SPQ

Book of Abstracts

16ENQO
9ENQMB

Book of Abstracts
16th National Organic Chemistry Meeting (16ENQO)
9th National Medicinal and Biological Chemistry Meeting (9ENQMB)
11–13 February 2026
Faculty of Sciences, University of Lisbon

Book of abstracts

16th National Organic Chemistry Meeting (16ENQO) and the 9th National Medicinal and Biological Chemistry Meeting (9ENQMB)

Faculty of Sciences, University of Lisbon, Portugal

11-13 February 2026

Editors

Susana Costa

Manuela Raposo

Jaime Coelho

Pedro Góis

Edition

Sociedade Portuguesa de Química

Av. da República, 45 – 3º Esq.

1050-187 Lisboa – Portugal

Date

February 2026

ISBN (digital version, PDF)

978-989-8124-51-7

ISBN 978-989-8124-51-7

9 789898 124517

Recommended cataloguing

Book of abstracts of the 16th National Organic Chemistry Meeting (16ENQO) and the 9th National Medicinal and Biological Chemistry Meeting (9ENQMB)

Faculty of Sciences, University of Lisbon, Portugal, 2026 – 228 p.

This book was produced from abstracts submitted directly by the authors, in accordance with the published template. Only minor formatting changes were made, which did not alter the scientific content, which is the sole responsibility of the authors.

INDEX

WELCOME

Organic, Medicinal and Biological Chemistry:
Advancing Sustainable Solutions for Global Challenges

The Divisions of Organic Chemistry and of Medicinal Chemistry & Chemical Biology of the Portuguese Chemical Society (SPQ) are delighted to welcome you to the 16th National Organic Chemistry Meeting (16ENQO) and the 9th National Medicinal and Biological Chemistry Meeting (9ENQMB), at the Faculty of Sciences of the Universidade de Lisboa, Portugal, from 11 to 13 February 2026.

The ability to synthesise increasingly complex molecules has transformed Organic Chemistry into a fundamental science, enabling advances across synthetic methodology, molecular design, and chemical innovation. Integrated with Medicinal and Biological Chemistry, these approaches address challenges in human health while also fostering environmentally friendly processes, safer materials, and sustainable solutions to global societal challenges.

At this unique and dynamic scientific interface, **16ENQO & 9ENQMB** will present an exciting multidisciplinary scientific programme, bringing together national and international experts. The event will feature a wide range of contributions, ranging from the development of new synthetic methodologies and novel molecular architectures to the design of molecules, complexes, and materials, as well as computational models that together advance our understanding of biological processes, drive chemical innovation, and contribute to sustainable solutions across health, industry, and the environment.

We warmly invite you to share your knowledge with us in Lisbon, where the meeting will offer numerous opportunities for oral communications, scientific awards, and a vibrant social programme in the heart of this beautiful city.

Manuela Raposo
Pedro Góis
Jaime Coelho

COMMITTEES

Scientific Committee

Joaquim Luís Faria (President of the Portuguese Chemical Society, FE-UP)
António Manuel Deométrio Pereira (UEvora)
Artur Silva (UAveiro)
Carlos Afonso (FF-UL)
Jorge Salvador (FF-UC)
Lucinda Reis (UTAD)
M. Matilde Marques (IST)
Maria Emília Sousa (FF-UP)
Maria Fernanda Proença (UMinho)
Maria Lurdes Cristiano (UAlgarve)
Paula Branco (NOVA-FCT)
Paula Gomes (FC-UP)
Paulo Almeida (UBI)
Teresa Pinho e Melo (FCT-UC)
Victor Freitas (FC-UP)

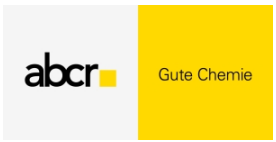
Organizing Commitee

Maria Manuela Marques Raposo (UMinho) – Chairperson & President of the Organic Chemistry Division
Pedro Miguel Pimenta Góis (FF-UL) – Chairperson & President of the Medicinal Chemistry & Chemical Biology Division
Jaime A. S. Coelho (FC-UL) - Chairperson of the 16ENQO / 9ENQMB
Duarte B. Clemente (FC-UL)
Fábio M. F. Santos (FF-UL)
Filipa Siopa (FF-UL)
João P. M. António (FF-UL)
João R. Vale (FF-UL)
Sílvia M. M. A. Pereira-Lima (UMinho)
Susana P. G. Costa (UMinho)

SUPPORT AND SPONSORS

Institutional support

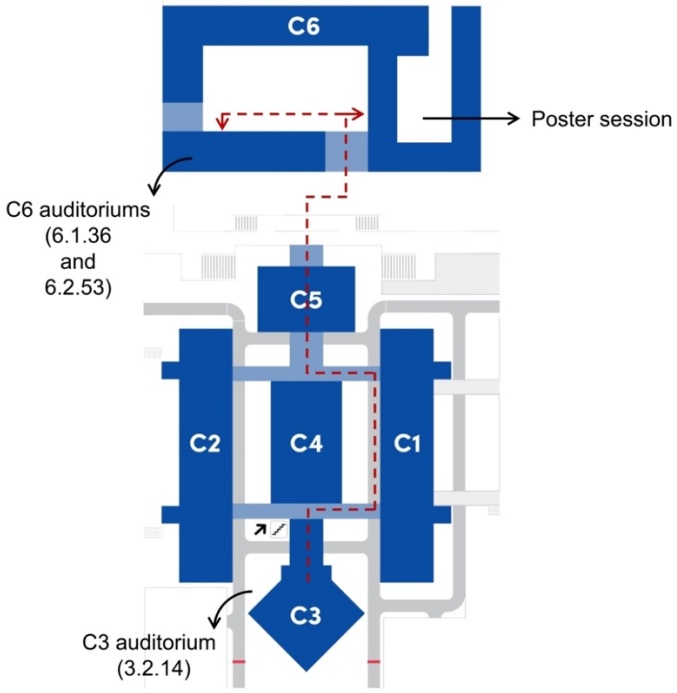
Sponsors



IMPORTANT INFORMATION

Venue

Faculty of Sciences of the University of Lisbon (FCUL), **Buildings C3** and **C6.**
Campo Grande, 1749-016 Lisboa, Portugal.
The FCUL campus is located in Campo Grande and is easily accessible by public transport.



Oral communications

All speakers are requested to adhere to the stipulated time in order to avoid delays in the programme.
Time allocation (including discussion):

Plenary Lecture	**Invited Lecture**	**Keynote**	**Invited OC**	OC	Flash OC
45 min	30 min	30 min	15 min	15 min	7 min

Poster communications

Maximum size : A0, 85 x 110 cm, vertical orientation.
The posters will be on permanent display and should be put up on the first day of the meeting and removed on the third day of the meeting, after the last poster session.
The poster sessions will take place during the Wednesday and Thursday afternoon coffee breaks.

Conference Dinner (for participants with Full registration)

Thursday, February 12, 2026
Museu da Cerveja, Terreiro do Paço – Ala Nascente nº 62 a 65, 1100-148 Lisboa.

