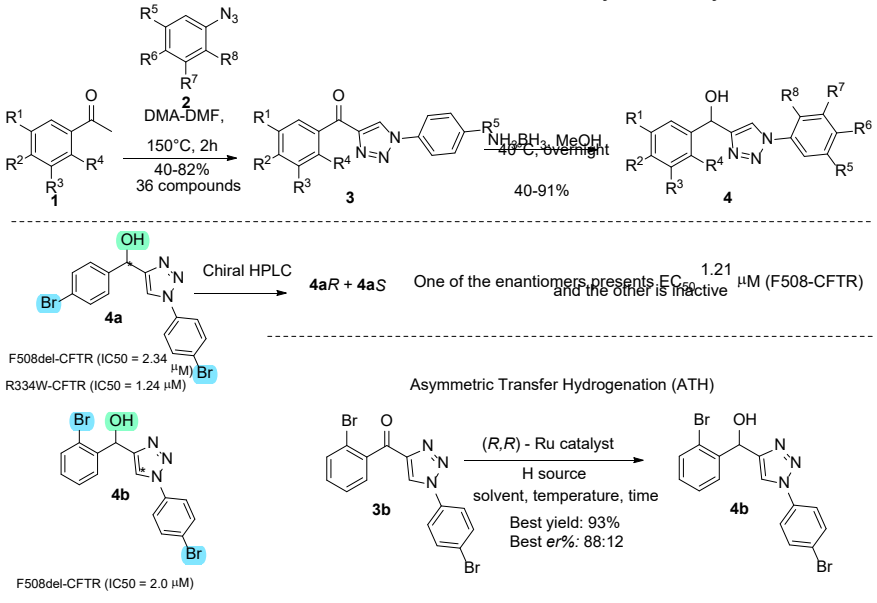
[2] *Instituto de Pesquisa de Produtos Naturais,UFRJ*

camilla-buarque@puc-rio.br

Keywords*: Acyl 1H-1,2,3-Triazoles, telescopic reaction, Asymmetric Transfer Hydrogenation, Cystic Fibrosis*

ABSTRACT

This work describes a straightforward methodology to obtain 4-acyl-1,2,3-triazoles in a solvent, and metal-free telescopic reaction using readily-available acetophenones and different aryl azides These compounds were used as precursors of bioactive 4-hydroxy-1,2,3-triazoles[1] as part of our research aimed at identifying new drug candidates based for the treatment of Cystic Fibrosis (CF) and compound **4a** presented the best activity toward F508del-CFTR and R334W-CFTR. The chiral resolution of the racemate and evaluation of each enantiomer individually allowed us to identify that there is only one enantiomer responsible for the biological activity. To obtain the bioactive *(R)* and (*S*)-4-hydroxy-1,2,3-triazoles, we are working on the ruthenium-catalyzed Asymmetric Transfer Hydrogenation (ATH)[2] employing different reaction conditions, starting from compound **3b,** due to the influence of the *ortho*-bromine for the catalyst activity.



Scheme 1. Synthesis of bioactive 4-hydroxy-1,2,3-triazoles as a racemate and enantioselective fashion

ACKNOWLEDGEMENTS

The authors would like to thank CAPES, CNPq, and FAPERJ for their financial support. Also, we link to thank PUC-Rio and CALPH for the structure that made the work possible.

REFERENCES

[1]. Bacalhau, M.; Ferreira, F.C.;Kmit, A.; Souza, Felipe, R.; da Silva, V.D.; Pimentel, A.S.; Amaral, M.D.; Buarque, C.D.; Lopes-Pacheco, M., *European Journal of Pharmacology* **2023**, *938*, 175396

[2] Zheng, Y.; Martinez-Acosta, J.A.; Khimji, M;. Barbosa L. C. A.; Clarkson, J.G.; Wills, M. *ChemCatChem.* **2021**, 13, 4384

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Merging gold and enzyme catalysis for asymmetric synthesis

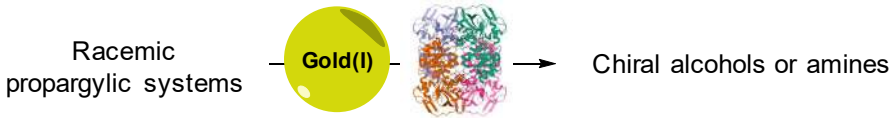
Vicente Gotor-Fernández, Sergio González-Granda, Lorena Escot and Iván Lavandera
Organic and Inorganic Chemistry Department, University of Oviedo, 33006 Oviedo (Asturias, Spain)
e-mail: vicgotfer@uniovi.es

Keywords: *Enzymes, Gold catalysis, Reaction cascades, Stereoselective synthesis*

ABSTRACT

The combination of metal- and enzyme-catalysis is a powerful tool for asymmetric synthesis, allowing the straightforward and stereoselective preparation of relevant organic molecules.[1] To overcome traditional limitations of stepwise sequence, the use of metalloenzymatic cascades is particularly attractive, the design of one-pot sequential or concurrent cascade approaches being highly dependent on the catalytic activity of both species under similar reaction conditions.[2] Gold catalysts has emerged in the last two decades as versatile tools to develop multiple C–C bond activation reactions under mild conditions,[3] therefore combining both catalytic worlds open a myriad of synthetic possibilities.

In this context, the use of gold(I) species, especially N-heterocyclic carbenes, and biocatalysts such as alcohol dehydrogenases or amine transaminases permits the transformation of alkynes into chiral alcohols and amines with exquisite selectivity. The development of gold-catalyzed Meyer-Schuster rearrangements[4,5] and hydration[6,7] reactions will be here considered, to subsequently developed asymmetric bioreduction or biotransamination transformations. Remarkably, the optimization of reaction parameters and the identification of stereocomplementary enzymes has been identified as key to success for the production of both alcohol or amine enantiomers through one-pot fashion protocols.



Scheme 1. Gold(I)-enzyme combinations for the development of stereoselective cascade transformations.

ACKNOWLEDGEMENTS

Financial support from the Spanish Ministry of Science and Innovation (MCI, PID2019-109253RB-I00) and Asturian Regional Government (AYUD/2021/51542) are gratefully acknowledged.

REFERENCES

[1]. S. González-Granda, J. Albarrán-Velo, I. Lavandera, V. Gotor-Fernández, *Chem. Rev.* **2023**, *123*, https://doi.org/10.1021/acs.chemrev.2c00454.
[2]. J. H. Schrittwieser, S. Velikogne, M. Hall, W. Kroutil, *Chem. Rev.* **2018**, *118*, 270–348.
[3]. R. Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, *115*, 9028–9072.
[4]. S. González-Granda, I. Lavandera, V. Gotor-Fernández, *Angew. Chem. Int. Ed.* **2021**, *60*, 13945–13951.
[5]. S. González-Granda, N. V. Tzouras, S. Nolan, I. Lavandera, V. Gotor-Fernández, *Adv. Synth. Catal.* **2022**, *364*, 3856–3866.
[6]. S. González-Granda, L. Escot, I. Lavandera, V. Gotor-Fernández, *ACS Catal.* **2022**, *12*, 2552–2560.
[7]. L. Escot, S. González-Granda, V. Gotor-Fernández, I. Lavandera, *Org. Biomol. Chem.* **2022**, *20*, 9650–9658.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Chemical Signaling in Insect Microbiomes

Mônica T. Pupo[1*]

1) School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, 14040-903
****e-mail: mtpupo@fcfrp.usp.br***

Keywords: *Specialized metabolites, Social insects, Chemical ecology.*

ABSTRACT

Specialized metabolites (natural products) play important roles in mediating symbiotic interactions between microorganisms and their eukaryotic hosts. Social insects establish multipartite symbioses with bacteria and fungi, ranging from mutualistic to parasitic interactions, some of them are mediated by specialized metabolites.[1,2] Brazil harbors a huge diversity of native insect species, which represent prolific sources for research focused on chemical ecology and natural product discovery.[3] Using a chemical ecology approach to study the microbiomes of neotropical social insects, our research group has described roles of microbial specialized metabolites in defensive and nutritional symbiosis in fungus growing ants and stingless bees.[4-10] We have found that microbial metabolites may contribute to evolutionary and biogeographic understanding of these symbiotic systems.[11] Additionally, some new compounds showed potential pharmaceutical applications as antimicrobials, which are probably related to their ecological roles.[12-14] During this presentation I will discuss our approach and some recent results in this exciting field.

ACKNOWLEDGEMENTS

FAPESP (2013/50954-0), CNPq/MS/NIH (404180/2019-1)

REFERENCES

[1] Menegatti C; Fukuda TTH; Pupo MT. *Planta Med.* **2021**, *87*: 38-48.
[2] De Paula GT; Menezes C; Pupo MT; Rosa CA. *Curr. Op. Ins. Sci.* **2021**, *44*: 41-47.
[3] Pupo MT; Currie CR; Clardy J. *J. Braz. Chem. Soc.* **2017**, 28: 393-401.
[4] Paludo CR; Menezes C; Silva-Junior EA; Vollet-Neto A; Andrade-Dominguez A; Pishchany G; Khadempour L; Nascimento FS; Currie CR; Kolter R; Clardy J; Pupo MT. *Sci. Rep.* **2018**, *8*: 1122.
[5] Silva-Junior EA; Ruzzini AC; Paludo CR; Nascimento FS; Currie CR; Clardy J; Pupo MT. *Sci. Rep.* **2018**, *8*: 2595.
[6] Menegatti C; Melo WGP; Carrao DB; Oliveira ARM; Nascimento FS; Lopes NP; Pupo MT. *J. Chem. Ecol.* **2018**, *44*: 1158-1169.
[7] Menegatti C; Lourenzon VB; Rodriguez-Hernandez DC; Melo WGP; Ferreira LLG; Nascimento FS; Pupo MT. *J. Nat. Prod.* **2020**, *83*: 610-616.
[8] Rodriguez-Hernandez D; Melo WGP; Menegatti C; lourenzon VB; Nascimento FS; Pupo MT. *New J. Chem*. **2019**, *43*: 10109-10117
[9] Paludo CR; Pishchany G; Andrade-Dominguez A; Silva-Junior EA; Menezes C; Nascimento FS; Currie CR; Kolter R; Clardy J; Pupo MT. *PLoS One* **2019**, *14*: e0219696.
[10] Bae M; Mevers E; Pishchany G; Whaley SG; Rock CO; Andes DR; Currie CR; Pupo MT; Clardy J. *Org. Lett*. **2021**, *23*: 1648–1652.
[11] Fukuda TTH; Helfrich EJN; Mevers E; Melo WGP; Van Arnam EB; Andes DR; Currie CR; Pupo MT; Clardy J. *ACS Cent. Sci*. **2021**, *7*: 292–299
[12] Chevrette MG; Carlson CM; Ortega HE; Thomas C; Ananiev GE; Barns KJ; Book AJ; Cagnazzo J; Carlos C; Flanigan W; Grubbs KJ; Horn HA; Hoffmann FM; Klassen JL; Knack JJ; Lewin GR; McDonald BR; Muller L; Melo WGP; Pinto-Tomás AA; Schmitz A; Wendt-Pienkowski E; Wildman S; Zhao M; Zhang F; Bugni TS; Andes DR; Pupo MT; Currie CR. *Nat. Comm*. **2019**, *10*: 516
[13] Ortega HE; Ferreira LLG; Melo WGP; De Oliveira AL; Alvarenga RFR; Lopes NP; Bugni TS; Andricopulo AD; Pupo MT. *PLoS Negl.Trop. Dis.* **2019**, *13*: e0007643
[14] Ortega HE; Lourenzon VB; Chevrette MG; Ferreira LLG; Ramos-Alvarenga RF; Melo WGP; Venâncio T; Currie CR; Andricopulo AD; Bugni TS; Pupo MT. *Bioorg. Med. Chem*. **2021**, 32: 116016.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Engineered protein-based biocatalysts, nanozymes, and biomaterials

Aitziber L. Cortajarena[1,2*]

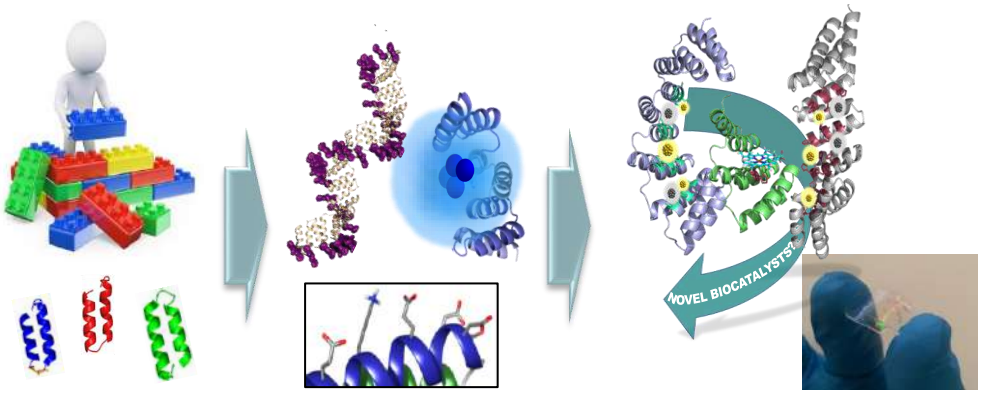
1) Center for Cooperative Research in Biomaterials (CIC biomaGUNE), Basque Research and Technology Alliance (BRTA), Paseo de Miramón 194, Donostia-San Sebastián 20014, Spain
2) Ikerbasque, Basque Foundation for Science, 48009 Bilbao, Spain
****e-mail: alcortajarena@cicbiomagune.es***

Keywords: *Bioorganic chemistry, Protein-bioconjugates, Biocatalysts, Nanozymes.*