SCHEDULE

		Wednesday, Feb 11	Thursday, Feb 12		Friday, Feb 13	
			Room 3.2.14		*Room 3.2.14*	
9:00	9:45		**PL3 Tanja Weil**		**PL5 Mariola Tortosa**	
9:45	10:15		**IL3 - Miguel Machuqueiro**		**IL5 - Vera Silva**	
10:15	10:45		Coffee break		Coffee break	
10:45	11:30		**PL4 Gonçalo Bernardes**		**PL6 Rui Moreira**	
11:30	12:00		**IL4 - Ivo Sampaio-Dias**		**IL6 – Mª João Matos**	
12:00	14:00	Registration	Lunch & Exhibition area (C6)		Lunch & Exhibition area (C6)	
		Room 3.2.14	*Room 6.1.36*	*Room 6.2.53*	*Room 6.1.36*	*Room 6.2.53*
14:00	14:30	Opening Ceremony	**KN1 - Rafael Gomes**	**KN2 - Mª M. Santos**	**KN5 - Nuno Candeias**	**KN6 - Tânia Morais**
14:30	14:45		IOC1- Kevin Cariou	IOC2 - Ana Pina	IOC6 - Milos Vavrik	IOC7 – João Sardinha
14:45	15:00	**PL1 Amir Hoveyda**	OC1- Mª Manuel Marques	OC3 - Ana Estrela	OC8 - João Vale	OC10- Rita Silva-Reis
15:00	15:15		OC2 - João Simões	OC4 - Ana Laura Dias	OC9 - Nuno Moura	OC11 - Márcia Martins
15:15	15:30		F1 - Bruno Guerreiro F2 - Domingos Manuel	F3 - Eurico Lima F4 - Eduarda Ramos	F9 - Raquel Silva F10 - Mariana Peixoto	F11 - Bruna Costa F12- Esther Calvino-Sanles
15:30	15:45	**IL1 - Carlos Baleizão**	Posters & Exhibition area (C6)		Posters & Exhibition area (C6)	
15:45	16:00					
16:00	16:15	Coffee break				
16:15	16:45		**KN3 - João Tomé**	**KN4- Vânia Moreira**	**KN7 - Paula Ferreira**	**KN8 – Mª João Moreno**
16:45	17:00	**PL2 Anna Hirsch**	IOC3 - João Borges	IOC4- Alberto Dal Corso	IOC8- Carlos Monteiro	IOC9 - Patrícia Rijo
17:00	17:15		OC5 - Nuno Basílio	OC7- Nicholas Bossons	OC12- Mª João Queiroz	OC13 - Gonçalo Justino
17:15	17:30		OC6 - Sandra Pinto	IOC5- Jessica Baiget	F13 - Ricardo Chagas F14 - Milene Fortunato	F15 - Jorge Gonçalves F16 - Vasco Castanheira
17:30	17:45	**IL2 – Filipa Marcelo**	F5 - Ana Amorim F6 - Ricardo Ferraz	F7- Anastasiya Voloshchuk F8 - Patrícia Correia	Closing ceremony & awards	
17:45	18:00	Welcome Reception	General Meeting			
			Congress Dinner			

Plenary Lecture 45 min	Invited Lecture 30 min	Keynote 30 min	Invited OC 15 min	OC 15 min	Flash OC 7 min

SCIENTIFIC PROGRAM

Wednesday, February 11	
14:00	**Opening Cerimony** **Joaquim Luís Faria** (President of the Portuguese Chemical Society, FE-UP) **António Casimiro** (Vice-Dean of the Faculty of Sciences of the University of Lisbon) **Jaime Coelho** (Organizing Commitee and Chairperson of the 16ENQO/9ENQMB, FC-UL)
	***Chair**: Manuela Raposo / Pedro Góis*
14:45	**Plenary Lecture 1** **Amir H. Hoveyda** (Boston College, Chestnut Hill, United States) *Established chemistry reprogrammed for precise remolding of alkaloids*
15:30	**Invited Lecture 1** **Carlos Baleizão** (Instituto Superior Técnico, Universidade de Lisboa, Portugal) *Bridging organic chemistry and functional nanomaterials*
16:00	Coffee break
	***Chair**: Matilde Marques / Giovanni Poli*
16:45	**Plenary Lecture 2** **Anna K. H. Hirsch** (Helmholtz Institute for Pharmaceutical Research Saarland, Saarbrücken, Germany) *Tackling underexplored drug targets as a pathway to antibiotics with a novel mode of action*
17:30	**Invited Lecture 2** **Filipa Marcelo** (NOVA School of Science and Technology, Caparica, Portugal) *Glycan recognition as Chemical Biology strategy in cancer therapy*
18:00	**Welcome reception**
Thursday, February 12	
	***Chair**: Paula Branco / Paula Gomes*
9:00	**Plenary Lecture 3** **Tanja Weil** (Max Planck Institute for Polymer Research, Mainz, Germany) *Synthesis in living environments for material–cell communication*
9:45	**Invited Lecture 3** **Miguel Machuqueiro** (Faculdade de Ciências da Universidade de Lisboa, Portugal) *Computational methods to capture pH effects in biomolecules*
10:15	Coffee break
	***Chair**: Paula Branco / Paula Gomes*
10:45	**Plenary Lecture 4** **Gonçalo Bernardes** (University of Cambridge, Cambridge, United Kingdom) *Translational Chemical Biology*
11:30	**Invited Lecture 4** **Ivo E. Sampaio-Dias (**LAQV/REQUIMTE - Faculdade de Ciências da Universidade do Porto, Portugal) *Rational design of proline derivatives for the assembly of bioactive peptides targeting neurological disorders*
12:00	Lunch

	Room 6.1.36
	***Chair**: Fernanda Proença*
14:00	**Keynote 1** **Rafael F. A. Gomes** (iMed.ULisboa, Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal) *Ultra-high-pressure enables electrocyclization reactions*
14:30	**Invited Oral communication 1** **Kevin Cariou** (Chimie ParisTech, PSL University, CNRS, Paris, France) *Organometallic derivatization of drugs for promising antiparasitic and antifungal treatments*
14:45	**Oral Communication 1** **Maria Manuel B. Marques** (LAQV-REQUIMTE, *NOVA School of Science and Technology,* UNL) *Next-generation cyclic iodine(III) reagents driving new frontiers in bond-forming chemistry*
15:00	**Oral Communication 2** **João C. S. Simões** (University of Coimbra, CQC-IMS and Department of Chemistry, Coimbra, Portugal) *A novel synthetic pathway to trans-A2B2-porphyrins: from serendipitous discovery to controlled macrocyclization*
15:15	**Flash Oral Communication 1** **Bruno C. Guerreiro** (CCMAR, Faculty of Sciences and Technology, University of Algarve) *Unanticipated reactivity towards nucleophilic attack in the synthesis of saccharyl-1,3,4-thiadiazolyl conjugates*
15:22	**Flash Oral Communication 2** **Domingos Morais Manuel** (iMed.ULisboa, FFUL; CQE-IMS, FCUL; Inst. Sup. C. Educação da Huíla, Angola) *Synthesis of novel D-glucuronamide-based nucleos(t)ide analogs as promising anticancer and antibacterial hits*
	Room 6.2.53
	***Chair**: Susana Costa*
14:00	**Keynote 2** **Maria M. M. Santos** (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa) *Small molecules to reclaim tumor suppressor p53 function in cancer*
14:30	**Invited Oral communication 2** **Ana S. Pina** (ITQB, Universidade NOVA de Lisboa, Portugal) *Liquid–liquid phase separation driven peptide microreactors as minimal hubs for emergent catalysis*
14:45	**Oral Communication 3** **Ana Estrela** (Fundação GIMM, Lisboa, Portugal; Faculdade de Ciências, Universidade de Lisboa) *In vitro evaluation of innovative peptides towards breast cancer metastization*
15:00	**Oral Communication 4** **Ana Laura Dias** (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa) *Machine learning-guided target identification and optimization of a scorpion-venom alkaloid*
15:15	**Flash Oral Communication 3** **Eurico Lima** (CQ-VR, UTAD, *Vila Real*; RISE-Health, Faculty of Health Sciences, UBI, Covilhã) *"Mild modifications with major biological effects": in vitro efficacy of squaraine dyes as anticancer photodynamic agents*
15:22	**Flash Oral Communication 4** **Eduarda Ramos** (RISE-Health, Faculty of Sciences, University of Beira Interior, Covilhã, Portugal) *Bioinspired metallophore analogues: synthetic approaches and applications in infection diagnostics*
15:30	Coffe break and Posters (C6)