ABSTRACT

Numerous challenging chemical reactions in nature are catalyzed by enzymes. In our laboratory, we work on protein engineering aiming at generating artificial biocatalysts based on proteins and mimicking nature in the coordination and bioconjugation of proteins with other functional elements. We have demonstrated the versatility of engineered protein-based scaffolds as biomolecular templates for patterning nanomaterials, organic molecules, and even carbon nanomaterials.[1] In particular we have developed a set of engineered protein scaffolds as stabilizing modules for luminescent and catalytic metal nanoclusters, allowing the fabrication of nanomaterials with defined properties.[2]

In the field of biocatalysis, taking advantage of the already demonstrated robustness of engineered protein modules we have developed robust protein platforms based on engineered super stable and modular protein scaffolds as the ideal candidates to encode novel catalytic properties[3] and to template functional catalytic elements, that include: 1) metal centers for the generation of libraries of nanozymes; 2) photocatalytic molecules for biorthogonal catalysis; and organometallic catalysts leading into active catalytic systems. In addition, we use engineered proteins to generate robust scaffolding units to arrange complex multi-enzymatic systems with unprecedented control over the spatial features and physicochemical properties, which results in the final enhanced catalytic performance of scaffolded systems. Finally, we not only work at the molecular level but by engineering the self-assembly features of the scaffolds can bring these novel biocatalysts into ordered solid materials[4] for heterogeneous catalysis and efficient reusability.



ACKNOWLEDGEMENTS

AEI: PID2019-111649RB-I00, MDM-2017-0720; ERA-CoBioTech- 61 HOMBIOCAT/ PCI2018-092984; ERC-CoG-ProNANO-648071

REFERENCES

[1]. Uribe, KB; Guisasola, E; Aires, A; ..., G; Sasselli, IR; Cortajarena, AL. *Acc. Chem. Res*. **2021**, 54, 4166-4177.
[2]. Aires, A; Llarena, I; Moller, M; ….; Cortajarena, AL. *Angew. Chem.* **2019**, 58, 6214-6219.
[3]. Rivilla, I; Odriozola-Gimeno, M; Aires, A; ...; Cortajarena, AL; Cossío, FP. *JACS* **2020**, 142, 762-776.
[4] Sanchez-deAlcazar, D; ..; Lopez-Gallego, F; Cortajarena,AL, *ChemBioChem* **2019**, 20, 1977-1985.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Enabling technologies for the sustainable chemical synthesis of high added-value compounds from renewable sources.

Julio C. Pastre,[1*]

1) Institute of Chemistry, University of Campinas (UNICAMP),
Josué de Castro St., Cidade Universitária Zeferino Vaz,
P.O. Box 6154, PC 13083-970, Campinas, São Paulo – Brazil.
****e-mail: jpastre@unicamp.br***

Keywords: *Renewable sources, Added-value compounds, Enabling Technologies, Flow chemistry.*

ABSTRACT

Raw materials from renewable sources, as well as agro-industrial waste, represent an attractive source of useful chemical functionalities.[1] Our research group has already identified continuous flow processing as a fundamental technology for the valorization of such materials. Flow chemistry offers unique opportunities for the conversion of biomass derivatives into chemical compounds with higher-added value, since it brings numerous advantages in terms of unique process experience, scalability, and reduced environmental footprint.[2] In this context, we will present our efforts for the synthesis of platform molecules (such as furanics)[3,4] and new chemicals (monomers, nitrogenated aromatics)[5] from biomass derivatives.

ACKNOWLEDGEMENTS

São Paulo Research Foundation - FAPESP (Award N.: 2021/06661-5;), the Brazilian National Council for Scientific and Technological Development - CNPq, and the Coordination for the Improvement of Higher Education Personnel - CAPES.

REFERENCES

[1] Gomes, G. R.; Scopel, E.; Breitkreitz, M. C.; Rezende, C. A.; Pastre, J. C. *Ind. Crops Prod.* **2023**, *191*, 115940.
[2] Sivo, A.; Galaverna, R. S.; Gomes, G. R.; Pastre, J. C.; Vilé, G. *React. Chem. Eng.* **2021**, *6*, 756-786.
[3] Galaverna, R.; Breitkreitz, M. C.; Pastre, J. C. *ACS Sustain. Chem. Eng.* **2018**, *6*, 4220-4230.
[4] Marçon, H. M.; Pastre, J. C. *RSC Advances* **2022**, *12*, 7980-7989.
[5] Galaverna, R.; Fernandes, L. P.; Browne, D. L.; Pastre, J. C. *React. Chem. Eng.* **2019**, *4*, 362-367.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Development of New Catalytic Systems. Applications in Asymmetric Catalysis

Rosario Fernández
Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, 41012 Sevilla (Spain)
e-mail: ffernan@us.es)

Keywords: *Asymmetric Catalysis, H-Bonding Organocatalysis, Anion Binding, Gold chemistry*

ABSTRACT

In our group we are involved in the rational design of reagents, ligands or catalysts with modulated steric and electronic properties and the development of new activation modes to be implemented in (enantio)selective Organic Synthesis. Over years we have exploited the nucleophilic character of hydrazones (masked acyl anion equivalents) in asymmetric synthesis. In particular, the use of formaldehyde *N-tert*-butylhydrazone in combination with bifunctional H-bonding organocatalysts enabled efficient enantioselective functionalization of neutral electrophiles, mainly carbonyl compounds.[1] On the basis of this knowledge, we have recently developed an interesting strategy of anion-binding catalysis which is based on the simultaneous chloride recognition by H-bonding organocatalysts and *N-tert*-butyl hydrazones, affording a tool for asymmetric dearomatization of isoquinolines with high stereocontrol.[2]

On the other hand, and concerning our interest in Gold chemistry, recent results on Au(I)-catalyzed alkynylation reactions will be also discussed.[3] Finally, results of silver-free gold-catalyzed heterocyclizations through intermolecular H-bonding activation using modulable monosulfonyl squaramides as an example of synergistic gold(I) and anion-binding catalysis, will be also presented.[4]

ACKNOWLEDGEMENTS

Spanish Ministerio de Ciencia, Innovación y Universidades (PID2019-106358GB-C21, PID2019-106358GB-C22), European FEDER funds (US-1262867), Junta de Andalucía (Grant P18-FR-3531)

REFERENCES

[1]. Reviews (a) Retamosa, G.; Matador, E.; Monge, D.; Lassaletta, J. M.; Fernández, R. *Chem. Eur. J.* **2016**, 22, 13430-13445; (b) Matador, E.; Retamosa, G.; Monge, D.; Fernández, R.; Lassaletta, J. M. *Chem. Commun*. **2020**, *56*, 9256-9267; For seminal examples, see : (c) Crespo-Peña, A.; Monge D.; Martín-Zamora, E.; Álvarez, E.; Fernández, R; Lassaletta, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 12912-12915; d) Matador, E.; Retamosa, G; Monge, D.; Iglesias- Sigüenza, J.; Fernández, R.; Lassaletta, J. M. *Chem. Eur. J.* **2018**, *24*, 6854-6960.
[2]. Matador, E.; Iglesias-Sigüenza, J.; Monge, D.; Merino, P.; Fernández, R.; Lassaletta, J. M. *Angew. Chem. Int. Ed.* **2021**, *60*, 5096-5101.
[3]. (a) García, P. D.; Izquierdo, C.; Iglesias-Sigüenza, J.; Díez, E.; Fernández, R.; Lassaletta, J. M. *Chem. Eur. J.* **2020**, *26*, 629-633. (b) García, P. D.; Iglesias-Sigüenza, J.; Rivero, P.; Díez, E.; Gómez-Bengoa, E.; Fernández, R.; Lassaletta, J. M. *J. Am. Chem. Soc*. **2020**, *142*, 16082-16089.
[4]. Elías-Rodríguez, P.; Matador, E.; Benítez, M.; Tejero, T.; Díez, E.; Fernández, R.; Merino, P.; Monge, D.; Lassaletta, J. M. *J. Org. Chem.* **2023**, DOI: 10.1021/acs.joc.2c02932.

7th Brazil-Spain Workshop on Organic Chemistry
BSWOC 2023
Ribeirão Preto - SP, Brazil
July 10-12, 2023

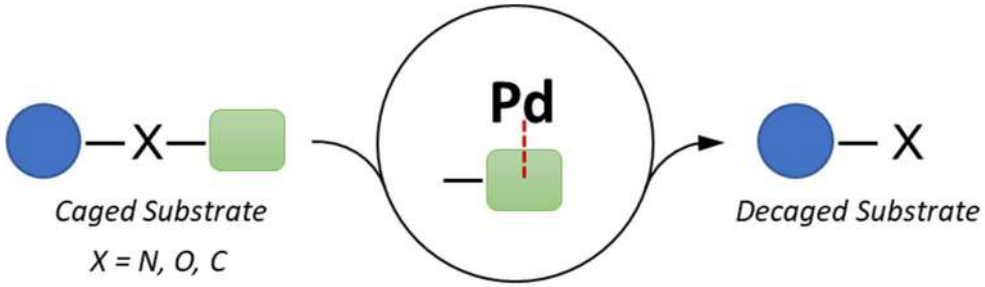
Palladium-triggered Deprotection Chemistry for Small Molecule Activation in Living Systems

Prof. Dr. Josiel Barbosa Domingos
Laboratory of Biomimetic Catalysis (LaCBio), Department of Chemistry, Universidade Federal de Santa Catarina, Florianópolis, Brazil, 88040-900
josiel.domingos@ufsc.br

Keywords: *Palladium, Bioorthogonal, Decaging, Prodrugs, Biological systems.*

ABSTRACT

Transitions metals have for a long time now proved their efficiency in catalyzing difficult bond-making reactions. But just recently, a new application field has emerged for the transition metals promotion of decaging (bond cleavage) reactions, under biological conditions, for the activation of exogenous substrates and biomolecules, such as prodrugs, fluorophores, and proteins. Compared with natural systems, transition metals can rapidly catalyze chemical transformations that cannot be realized by enzymes for specific biological applications. Among the transition metals, the palladium-mediated decaging reaction is the most studied method for substrate activation within living systems, which relies on the cleavage of propargylic, allylic or allenylic moieties introduced into the target molecule.[1] These methods have great potential to achieve spatiotemporally controlled release of substrates within biological systems. This lecture will show the latest efforts of the LaCBio in the development of palladium promoted decaging reactions for the activation of small molecules under biological conditions.



Scheme 1. Pd triggered decaging reaction scheme.

ACKNOWLEDGEMENTS

CNPq (408534/2022-2), CNPq (310493/2021-8) and CAPES-PrInt (88881.310570/2018-01)

REFERENCES

[1] Eloah Latocheski, Gean M. Dal Forno, Thuany M. Ferreira, Bruno L. Oliveira, Gonçalo J.L. Bernardes, Josiel B. Domingos. Mechanistic insights into transition metal-mediated bioorthogonal uncaging reactions. *Chem. Soc. Rev.*, **2020**, 49, 7710-7729.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Organocatalytic Enantioselective Reactions Driven by the Release of Ring Strain

Jose L. Vicario,[1*]

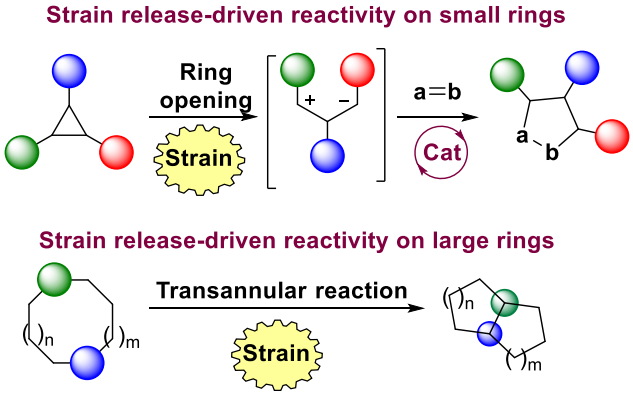
1) *Department of Organic and Inorganic Chemistry, University of the Basque Country. P.O. Box 644, 48080 Bilbao (Spain)*

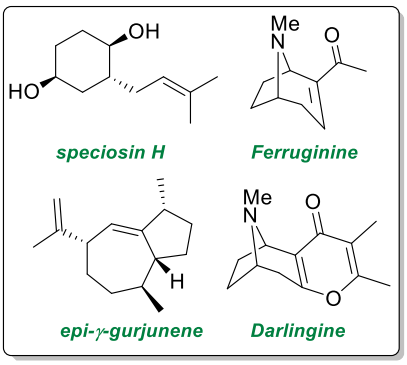
****e-mail: joseluis.vicario@ehu.es***

Asymmetric Organocatalysis, Ring Strain, Cyclopropanes, Transannular reactions

ABSTRACT

In the last years, our group has focussed in the use of the strain release associated to the ring-opening process of cyclopropanes as an expedient thermodynamic driving force that can lead to the identification of unconventional reactivity patterns under organocatalytic activation. In addition, ring strain does not only appear within small cycles but also shows up in compounds incorporating medium and large size carbo- and heterocyclic scaffolds in which unnatural bond angles are needed in order to close the cyclic architecture. In this lecture, the different methodologies developed in our group for the stereoselective synthesis of relatively complex carbo- or heterocyclic compounds starting from strained starting materials will be presented. Two different approaches have been taken: (a) using ring strain to promote ring-opening processes on cyclopropane-containing substrates, generating a reactive polyfunctional intermediate, which can undergo subsequent chemical transformations, (typically a cycloaddition or rearrangement process)[1] and (b) using ring strain to promote a transannular reaction[2] in a conveniently functionalized large sized cyclic starting material.[3] These reactions have been applied to the total synthesis of several examples of natural products or scaffolds with relevant biological activities.





Scheme 1.

ACKNOWLEDGEMENTS

This research was supported by the Spanish MCINN (FEDER-PID2020-118422GB-I00), the Basque Government (Grupos IT1558-22) and the University of the Basque Country (UPV/EHU).