	Room 6.1.36
	***Chair**: Teresa Pinho e Melo*
16:15	**Keynote 3** **João P. C. Tomé** (Instituto Superior Técnico, Universidade de Lisboa, Portugal) *Visible-light-activatable molecules: porphyrins and related compounds*
16:45	**Invited Oral communication 3** **João Borges** (CICECO, Universidade de Aveiro, Portugal) *DNA-inspired supramolecular hydrogels assembled by combining non-covalent and covalent strategies*
17:00	**Oral Communication 5** **Nuno Basílio** (LAQV-REQUIMTE, Faculdade de Ciências e Tecnologia, Universidade NOVA de Lisboa) *Calixarene–pyrene conjugates for induced-fit recognition and dual-wavelength fluorescence sensing in water*
17:15	**Oral Communication 6** **Sandra N. Pinto** (iBB, Instituto Superior Técnico, Universidade de Lisboa, Lisbon, Portugal) *Dendrimer-induced biofilm disruption is accompanied by a global shift in Listeria monocytogenes gene expression*
17:30	**Flash Oral Communication 5** **Ana C. Amorim** (CQC-IMS, Department of Chemistry, University of Coimbra, Portugal) *Molecular design of new organic emitters for light-emitting devices*
17:37	**Flash Oral Communication 6** **Ricardo Ferraz** (LAQV-REQUIMTE, FCUP; RISE-Health, TBIO, ESS, Polytechnic of Porto) *How click chemistry could enhance antimalarial drugs with antimicrobial ionic liquids*
	Room 6.2.53
	***Chair**: João António*
16:15	**Keynote 4** **Vânia M. Moreira** (Faculdade de Farmácia da Universidade de Coimbra, Portugal) *Unlocking the potential of the diterpenoids for the treatment of infection*
16:45	**Invited Oral communication 4** **Alberto Dal Corso** (Università degli Studi di Milano, Italy) *A bispecific small molecule mediates armed antibodies targeting of bone mineral matrix*
17:00	**Oral Communication 7** **Nicholas Bossons** (Chemprecise Lda, Torres Vedras, Portugal; iMed.ULisboa, FFUL) *A scorpion venom derived natural product as a TRPV1 antagonist for the treatment of neuropathic pain*
17:15	**Invited Oral Communication 5 (Industry)** **Jessica Baiget (BIAL)** *Identification of a brain penetrant DβH inhibitor for the treatment of panic and anxiety disorders*
17:30	**Flash Oral Communication 7** **Anastasiya Voloshchuk** (iMed.Ulisboa, Faculty of Pharmacy, Universidade de Lisboa, Portugal) *Ferroptosis-inducing PROTACs for targeted cancer therapy*
17:37	**Flash Oral Communication 8** **Patrícia Correia** (REQUIMTE/LAQV, Department of Chemistry and Biochemistry, Faculty of Sciences, Porto) *When light heals: flavylium derivatives as a new class of photosensitizers for photodynamic antimicrobial therapy*
17:45	**General Meeting**

Friday, February 13	
	***Chair**: Emília Sousa/ Carlos Afonso*
9:00	**Plenary Lecture 5** **Mariola Tortosa** (Autonomous University of Madrid, Madrid, Spain) *Catalysis to increase complexity: stereoselective synthesis of sp^3-rich building blocks*
9:45	**Invited Lecture 5** **Vera L. M. Silva** (Universidade de Aveiro, Portugal) *Synthesis of novel glycosylated quinolone and acridone scaffolds and evaluation of their cytotoxic activity*
10:15	Coffee break
	***Chair**: Emília Sousa/ Carlos Afonso*
10:45	**Plenary Lecture 6** **Rui Moreira** (Faculdade de Farmácia da Universidade de Lisboa, Portugal) *Chemical Modalities and Precision Medicine. New tools for targeted drug release and targeted degradation of challenging proteins*
11:30	**Invited Lecture 6** **Maria J. Matos** (Faculty of Pharmacy, University of Santiago de Compostela, Spain) *Tackling underexplored drug targets as a pathway to antibiotics with a novel mode of action*
12:00	Lunch
	Room 6.1.36
	***Chair**: Victor Freitas*
14:00	**Keynote 5** **Nuno R. Candeias** (Universidade de Aveiro, Portugal) *Exploring the carbon-centred radical chemical space: from quinic acid to peroxysilanes*
14:30	**Invited Oral communication 6** **Milos Vavrik** (Department of Organic Chemistry, University of Vienna, Austria) *Regiodivergent cation sampling for distal Csp3-functionalization*
14:45	**Oral Communication 8** **João R. Vale** (iMed.ULisboa, Faculty of Pharmacy, Universidade de Lisboa) *Photocatalytic synthesis of indoles*
15:00	**Oral Communication 9** **Nuno M. M. Moura** (LAQV-Requimte and Department of Chemistry, University of Aveiro, Portugal) *Strategic synthetic approaches to push–pull porphyrin–carbazole derivatives*
15:15	**Flash Oral Communication 9** **Raquel Nunes da Silva** (LAQV-REQUIMTE; Chemistry and Biochemistry Department, Faculty of Sciences, University of Porto) *Bioactive recovery from tomato by-products: green chemical strategies for circular and sustainable food preservation*
15:22	**Flash Oral Communication 10** **Mariana Peixoto** (CQC– IMS, Department of Chemistry, University of Coimbra, Portugal) *Unlocking AIEgen potential via green multicomponent reactions*
	Room 6.2.53
	***Chair**: Fábio Santos*
14:00	**Keynote 6** **Tânia S. Morais (CQE-IMS, Faculdade de Ciências, Universidade de Lisboa; *IST-ID*)** *Unlocking the potential of ruthenium(II)-based compounds as anticancer chemotherapeutic and targeted agents*