REFERENCES

[1] (a) Sanchez-Diez, E.; Vesga, D. L., Reyes, E.; Uria, U.; Carrillo, L. Vicario, J. L. *Org. Lett.* **2016**, *18*, 1270. (b) Prieto, L.; Sanchez-Diez, E.; Uria, U., Reyes, E.; Carrillo, L. Vicario, J. L. *Adv. Synth. Catal.* **2017**, *359*, 1678. (c) Ortega, A.; Manzano, R.; Uria, U.; Carrillo, L.; Reyes, E.; Tejero, T.; Merino, P. *Angew. Chem. Int. Ed.* **2018**, *57,* 8225. (d) Ortega, A.; Uria, U.; Tejero, T.; Prieto, L.; Reyes, E.; Merino, P.; Vicario, J. L. *Org. Lett.* **2021**, *23*, 2326

[2] For focused reviews see (a) Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *Tetrahedron* **2014**, *70*, 9461. (b) Rizzo, A.; Harutyunyan, S. R. *Org. Biomol. Chem*. **2014**, *12*, 6570.

[3] (a) Mato, R.; Manzano, R.; Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *J. Am. Chem. Soc.* **2019**, *141,* 9495. (b) Sendra, J.; Manzano, R.; Reyes, E.; Vicario, J. L.; Fernandez, E. *Angew. Chem. Int. Ed*. **2020**, *59*, 2100. (c) Rodriguez, S.; Uria, U.; Reyes, E.; Carrillo, L.; Tejero, T.; Merino, P.; Vicario, J. L. *Angew. Chem. Int. Ed.* **2020**, *59*, 6780. (d) Mato, R.; Reyes, E.; Carrillo, L.; Uria, U.; Prieto, L.; Manzano, R.; Vicario, J. L. *Chem. Commun.* **2020**, *56*, 13149. (e) Sendra, J.; Reyes, E.; Prieto, L.; Fernández, E.; Vicario, J. L. *Org. Lett.* **2021**, *23*, 8738.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

New approaches to the synthesis of polysubstituted aromatic compounds containing chalcogens

Paulo Henrique Schneider*

Instituto de Química, Universidade Federal do Rio Grande do Sul (UFRGS). Av. Bento Gonçalves 9500. CEP 91501-970, PO Box 15003, Porto Alegre, RS, Brazil. ORCID 0000-0003-4082-7152

e-mail: paulos@iq.ufrgs.br

Keywords: *Indolizines, Indoles, Selanylfurans, Chalcogenophenes, organochalcogen Compounds*

ABSTRACT

Polysubstituted aromatic compounds are an important class of molecules and have attracted much interest in recent years. Some examples describe their biological activity or, most commonly, their applicability in organic conductor materials due their high rigidity and π conjugation, which may facilitate electronic flow. The introduction of a chalcogen atom can improve these properties and for that reason, lead us to develop alternative synthetic routes for their synthesis.

In addition, the balance between the development of new synthetic approaches with the extremely important and increasing need for efficient and easy procedures, is fundamental. In this sense, we have focused our effords in propouse some advances, based on easy and environmentally benign procedures for the synthesis of aromatic compounds containing chalcogens.[1]

ACKNOWLEDGEMENTS

The authors would like to acknowledge FAPERGS (PRONEX and RITEs-RS), CNPq (404503/2021-7, 308487/2021-4), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) – Finance Code 001 and INCT-CNM for the financial support.

REFERENCES

(a) Paixão, D. B.; Soares, E, G. O.; Salles, H. D.; Silva, C. D. G.; Rampon, D. S.; Schneider, P. H. *Org. Chem. Front.*, **2022**, *9*, 5225-5236. (b) Salles, H. D.; Coelho, F. L.; Paixão, D. B.; Barboza, C. A.; Rampon, D. S.; Rodembusch, F. S.; Schneider, P. H. *J. Org. Chem.* **2021**, *86*, 10140-10153. (c) Dalberto, B. T.; Schneider, Paulo H. S. *RSC Advances*, 2020, *10*, 10502-10509. (d) Vieira, M. M. Dalberto, B. T.; Coelho, F. L.; Schneider, P H. *Ultrason. Sonochem.*, **2020**, 68, 105228. (e) Paixão, D. B.; Rampon, D. S.; Salles, H. D.; Soares, E, G. O.; Bilheri, F. N. Schneider, P H. *J. Org. Chem.*, **2020**, *85,* 12922–12934.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Catalytic Approaches for Stereoselective Hydrocarbon Difunctionalization

Martín Fañanás-Mastral[1*]

1) Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS), Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain

****e-mail: martin.fananas@usc.es***

Keywords: *Asymmetric catalysis, Carboboration, Hydrocarbons.*

ABSTRACT

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

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

ACKNOWLEDGEMENTS

Financial support from the AEI (PID2020-118237RB-I00), European Research Council (863914), Xunta de Galicia (ED431C 2022/27; Centro singular de investigación de Galicia accreditation 2019-2022, ED431G 2019/03) and the European Regional Development Fund (ERDF) is gratefully acknowledged.

REFERENCES

[1] Rivera-Chao, E.; Fañanás-Mastral, M. *Angew. Chem. Int. Ed.* **2018**, *57*, 9945-9949.
[2] Rivera-Chao, E.; Mitxelena, M.; Varela, J. A.; Fañanás-Mastral, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 18230-18234.
[3] Rivera-Chao, E.; Fañanás-Mastral, M. *Angew. Chem. Int. Ed.* **2021**, *60*, 16922-16927.
[4] Chaves-Pouso, A.; Álvarez-Constantino, A. M.; Fañanás-Mastral, M. *Angew. Chem. Int. Ed.* **2022**, *61*, e202117696.
[5] Pérez-Saavedra, B.; Velasco-Rubio, A.; Rivera-Chao, E.; Varela, J. A.; Saá, C.; Fañanás-Mastral, M. *J. Am. Chem. Soc.* **2022**, *144*, 16206-16216.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Why to inhibit ureases from agricultural and medicinal perspectives?

Ângelo de Fátima[1*] and Luzia V. Modolo[2]

1) Departamento de Química, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil
2) Departamento de Botânica, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil
****e-mail: adefatima@qui.ufmg.br***

Keywords: *Urease, Urease Inhibitors, Nitrogen Fertilizer, Virulence Factor.*

ABSTRACT

Ureases (urea amidohydrolases EC 3.3.1.5) are nickel ion-dependent enzymes produced by plants, fungi, and microorganisms, which fasten up the hydrolysis of urea to NH_3 and CO_2[1,2]. Urease activity is considered a natural response to urea availability in different matrices, contributing to nitrogen metabolism by plants and as a mechanism for the survival of pathogenic microorganisms[3,4]. We have been developing potent and versatile urease inhibitors for agricultural and medicinal purposes. To achieve this goal, synthetic strategies were designed for Biginelli adducts, Schiff bases, benzothiazoles, benzimidazoles, (thio)hydatoins, benzoylthioureas, and benzylisothiocyanate among others. Reaction development, mechanistic investigations, and synthetic applications of the urease inhibitors synthesized by our research groups will be covered in this lecture.

ACKNOWLEDGEMENTS

This work was made possible partly by the Network for the Development of Novel Urease Inhibitors (https://www.redniu.org/), which is financially supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brazil (CAPES, Finance Code 001), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG). LVM and AF are recipients of research fellowships from CNPq.