14:30	**Invited Oral communication 7 (Industry)** **João Sardinha** (Hovione) *Micellar catalysis: enabling sustainable chemistry in water*
14:45	**Oral Communication 10** **Rita Silva-Reis** (LAQV-REQUIMTE, University of Aveiro; CITAB, Inov4Agro, UTAD, Vila Real, Portugal) *Solvent choice and decarboxylation as critical modulators of the antitumor activity of Cannabis sativa L. extracts*
15:00	**Oral Communication 11** **Márcia S. Martins** (Laboratório de Química Orgânica e Farmacêutica, FFUP; CIIMAR) *Discovery of new marine inspired therapeutic agents for topical treatment of inflammatory dermatological diseases*
15:15	**Flash Oral Communication 11** **Bruna D. P. Costa** (CCC-IMS and Department of Chemistry, University of Coimbra, Portugal) *Photodynamic therapy of endometrial cancer using newly designed hydrazone-functionalized corroles*
15:22	**Flash Oral Communication 12** **Esther Calvino-Sanles** (GIMM, Lisbon, Portugal; iMed.ULisboa, Faculty of Pharmacy, University of Lisbon) *Metal chelation mediated development of PET tracers based on de novo designed mini binders*
15:30	Coffe break and Posters (C6)
	Room 6.1.36
	***Chair**: Lucinda Reis*
16:15	**Keynote 7** **Paula M. T. Ferreira** (Centro de Química da Universidade do Minho, Braga, Portugal) *Liquid–liquid phase separation of dehydropeptides: from molecular design to functional assemblies*
16:45	**Invited Oral communication 8 (Industry)** **Carlos Monteiro** (Ascenza Agro) *Synthesis laboratory in the agrochemical industry*
17:00	**Oral Communication 12** **Maria-João R. P. Queiroz** (Centro de Química da Universidade do Minho (CQ-UM), Braga, Portugal) *One-pot CuAAC strategies for 1,4-disubstituted 1,2,3-triazoles on (hetero)aromatics, including a green protocol in PEG_{400}*
17:15	**Flash Oral Communication 13** **Ricardo Chagas** (LAQV REQUIMTE, NOVA FCT, Caparica, Portugal) *Design and site-specific grafting of fluorescent probes onto cellulose via orthogonal coupling strategies*
17:22	**Flash Oral Communication 14** **Milene A. G. Fortunato** (iMed.ULisboa, Faculty of Pharmacy, Universidade de Lisboa, Portugal) *In-situ derivatization and isolation strategy of marine natural products for bioactive analogue discovery*
	Room 6.2.53
	***Chair**: Filipa Siopa*
16:15	**Keynote 8** **Maria João Moreno** (Faculdade de Ciências e Tecnologia da Universidade de Coimbra, Portugal) *Why membranes matter: lipid bilayers and 3D drug descriptors in PK/PD prediction*
16:45	**Invited Oral communication 9** **Patrícia Rijo** (CBIOS, Universidade Lusófona; iMed.ULisboa, FFUL; CQE-IMS, Universidade de Lisboa) *Abietane diterpenoids: natural scaffolds for antitumor drugs*
17:00	**Oral Communication 13** **Gonçalo C. Justino** (CQE-IMS, IST-UL, Lisbon, Portugal) *Mass Spectrometry multi-omics reveals mortality biomarkers and ECMO-induced molecular stress in critical illness*

17:15	**Flash Oral Communication 15** **Jorge M. Gonçalves** (Chemistry Centre of University of Minho (CQUM), Braga, Portugal) *Fluorescent 2-aminopurine derivatives: synthesis, photophysical properties and quantum chemical calculations*
17:22	**Flash Oral Communication 16** **Vasco M. S. Castanheira** (LAQV-REQUIMTE, Department of Chemistry, University of Aveiro, Portugal) *Targeting Gram-positive bacteria with tailored cationic diketopyrrolopyrroles as photosensitizers*
	Room 3.2.14
17:30	**Closing ceremony & awards** **Manuela Raposo** (President of the Organic Chemistry Division, UMinho) **Pedro Góis** (President of the Medicinal Chemistry & Chemical Biology Division, FFUL) *Portuguese Award for Best PhD Thesis in Organic Chemistry 2025* *Portuguese Award for Best PhD Thesis in Medicinal Chemistry & Chemical Biology 2025* *Portuguese Award for Best Master Thesis in Organic Chemistry 2025* *Portuguese Award for Best Master Thesis in Medicinal Chemistry & Chemical Biology 2025*

LIST OF COMMUNICATIONS

	Plenary Lectures
PL1	**Amir H. Hoveyda** *Established chemistry reprogrammed for precise remolding of alkaloids*
PL2	**Anna K. H. Hirsch** *Tackling underexplored drug targets as a pathway to antibiotics with a novel mode of action*
PL3	**Tanja Weil** *Synthesis in living environments for material–cell communication*
PL4	**Gonçalo Bernardes** *Translational Chemical Biology*
PL5	**Mariola Tortosa** *Catalysis to increase complexity: stereoselective synthesis of sp^3-rich building blocks*
PL6	**Rui Moreira** *Chemical Modalities and Precision Medicine. New tools for targeted drug release and targeted degradation of challenging proteins*

	Invited Lectures
IL1	**Carlos Baleizão** *Bridging organic chemistry and functional nanomaterials*
IL2	**Filipa Marcelo** *Glycan recognition as Chemical Biology strategy in cancer therapy*
IL3	**Miguel Machuqueiro** *Computational methods to capture pH effects in biomolecules*
IL4	**Ivo E. Sampaio-Dias** *Rational design of proline derivatives for the assembly of bioactive peptides targeting neurological disorders*
IL5	**Vera L. M. Silva** *Synthesis of novel glycosylated quinolone and acridone scaffolds and evaluation of their cytotoxic activity*
IL6	**Maria J. Matos** *Tackling underexplored drug targets as a pathway to antibiotics with a novel mode of action*

	Keynotes
KN1	**Rafael F. A. Gomes** *Ultra-high-pressure enables electrocyclization reactions*
KN2	**Maria M. M. Santos** *Small molecules to reclaim tumor suppressor p53 function in cancer*
KN3	**João P. C. Tomé** *Visible-light-activatable molecules: porphyrins and related compounds*
KN4	**Vânia M. Moreira** *Unlocking the potential of the diterpenoids for the treatment of infection*
KN5	**Nuno R. Candeias** *Exploring the carbon-centred radical chemical space: from quinic acid to peroxysilanes*
KN6	**Tânia S. Morais** *Unlocking the potential of ruthenium(II)-based compounds as anticancer chemotherapeutic and targeted agents*
KN7	**Paula M. T. Ferreira** *Liquid–liquid phase separation of dehydropeptides: from molecular design to functional assemblies*
KN8	**Maria João Moreno** *Why membranes matter: lipid bilayers and 3D drug descriptors in PK/PD prediction*

	Invited oral communications
IOC1	**Kevin Cariou** *Organometallic derivatization of drugs for promising antiparasitic and antifungal treatments*
IOC2	**Ana S. Pina** *Liquid–liquid phase separation driven peptide microreactors as minimal hubs for emergent catalysis*
IOC3	**João Borges** *DNA-inspired supramolecular hydrogels assembled by combining non-covalent and covalent strategies*
IOC4	**Alberto Dal Corso** *A bispecific small molecule mediates armed antibodies targeting of bone mineral matrix*
IOC5	**Jessica Baiget** *Identification of a brain penetrant DβH inhibitor for the treatment of panic and anxiety disorders*
IOC6	**Milos Vavrik** *Regiodivergent cation sampling for distal Csp3-functionalization*
IOC7	**João Sardinha** (Hovione) *Micellar catalysis: enabling sustainable chemistry in water*
IOC8	**Carlos Monteiro** *Synthesis laboratory in the agrochemical industry*
IOC9	**Patrícia Rijo** *Abietane diterpenoids: natural scaffolds for antitumor drugs*