REFERENCES

[1] de Fátima, Â.; Pereira, C.P.; Olímpio, C.R.S.D.G. *et al.* Schiff bases and their metal complexes as urease inhibitors - a brief review. *Journal of Advanced Research*, **2018**, *13*, 113-126.
[2] Modolo, L.V.; de Souza, A.X.; Horta, L.P. *et al.* An overview on the potential of natural products as ureases inhibitors: A review. *Journal of Advanced Research*, **2015**, *6*, 35-44.
[3] Rego, Y.F.; Queiroz, M.P.; Brito, T.O. *et al.* A Review on the Development of Urease Inhibitors as Antimicrobial Agents against Pathogenic Bacteria. *Journal of Advanced Research*, **2018**, *13*, 69-100.
[4] Chaves-Silva, S.; Horta, L.P.; de Souza, L.T. *et al.* Do Schiff Bases-based Urease Inhibitors Improve Plant Growth and Affect the Activity of Soil Arginase? *Industrial Crops and Products*, **2020**, *145*, 111995.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

From ligand design to the synthesis of biologically active molecules

Manuel Alcarazo*
Georg August Universität Göttingen, Tammannstr 2, 37077-Göttingen, Germany
e-mail: malcara@gwdg.de

Keywords: *cationic phosphines, sulfonium salts, asymmetric catalysis*

ABSTRACT

In α-cationic phosphines at least one of the three substituents at phosphorus corresponds to a cationic (normally, but not always heteroaromatic) group, which is attached without any spacer by a relatively inert P-C bond. This unique architecture confers the resulting ligand strong acceptor properties, which frequently surpass those of traditional acceptor ligands such as phosphites or polyfluorinated phosphines. In addition, the fine tuning of the stereoelectronic properties of α-cationic phosphines is also possible by judicious selection of the number and nature of the cationic groups.

The opportunities offered in catalysis by α-cationic ligands arise from this ability to deplete electron density from the metals they coordinate. Thus, if in a hypothetical catalytic cycle the step that determines the rate is facilitated by an increase of the Lewis acidity at the metal center then, an acceleration of the whole process is expected by their use as ancillary ligands. In this regard our group has observed remarkable ligand acceleration effects by the employment of α-cationic phosphines in Au(I) and Pt(II)-promoted hydroarylation and cycloisomerization reactions. The applications of such ligands in natural product synthesis.

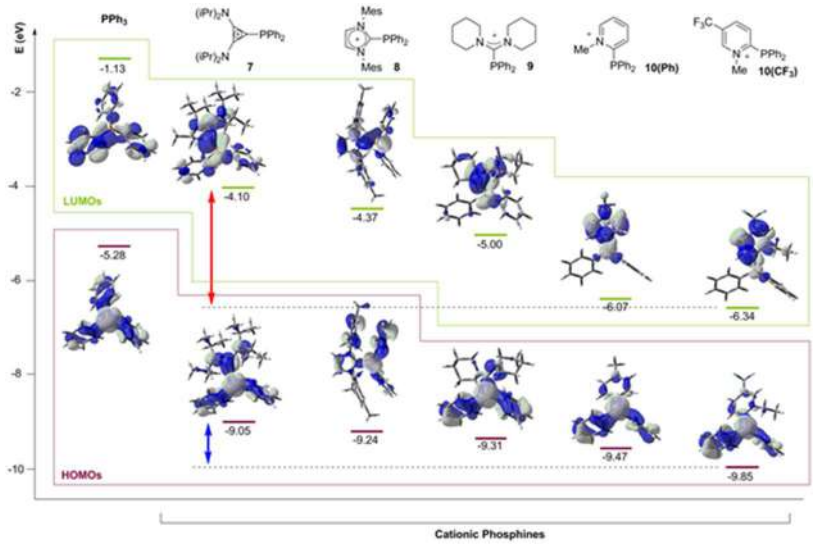


Figure 1: HOMO and LUMO of selected α-cationic phosphines

The references should be numbered in the text[1] in order following the punctuation symbol.[2]

ACKNOWLEDGEMENTS

The Deutsche Forschungsgemeinschaft is acknowledged for continuous support of our research programs

REFERENCES

[1] L. D. M. Nicholls, M. Alcarazo. *Chem. Lett.* **2019**, *48*, 1-13.
[2] M. Alcarazo, *Acc. Chem. Res.* **2016**, *49*, 1797-1805.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Bicolor Fluorescent Sensors for Barium Tagging in the Neutrinoless Double Beta Decay Reaction of Xe-136

Fernando P. Cossío,[1,2*] Iván Rivilla,[2,3] Fernando Auria-Luna,[1]- Juan Molina-Canteras,[1]Amaia Larumbe,[1] Iosune Arrastia[1] and Nerea Alberro[1]

1) Department of Organic Chemistry I and ORFEO-CINQA, University of the Basque Country (UPV/EHU), Manuel Lardizabal, 3, 20018 San Sebastian / Donostia, Spain

2) Donostia International Physics Center (DIPC), Manuel Lardizabal, 4, 20018 San Sebastian / Donostia, Spain

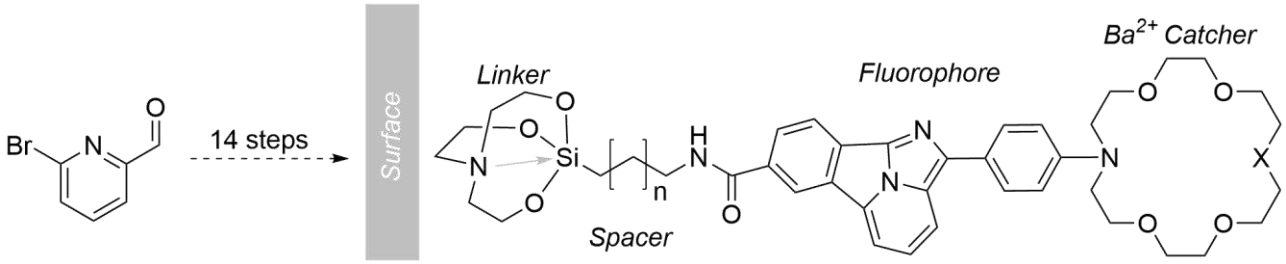
3) Ikerbasque, Basque Foundation for Science, Euskadi Plaza, 5, 48009 Bilbao / Bilbo, Spain

e-mail: fp.cossio@ehu.es

Keywords: *Cycloadditions, C-C Coupling, Fluorescence, Neutrinos.*

ABSTRACT

Neutrinoless double beta decay (*bb0n*) processes constitute a very promising method to find out whether neutrinos are they own antiparticles. Demonstrating this hypothesis would constitute a major discovery in physical sciences and cosmology. One useful *bb0n* nuclear reaction involves the Xe-136 isotope and leads to the emission of two electrons, whose drift and energy can be recorded, together with a barium cation. Therefore, the second essential component to monitor this reaction is the BTD (Barium Tagging Detector). The BTD must incorporate a fluorescent sensor [1] whose photophysical properties are adequate to distinguish the free and Ba^{2+}-bound states, thus giving rise to a bicolor fluorescent indicator (FBI) potentially useful for barium tagging [2,3]. The different emission spectra of the free and coordinated states stem from the decoupling between the aromatic components of the fluorophore after barium capture.