	Oral communications
OC1	**Maria Manuel B. Marques** *Next-generation cyclic iodine(III) reagents driving new frontiers in bond-forming chemistry*
OC2	**João C. S. Simões** *A novel synthetic pathway to trans-A2B2-porphyrins: from serendipitous discovery to controlled macrocyclization*
OC3	**Ana Estrela** *In vitro evaluation of innovative peptides towards breast cancer metastization*
OC4	**Ana Laura Dias** *Machine learning-guided target identification and optimization of a scorpion-venom alkaloid*
OC5	**Nuno Basílio** *Calixarene–pyrene conjugates for induced-fit recognition and dual-wavelength fluorescence sensing in water*
OC6	**Sandra N. Pinto** *Dendrimer-induced biofilm disruption is accompanied by a global shift in Listeria monocytogenes gene expression*
OC7	**Nicholas Bossons** *A scorpion venom derived natural product as a TRPV1 antagonist for the treatment of neuropathic pain*
OC8	**João R. Vale** *Photocatalytic synthesis of indoles*
OC9	**Nuno M. M. Moura** *Strategic synthetic approaches to push–pull porphyrin–carbazole derivatives*
OC10	**Rita Silva-Reis** *Solvent choice and decarboxylation as critical modulators of the antitumor activity of Cannabis sativa L. extracts*
OC11	**Márcia S. Martins** *Discovery of new marine inspired therapeutic agents for topical treatment of inflammatory dermatological diseases*

OC12	**Maria-João R. P. Queiroz** *One-pot CuAAC strategies for 1,4-disubstituted 1,2,3-triazoles on (hetero)aromatics, including a green protocol in PEG_{400}*
OC13	**Gonçalo C. Justino** *Mass Spectrometry multi-omics reveals mortality biomarkers and ECMO-induced molecular stress in critical illness*

	Flash oral communications
F1	**Bruno C. Guerreiro** *Unanticipated reactivity towards nucleophilic attack in the synthesis of saccharyl-1,3,4-thiadiazolyl conjugates*
F2	**Domingos Morais Manuel** *Synthesis of novel d-glucuronamide-based nucleos(t)ide analogs as promising anticancer and antibacterial hits*
F3	**Eurico Lima** *"Mild modifications with major biological effects": in vitro efficacy of squaraine dyes as anticancer photodynamic agents*
F4	**Eduarda Ramos** *Bioinspired metallophore analogues: synthetic approaches and applications in infection diagnostics*
F5	**Ana C. Amorim** *Molecular design of new organic emitters for light-emitting devices*
F6	**Ricardo Ferraz** *How click chemistry could enhance antimalarial drugs with antimicrobial ionic liquids*
F7	**Anastasiya Voloshchuk** *Ferroptosis-inducing PROTACs for targeted cancer therapy*
F8	**Patrícia Correia** *When light heals: flavylium derivatives as a new class of photosensitizers for photodynamic antimicrobial therapy*
F9	**Raquel Nunes da Silva** *Bioactive recovery from tomato by-products: green chemical strategies for circular and sustainable food preservation*
F10	**Mariana Peixoto** *Unlocking AIEgen potential via green multicomponent reactions*
F11	**Bruna D. P. Costa** *Photodynamic therapy of endometrial cancer using newly designed hydrazone-functionalized corroles*
F12	**Esther Calvino-Sanles** *Metal chelation mediated development of PET tracers based on de novo designed mini binders*
F13	**Ricardo Chagas** *Design and site-specific grafting of fluorescent probes onto cellulose via orthogonal coupling strategies*
F14	**Milene A. G. Fortunato** *In-situ derivatization and isolation strategy of marine natural products for bioactive analogue discovery*
F15	**Jorge M. Gonçalves** *Fluorescent 2-aminopurine derivatives: synthesis, photophysical properties and quantum chemical calculations*
F16	**Vasco M. S. Castanheira** *Targeting Gram-positive bacteria with tailored cationic diketopyrrolopyrroles as photosensitizers*

	Poster communications
P1	**Zayra B. Silva** *Docking molecular and ADMET analysis of compounds derived from Catharanthusroseus against the E2 protein of CHIKV*
P2	**João Vaz** *Targeting cancer with near-infrared activated prodrugs*
P3	**Bárbara Bahls** *Design, screening and synthesis of new pyrrolo[4,3,2-de]quinolinone derivatives as new G4 targeting molecules*
P4	**Francisca Almeida-Pinto** *SARS-CoV-2 M^{pro}-targeting PROTACs to bypass antiviral resistance*
P5	**Bárbara Marques** *Anticancer potential of RuCp(II) complexes bearing (iso)nicotinic acid ligands*
P6	**Raquel M. Durão** *Easy access to functionalized sparteine derivatives via electrochemical cyanation of quinolizidine alkaloids*
P7	**Daiane N. Maronde** *Light-activated porphyrin for the photodynamic inactivation of S. aureus and E. coli*
P8	**João P. Telo** *Monoterpenoid selenophenes derived from (-)-carvone with GPx-like activity*
P9	**Cláudia Alves** *Cross-coupling approaches towards novel tryptanthrin derivatives*
P10	**Mariana P. Silva** *Selective synthesis of purple versus green-coloured azo-dyes with halochromic and antimicrobial properties*
P11	**Tiago Delgado** *Design, synthesis and activity of flexible nitrobenzamides as antitubercular agents targeting DprE1*
P12	**Catarina Henriques** *Breaking cancer resistance through the combinatorial use of Ru- and Se-based compounds*
P13	**Maria G. Rodrigues** *Developing an asymmetric catalytic version of the Barbier reaction: seeking new BACE-1 inhibitors*
P14	**Sara Hummeid** *Light-triggered modulation of VEGFR2: photoresponsive Sorafenib derivatives as antiangiogenic agents*
P15	**Inês Costa** *Length-dependent antimicrobial properties of peptide-ionic liquid conjugates*
P16	**Joana Agostinho** *Luminol-based chemiluminescent cyanines as new internal light sources in photodynamic therapy*
P17	**Gustavo Caldeira** *Photoactive glycodendritic conjugates for cancer imaging and therapy*
P18	**Bernardo Fragoso** *Optimizing SIRT1 activators for selectivity: a structure-based strategy to reduce off-target effects*
P19	**Margarida Fernandes** *Synthesis of magenta-coloured imidazole-based azo dyes*
P20	**Tomás G. Monteiro** *Design and synthesis of tryptophanol-derived PROTACs for selective degradation of DNA-contact p53 mutants*
P21	**Mathilde L. Boland** *Amphiphilic D-A-π-A benzothiadiazoles: photophysical insights for sensing and bioimaging applications*
P22	**Alice M. Dias** *Synthesis of 2-aminopurines and pyrrolo[2,3-d]imidazoles from common imidazole precursors: mechanistic studies*
P23	**Maria da Graça P. M. S. Neves** *1,3-Dipolar cycloaddition of N-allyl rhodanines: synthesis and anticancer evaluation of spiro derivatives*
P24	**Diogo Videira-Quintela** *First identification and characterization of a novel psychoactive substance: N-isopropylbutylone in a portuguese seized sample*

P25	**Juliana P. Sousa** *Synthesis, antiparasitic activity and SARs of methyl 5-(hetero)aryl or alkylaminothieno[2,3-b]pyridine-2-carboxylates*
P26	**Eduardo Reis** *AZABY as a novel pH-sensitive linker for targeted drug conjugates*
P27	**Marco Sá** *pH-Responsive ruthenium-peptide conjugates for metastatic breast cancer targeting*
P28	**Yaryna S. Buzan** *Evaluating toxicity and anti-osteogenic activity of Artemisinin-inspired endoperoxides in zebrafish larvae*
P29	**Sara R. D. Gamelas** *Detection of microRNA biomarkers using an optical nanosensor*
P30	**Rita P. Lopes** *Metabolite profile and neurotoxic effects of synthetic cannabinoids mixtures seized in Portugal*
P31	**Carla F. Ferreira** *New psychoactive substance N-propyl ephenidine detected and identified in a portuguese police seizure: the first notification in Europe*
P32	**Ricardo J. F. Ferreira** *Optimized tryptophanol-derived ligands targeting R273H and R280K mutant p53*
P33	**Samuel Silvestre** *Reductive heterocyclization of 2-nitrobenzylidenes for selective quinoline N-oxide synthesis*
P34	**Maria Carvalho** *Biofilm dynamics and extracellular vesicle profiles of mosquito-derived Pseudomonas spp.*
P35	**Pedro Santos** *Synthesis and photophysical characterization of axially functionalized silicon(IV) naphthalocyanines with phototheranostic potential*
P36	**Nuno Ferreira** *Targeting PI3K overexpression in cancer cells: molecular docking-guided design of novel 2,6,9-trisubstituted purine derivatives*
P37	**Luis Miguel N. F. S. Cruz** *Design of pH-dependent fluorescent complexes between a boronic acid-pyranoflavylium dye and diol-rich bioactives*
P38	**Mpanzu Nelo** *Synthesis of nucleos(t)ide analogs based on sugar-fused 1,4-diox-2-ene scaffolds*
P39	**Helena L. M. Nangacovié** *Valorization of Iris pseudacorus L.: metabolomic profiling by GC-MS*
P40	**Nina Wang** *Synthesis and functionalization of diketopyrrolopyrrole derivatives for biological applications*
P41	**Svilen Simeonov** *Copper-catalyzed synthetic transformations of biorenewable synthons to metabolites*
P42	**Tânia Moreira** *Synthesis of novel potentially bioactive azido nucleosides and related hydroxymethyl triazole derivatives*
P43	**Yasmine Fernine** *Novel chiral amino tryptantrins: new functional materials for chiroptical applications*
P44	**Margarida Pereira** *Exploring the potential of urea-based scaffolds for new therapeutic options in cystic fibrosis*
P45	**Gabriel V. L. Marques** *Synthesis and chiral resolution of biologically active terpene-based cannabidiol analogues*
P46	**Jéssica Macedo** *Electrochemical C7 functionalization of abietic and dehydroabietic acids: a greener oxidation strategy*
P47	**Paula M. Marcos** *Fluorescent dihomooxacalix[4]arenes for the detection of nitroaromatic explosives in solution and in the vapour phase*

P48	**Nuna Ramos** *Next-generation of organic upconverters: dithienopyrrole annihilators for TTA-UC-based bioimaging probes*
P49	**Catarina Maria** *Synthesis of carbohydrate-based antibacterial agents with potential against multidrug-resistant Gram-negative bacteria*
P50	**Mariana E. Linhares** *Targeted unnatural amino acid substitutions in the polymyxin B scaffold drive broad antibacterial activity*
P51	**Maria João Ferreira** *Exploring iridium apigenin complexes: synthesis and cytotoxic studies*
P52	**Terver John Sase** *A synthetic strategy towards novel aziridine-fused steroids*
P53	**Inês S. Martins** *Stereoselective electrochemical 1,4-dicyanation of abietanes*
P54	**Gustavo F. M. Mourinho** *Phosphine-driven Umpolung gamma-addition of iminochromanes to allenoates for the synthesis of functionalized 2H-chromenes*
P55	**Carla Fernandes** *Synthesis of analogues of marine-derived cyclopeptides and evaluation of antifungal synergistic effect with fluconazole*
P56	**A. Francisca G. Silva** *Synthesis, structural and antimicrobial assessments of a modified CW49 peptide for enhanced wound repair*
P57	**Daniel Almeida-Santos** *Mechanochemical synthesis of pyridines from furans*
P58	**Daniela R. Ferreira** *Exploring the 2-benzylbenzimidazole scaffold: synthetic strategies for toxicological insights*
P59	**Inês M. Bastos** *Novel pyrazole-based compounds as potent PARP-1 inhibitors in cancer cells*
P60	**M. Margarida Martins** *Aromatic aminopropyl lactams as potential anticancer agents for glioblastoma and hepatocellular carcinoma*
P61	**Festus O. Ogungbemiro** *Structure-based discovery of small-molecule inhibitors targeting a bacterial efflux pump through Fab-mimetic interactions*
P62	**Paula S. Branco** *Synthesis and modulation of human neutrophils' oxidative burst by floridoside phosphotriesters*
P63	**Ricardo M. Gomes** *Photochemical and electrochemical oxidation pathways for the conversion of alpha-pinene to pinocarvone*
P64	**Rafaela Silva** *In vitro validation of PARPi derivatives activity for metastatic triple negative breast cancer*
P65	**Ana Guerreiro** *PMC79 derivates for KRAS-mutated cancers: synthesis and characterization*
P66	**João P. S. Silva** *Allene-driven construction of structurally diverse chiral spiro-beta-lactams from 6-alkylidenepenicillanates*
P67	**Daniel Cavaco** *Porphyrin-nanodiamond conjugates for photodynamic therapy and fluorescence imaging*
P68	**Elizabeth A. Lopes** *Butyrolactones from marine-derived Aspergillus terreus as anti-aging agents*
P69	**Ricardo G. Rocha** *Increasing aqueous solubility of porphyrins using machine learning and hydrotropy*
P70	**Ana Sofia Almeida** *Synthesis and structure elucidation of major metabolites of methylone and pentedrone for further toxicological studies*