Scheme 1. Basic components of bicolor fluorescent sensors for barium tagging in bb0n experiments.

The basic components of our FBI molecules (Scheme 1) are an aza-crown ether to catch Ba^{2+}, a coupled fluorophore incorporating aromatic rings whose photophysical properties are different at the free and bound states, a spacer and, finally, a linker to anchor the sensor to a suitable functionalized surface. In our presentation, details about the chemical synthesis and properties of these FBI sensors will be discussed, as well as the suitability of these FBI sensors for barium tagging experiments in bb0n reactions.

ACKNOWLEDGEMENTS

The following agencies and institutions supported the present work: the European Research Council (ERC-2020-SyG 951281), the Spanish MICINN (PID2019-104772GB-100, RED2018-102387-T) and the Basque Government (IT-1553-22).

REFERENCES

[1] Freixa, Z.; Rivilla, I.; Monrabal, F; Gómez-Cadenas, J. J.; Cossío. F. P. *Phys. Chem. Chem. Phys.* **2021**, *23*, 15440-15457.
[2] Rivilla, I.; Aparicio, B.; Bueno, J. M.; Casanova, D.; Tonnelé, C.; Freixa, Z.; Herrero, P.; Rogero, C.; Miranda, J. I.; Martínez-Ojeda, R. M.; Monrabal, F.; Olave, B.; Schäfer, T.; Artal, P.; Nygren, D.; Cossío, F. P.; Gómez-Cadenas, J. J. *Nature*, **2020**, *583*, 48-54.
[3] Herrero-Gómez, P.; Calupitan, J. P.; Ilyn, Berdonces-Layunta, M. A.; T. Wang., de Oteyza, T. G. G.; Corso, M.; González-Moreno,. R.; Rivilla, I., Aparicio, B., Aranburu, A. I.; Freixa, Z.; Monrabal, F.; Cossío, F. P.; Gómez-Cadenas, J. J.; Rogero, C. *Nat. Commun.* **2022**, *13*, 7741.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Visible-Light-Driving Organic Chemistry: Synthesis of Small Molecules and Biomolecules Modifications

Marcio Weber Paixão

Federal University of São Carlos, Centre of Excellence for Research in Sustainable Chemistry, São Carlos – São Paulo – Brazil
****e-mail: mwpaixao@ufscar.br***

Keywords: *Photochemistry, Sustainability, Biomolecules*

ABSTRACT

In the last decades, the emphasis and application of sustainable chemistry principles have driven a change in behavior of both chemical industry and academy. They aim to obtain the desired product with fewest step, high yield and by using non-toxic reagents. Therefore, the recognition of environmental benefits presented in photochemical reactions has motivated the scientific community to develop efficient and simple strategies for the synthesis of biologically relevant organic compounds. In this regard, we will present our recent findings on visible-light-driving the synthesis of heterocyclic scaffolds [1] and modifying biomolecules.[2] Moreover, a versatile and robust photocatalytic methodology to forge amide functional groups from 1,3-dipoles will be also presented.[3]

ACKNOWLEDGEMENTS

We are grateful to CNPq - INCT Catálise, Grant No 444061/ 2018-5 and Universal Project 405052/2021-9 and FAPESP (21/06099-5).

REFERENCES

[1] For a review see: Correia, J. T. M.; Santos, M. S.; Pissinati, E. F.; da Silva, G. P.; Paixão, M. W. *Chem. Rec.* **2021**, *21*, 2666-2687.
[2]. Lima, R. N.; Delgado, J. A. C.; Bernardi, D. I.; Berlinck, R. G. S.; Nikolaos, K.; Ackermann, L.; Paixão, M. W. *Chem. Commun.* **2021**, *57*, 5758–5761.
[3]. (a) Matsuo, B. T.; Correia, J. T. M.; Paixão, M. W. *Org. Lett.* **2020**, *22*, 7891–7896. (b) Matsuo, B. T.; Oliveira, P. H. R.; Correia, J. T. M.; Paixão, M. W. *Org. Lett.* **2021**, *23*, 6775–6779. (c) Oliveira, P. H. R.; Tordato, E. A.; Vélez, J. A. C.; Carneiro, P. S.; Paixão, M. W. *J. Org. Chem.* **2022**, https://doi.org/10.1021/acs.joc.2c02266.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Obtaining and characterizing studies of novel solid forms of ciprofibrate.

Borges, B. A.,[1*] Silva, U. C.,[1] Doriguetto, A. C.,[1] Reis, K. S.,[1] Araújo, M. B., [1] Bonfilio, R.[1]

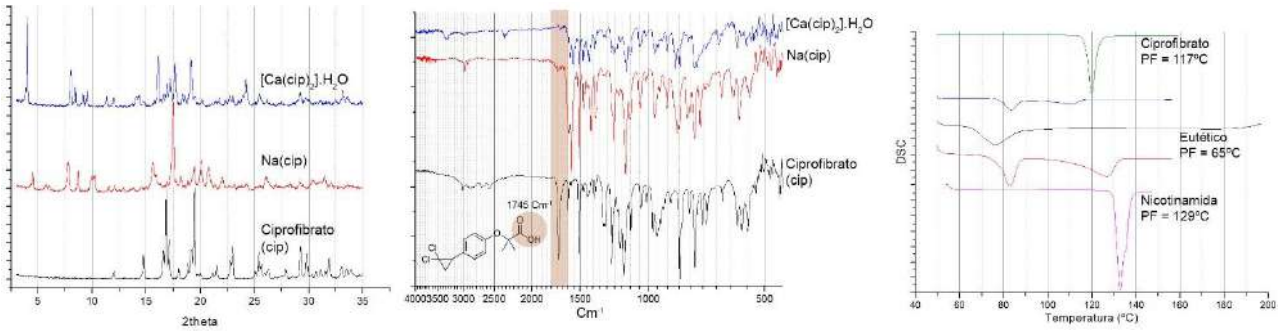
1) Postgraduate Program in Pharmaceutical Sciences, Faculty of pharmaceutical sciences, Federal University of Alfenas (UNIFAL), 37130-001.

****e-mail: bruno.borges@sou.unifal-mg.edu.br***

Keywords: Ciprofibrate; Pharmaceutical salts; Co-crystals; Polymorphism; PXRD; Thermal analysis.

ABSTRACT

Ciprofibrate is an API used for hyperlipidemia and dyslipidemia[1–3]. It has solubility issues due to its hydrophobic nature[4]. Different solid forms like salts, co-crystals or polymorphs can improve solubility[5,6]. In this work, attempts to obtain co-crystals and polymorphs were unsuccessful, but sodium and calcium salts of ciprofibrate and a eutectic mixture with nicotinamide were obtained using solvent evaporation and mechanochemistry techniques. The solid forms were characterized by thermal analysis (TG/DSC), elemental analysis (CHN), X-ray powder diffraction (XRD), infrared (FTIR) and scanning electron microscopy (SEM). Stability, solubility, and dissolution tests will be conducted. Quantification will be done using an HPLC method validated according to RDC 166 of 2017 regulations. Images below show the analysis by PXRD and FTIR of the obtained salts and the DSC results of the eutectic mixture.