P71	**Rita Lima** *Synthesis of chitosan-based chiral conjugates for liquid chromatography and biological evaluation*
P72	**Joana Moreira** *Lysine N-acylated dehydropeptides as potential substrates for histone deacetylase-triggered intracellular transformations*
P73	**Mariana Cruz** *Dehydrophenylalanine-driven adaptive peptide dispersions enable controlled encapsulation and adhesion*
P74	**Fábio M. F. Santos** *Structural optimization of BASHY platform for bioimaging*
P75	**Inês L. Roque** *Engineering DAB units as self-immolative modules for ROS responsive linkers*
P76	**Honorina Cidade** *Flavonoids as potential antimitotic agents: synthesis, bioactivity evaluation and structure-activity relationship studies*
P77	**Inês Costa** *Targeting oxidative stress in Alzheimer's disease: synthesis and neuroprotective potential of novel xanthene derivatives*
P78	**Sónia C. S. Pinto** *Design, synthesis, and biological evaluation of triphenylamine-benzothiadiazole derivatives for enhanced photodynamic therapy*
P79	**Daniel J. V. A. dos Santos** *On the search for TMBIM4 pharmacological inhibitors*
P80	**Afonso S. G. M. Verde** *Catalyst free synthesis of trans-3,4,5-triamino-cyclopent-2-enones*
P81	**Vera M.S. Isca** *Abietane diterpenoids from Plectranthus: stability, drug-likeness, and anticancer potential*
P82	**Rafaela A. N. Cavadas** *N-Terminal cysteine bioconjugation enables direct benzodiazaborine formation on peptides*
P83	**Rita D. Felisberto** *Sphaerococcenol A derivatives for the treatment of Parkinson's disease*
P84	**Bruna F. L. Guerreiro** *Customized non-conventional solvents for improved solubility and stability of nucleic acids*
P85	**João P. M. António** *Click! Bioconjugate! Release!: a unified diazaborine platform for stimuli-responsive therapeutics*
P86	**Catarina Cipriano** *Hypervalent iodine reagents as mediators of N-glycosylation*
P87	**Maria B. Igreja-Cardoso** *New sila-based ligands of vitamin D receptor for application in breast cancer therapy*
P88	**André Peralta** *Photochemical oxidation of enaminones*
P89	**Abdullahi A. Muiz** *Chiral sparteine thioureas: synthesis and characterization*
P90	**Tiago M. P. Santos** *Emerging technologies for the transformation of biomass-derived nitrogen-rich furans*
P91	**Mariana C. Monteiro** *Synthesis of new pyrazoline derivatives via photoinduced 1,3-dipolar cycloaddition*
P92	**Francisco P. Nascimento** *DFT insights into the electrochemical 1,4-dicyanation of abietanes*
P93	**Xavier C. Correia** *A green and scalable strategy for the multigram synthesis of (hydroxyethyl)sulfonamide peptidomimetics*
P94	**Hugo F. Costa-Almeida** *Cispentacin-based melanostatin peptidomimetics as ago-allosteric modulators of the dopamine D_2 receptors*

P95	**Ana Rita Pereira** *Bioactive potential of pomegranate peel: from food waste to functional extracts*
P96	**Rodrigo S. Gomes** *Late-stage hydroxylation of agrochemical active ingredients using commercial continuous flow electrochemical cells*
P97	**Catarina A. R. Vilão** *Designing smart linkers for next-generation antibody-drug conjugates*
P98	**Sara Moura** *Design, synthesis and biological evaluation of novel carnosic acid derivatives with anticancer activity*
P99	**Rafael F. P. Mascarenhas** *pH-sensitive boron based platform (AZABY) for biological applications*
P100	**Duarte B. Clemente** *Electrochemical lactonization of ketones through anodic oxidation of benzoate anions*
P101	**João F. Felicidade** *HQ-BASHYs as an innovative multimodal platform for advanced photodynamic therapy*
P102	**João E. Leite** *BLOCKBI platform: multifunctional and fluorescent constructs for bioimaging and therapeutics*
P103	**Emília Sousa** *Development and evaluation of new depigmenting agents using a Safe and Sustainable by Design approach*
P104	**Beatriz L. Pires-Lima** *Structure-neurotoxicity relationships of pyridine-based melanostatin derivatives for application in Parkinson's disease*
P105	**Luís C. Branco** *Pharmaceutical ionic systems for drug delivery applications*
P106	**Ana Maria F. Phillips** *Study of the chemical profile of the alga Rugulopteryx okamurae*
P107	**Rita I. Oliveira** *Rational identification of novel ubiquitin specific protease 7 (USP7) inhibitors through chemoinformatics and high-throughput screening*
P108	**Ana Maria Marques** *A novel click-to-kill dual strategy based on oxygen and light: modified BASHY dyes as smart photosensitizers*
P109	**Carolina M. D. Catarino** *Insights into the electrochemical reactions of aryl ketones*
P110	**Inês M. F. Santos** *A novel macrocyclization strategy for antimicrobial peptides using cyclopentenones*
P111	**Carla I. M. Santos** *Porphyrin-carbon dots conjugates: enhancing the photodynamic performance of tetrapyrrolic photosensitizers*
P112	**Tiago P. Santos** *Synthesis of chromanones with a quaternary carbon center via phosphine-catalyzed inverse conjugate addition*
P113	**Olha Antoniuk** *Facile epimerization of (+)-sclareolide: a versatile experiment for laboratory education*
P114	**Adriana G. Casteleiro** *Synthesis of (-)-agelastatin A*

PLENARY LECTURES

Short Bio

Amir H. Hoveyda is the Vanderslice Millennium Professor of Chemistry at Boston College (since 1998) as well as the Director of Catalysis in Chemical Synthesis at the Institute for Supramolecular Science and Engineering at the University of Strasbourg (since 2019). He received his B. A. degree at Columbia, was a graduate student at Yale (Stuart Schreiber), and an American Cancer Society postdoctoral fellow at Harvard (David Evans). His honors include an NIH MERIT Award (2005), the Yamada-Koga Prize (2010), the American Chemical Society Award
for Creative Work in Organic Synthesis (2014), the Eni Prize for Hydrocarbon Research (2014), and the American Chemical Society H. C. Brown Award for Creative Research in Synthetic Methods (2020). His scholarly interests are in the development of new catalysts and catalytic strategies and methods. Hoveyda's program encompasses organometallic chemistry, detailed mechanistic investigations, development of catalytic click processes, complex molecule total synthesis, and programmable remodeling of complex molecules with an eye toward accelerating hit discovery for drug development. Hoveyda and Richard Schrock are the cofounders of XiMo.

Established chemistry reprogrammed for precise remolding of alkaloids

Amir H. Hoveyda

Boston College, Chestnut Hill, United States
E-mail: amir.hoveyda@bc.edu

In this Lecture, it will be demonstrated how a small number of well-known synthesis methods can be reprogrammed to constitute a streamlined strategy for efficient and precise remodeling of alkaloids. We show how C–N s-bonds in ubiquitous piperidine rings can be site-selectively cleaved by Hofmann elimination to afford deconstructed and easily diversifiable products. Ensuing constitutional alterations are made through Stevens and/or Meisenheimer rearrangements. Expanded and contracted frameworks may then be secured after ring-closing metathesis and intramolecular hydroamination, respectively. With a small selection of catalysts and reagents, we were thus able to access 26 altered frameworks in 51 steps (~2 steps/remodeled skeleton). As an illustration of the utility of the approach, in vitro studies show that, while the parent alkaloid natural product is inactive, a deconstructed tricyclic analog exhibits 16 nM activity against a lung carcinoma cell line.

.