Scheme 1. PXRD and FTIR of the salts obtained in comparison with the free form and the thermograms by DSC of the mixtures with nicotinamide in molar proportions of 2:1, 1:1 and 1:2.

ACKNOWLEDGEMENTS

CAPES (Financing Code 001) and FAPEMIG (Master's Scholarship).

REFERENCES

[1]. Atmosudigdo, I. S.; Lim, M. A.; Radi, B.; Henrina, J.; Yonas, E.; Vania, R.; Pranata, R. *Clinical Medicine Insights: Endocrinology and Diabetes* **2021**, *14*.

[2]. Winthrop, S. *et* al. Biochemical Pharmacology **1994**, *48* (12), 2163–2171.

[3]. Kamata, S.; Oyama, T.; Saito, K.; Honda, A.; Yamamoto, Y.; Suda, K.; Ishikawa, R.; Itoh, T.; Watanabe, Y.; Shibata, T.; Uchida, K.; Suematsu, M.; Ishii, I. *iScience* **2020**, *23* (11), 101727.

[4]. Corrêa, R. L. G. Q.; Dos Santos, R.; Albuquerque, L. J. C.; de Araujo, G. L. B.; Edwards-Gayle, C. J. C.; Ferreira, F. F.; Costa, F. N. *Polymers* **2021**, *13* (18).

[5]. Aitipamula, S. *et al. Crystal Growth and Design* **2012**, *12* (5), 2147–2152.

[6]. Domingos, S.; André, V.; Quaresma, S.; Martins, I. C. B.; Minas Da Piedade, M. F.; Duarte, M. T. *Journal of Pharmacy and Pharmacology* **2015**, *67* (6), 830–846.

7th Brazil-Spain Workshop on Organic Chemistry

BSWOC 2023

Ribeirão Preto - SP, Brazil
July 10-12, 2023

Screening of new solid forms of domperidone.

Reis, K. S.,[1*] Borges, B. A., [1] Leite, M. F., [1] Bonfilio, R.[1, *]

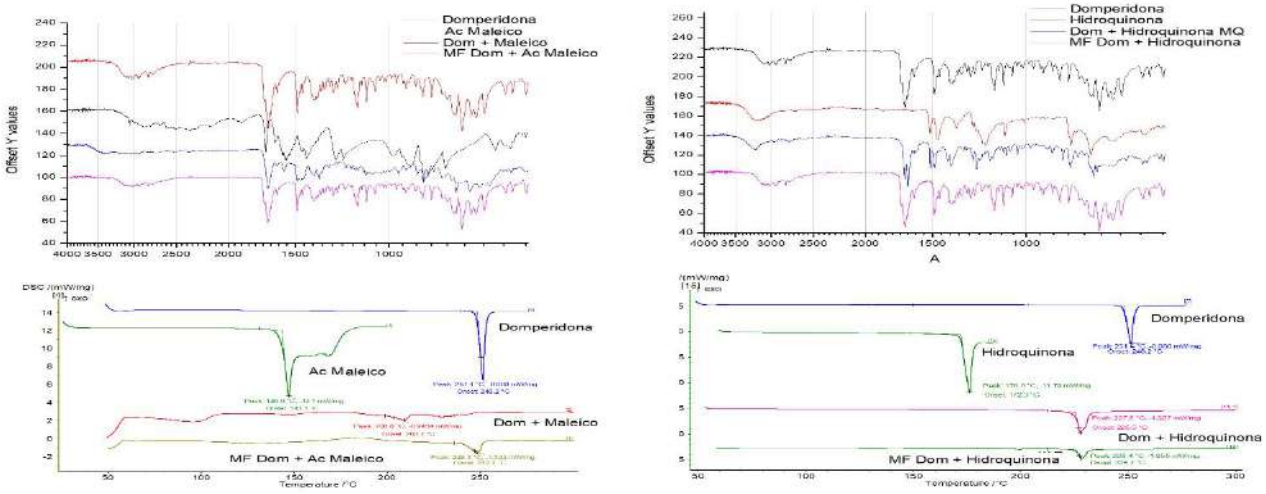
1) Postgraduate Program in Pharmaceltical Sciences, Faculty if Pharmaceutical Sciences, Federal University of Alfenas (UNIFAL), 37130-001.

****e-mail: kassius.reis@sou.unifal-mg.edu.br***

Keywords: Domperidone; Co-crystals; Salts; Characterization.

ABSTRACT

Domperidone is an antiemetic medication used for symptoms like nausea, reflux, epigastric pain and gastroparesis. Its therapeutic effectiveness is hindered by low water solubility and extensive first-pass metabolism, resulting in poor bioaivability. [1] Strategies to enhance its properties involve obtaining new solid forms like salts or co-crystals and combining with orodispersible tablets for better solubility, dissolution and bioavailability. [2,3,4] [5] This research aims obtaining new forms of domperidone using mechanochemical synthesis. Initially, the Cambridge Structural Database (CSD) was used as a tool for designing co-crystals based on supramolecular synthons. [6] Subsequently, various substances were tested as co-formers to achieve desired solid forms. Attempts to obtain new solid forms were carried out through solvent-assisted mechanochemical synthesis followed by characterization using differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD) and Fourier transform infrared spectroscopy (FTIR). The data below was obtained by analysis of domperidone, co-formers (hydroquinone and maleic acid), synthesized product and physical mixture in a 1:1 molar ratio.



Scheme 1. Comparison of FTIR spectra and thermograms obtained by DSC from domperidone with the co-former, product of the mechanochemical synthesis and physical mixture.

ACKNOWLEDGEMENTS

CAPES (Financing Code 001) and FAPEMIG (Master's Scholarship).

REFERENCES

[1]. Enteshari, S.; Varshosaz, J. Solubility Enhancement of Domperidone by Solvent Change In situ Micronization Technique. *Advanced Biomedical Research.* **2011,** 7, 109.

[2]. Bruni, G. et al. Structure and properties of domperidone and its succinate salt. *Acta Crystallographica Section B: Structural Science, Crystal Engineering and Materials.* **2013**, 69, 362-370.

[3]. Garg, A.; Gupta, M. M. Mouth Dissolving Tablets: A Review. *Journal of Drug Delivery & Therapeutics.* **2011**, 2013, 207.

[4]. Naik, V.; Roshanarai, R.; Chirra, P.; & Thanda, V. *International Journal of Preclinical and Pharmaceutical Research.* **2012**, 1, 23-32.

[5]. Abay, F. B.; Ugurlu, T. Orally Disintegrating Tablets: A Short Review. *Journal of Pharmaceutics and Drug Development.* **2015**, 3**.**

[6]. Fábián, L. Cambridge Strucutral Database Analysis of Molecular Complementarity in Cocrystals. *Crystal Growth and Design.* **2009**, 9, 1436-1443.