Short Bio

Anna K. H. Hirsch is W3 (full) professor for Pharmaceutical Chemistry at Saarland University and head of the department for drug design and optimization at the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS). She read Natural Sciences with a focus on Chemistry at the University of Cambridge and spent her third year at the Massachusetts Institute of Technology, doing a research project with Prof. Timothy Jamison. She carried out her Master's research project in the group of Prof. Steven V. Ley at the University of Cambridge. She received her Ph.D. from the ETH Zurich in 2008 in the group of Prof. François Diederich. Subsequently, she joined the group of Prof. Jean-Marie Lehn at the Institut de Science et d'Ingénierie Supramoléculaires (ISIS) in Strasbourg as an HFSP postdoctoral fellow, before taking up a position as assistant professor at the Stratingh Institute for Chemistry at the University of Groningen in 2010 where she was promoted to associate professor in 2015.

Her work focuses on anti-infective drug design by adopting rational approaches such as structure- and fragment-based drug design in combination with the protein-templated strategies dynamic combinatorial chemistry and kinetic target-guided synthesis.

Anna has authored more than 200 peer-reviewed papers and has received numerous awards such as the Gratama Science Prize in 2014, the SCT-Servier Prize for Medicinal Chemistry in 2015, the Innovation Prize for Medicinal Chemistry of the GdCh/DPhG in 2017, the EFMC Young Medicinal Chemist in Academia runner-up Prize in 2019, the RSC-BMCS Capps Green Zomaya Award for Medicinal or Computational Chemistry in 2024, and in 2025 the SCT Award for Drug Discovery Chemistry and the Grand Prix en Sciences Chimiques of the Institut Grand-Ducal, Luxembourg.

Tackling underexplored drug targets as a pathway to antibiotics with a novel mode of action

Anna K. H. Hirsch

Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) – Helmholtz Center for Infection Research (HZI), Department of Drug Design and Optimization, Campus Building E8.1, 66123 Saarbrücken, Germany and Saarland University, Department of Pharmacy, Campus Building E8.1, 66123 Saarbrücken, Germany
E-mail: anna.hirsch@helmholtz-hips.de

The challenges associated with anti-infective drug-discovery are tackled by combining various hit-identification strategies with phenotypic antibacterial screening.[1] I will illustrate this approach with a selection of un(der)explored targets. The first is a vitamin transporter from the energy-coupling factor (ECF) class unique to Gram-positive bacteria.[2] We report on a structure-based virtual screening campaign to afford the first selective inhibitors of the ECF transporters with good *in vitro* and whole-cell activity and a good *in vitro* ADMET and *in vivo* PK profiles.[3]
Secondly, we succeeded in the identification of synthetic small-molecule inhibitors of the b-sliding clamp DnaN,[4] showing good affinity, functional inhibition, broad-spectrum antibacterial activity and a balanced *in vitro* ADMET profile. Our synthetic molecules are an important starting point for the development of novel antibiotics.
Finally, we succeeded in fragment merging and linking, affording highly selective and potent inhibitors of the extracellular metalloprotease and virulence factor of *Pseudomonas aeruginosa*, the elastase LasB.[4–6] Multiparameter optimisation based on extensive biological profiling, including the establishment of complex biological assays led to chemically diverse lead compounds with good lung exposure and *in vivo* efficacy in lung- and eye-infection models. Our approach promises to deliver the urgently needed anti-infective agents featuring both new chemical scaffolds and unprecedented modes of action.

References

[1] M. Miethke, et al., *Nat. Rev. Chem.* **2021**, *5,* 726.
[2] S. Bousis, I. Setyawati, E. Diamanti, D. J. Slotboom, A. K. H. Hirsch, *Adv. Ther.* **2019**, *2,* 1800066.
[3] E. Diamanti, P. C. T. Souza, I. Setyawati, S. Bousis, L. M. Gómez, L. J. Y. M. Swier, A. Shams, A. Tsarenko, W. Stanek, M. Jaeger, S. Marrink, D. J. Slotboom, A. K. H. Hirsch, *Commun. Biol.* **2023**, *6*, 1182, DOI 10.1038/s42003-023-05555-x.
[4] W. Elgaher, V. Hapko, S. Rasheed, R. Müller, A. K. H. Hirsch, *Ann. Rep. Med. Chem.* **2023**, 163–195.
[5] C. Kaya, I. Walter, S. Yahiaoui, A. Sikandar, A. Alhayek, J. Konstantinović, A. M. Kany, J. Haupenthal, J. Köhnke, R. W. Hartmann, A. K. H. HIrsch, *Angew. Chem. Int. Ed.* **2021**, *61,* e202112295.
[6] J. Konstantinović, A. M. Kany, A. Alhayek, A. S. Abdelsamie, A. Sikandar, K. Voos, Y. Yao, A. Andreas, R. Shafiei, B. Loretz, E. Schönauer, R. Bals, H. Brandstetter, R. W. Hartmann, C. Ducho, C.-M. Lehr, C. Beisswenger, R. Müller, K. Rox, J. Haupenthal, A. K. H. Hirsch, *ACS Cent. Sci.* **2023**, *9*, 2205.
[7] A. F. Kiefer, C. Schütz, C. N. Englisch, D. Kolling, S. Speicher, A. M. Kany, R. Shafiei, N. A. Wadood, A. Aljohmani, N. Wirschem, R. P. Jumde, A. Klein, A. Sikandar, Y.-M. Park, G. Krasteva-Christ, D. Yildiz, A. S. Abdelsamie, K. Rox, J. Köhnke, R. Müller, M. Bischoff, J. Haupenthal, A. K. H. Hirsch, *Adv. Sci.* **2025**, *asap*

.

Short Bio

Tanja Weil joined the Max Planck Society in 2017 as a Director at the Max Planck Institute for Polymer Research, where she heads the division Synthesis of Macromolecules. She studied chemistry from 1993 to 1998 at TU Braunschweig (Germany) and the University of Bordeaux I (France), and completed her PhD at the Max Planck Institute for Polymer Research under the supervision of K. Müllen. From 2002 to 2008, she held several senior leadership positions at Merz Pharmaceuticals GmbH (Frankfurt), ranging from Section Head of Medicinal Chemistry to Director of Chemical Research and Development. In 2008, she accepted an Associate Professorship at the National University of Singapore, and in 2010 she joined Ulm University as Director of the Institute of Organic Chemistry III / Macromolecular Chemistry. Prof. Weil has received scientific honors and competitive funding, including the Otto Hahn Medal of the Max Planck Society, the Karl Ziegler Award, and an ERC Synergy Grant. She serves as an Associate Editor of the Journal of the American Chemical Society. Her research focuses on the development of synthetic chemical systems that interact with and control cellular function.

Synthesis in living environments for material–cell communication

Tanja Weil

Max Planck Institute for Polymer Research, Ackermannweg 10, 55128 Mainz, Germany
E-mail: weil@mpip-mainz.mpg.de

We present the synthesis of supramolecular systems that form and operate within living environments to control cellular function. Our in-cell synthesis strategies use endogenous redox, enzymatic, and metabolic inputs or light to trigger supramolecular assembly and catalytic activity, enabling state-dependent modulation of mitochondrial metabolism and immune function. In parallel, we design artificial cells with chemically encoded sensing and actuation capabilities that exchange metabolites with natural cells, forming hybrid systems with bidirectional communication capabilities. These approaches establish a biomaterials-based route to influence cellular fate without genetic manipulation and provide design principles for autonomous therapeutic systems and synthetic organelles.

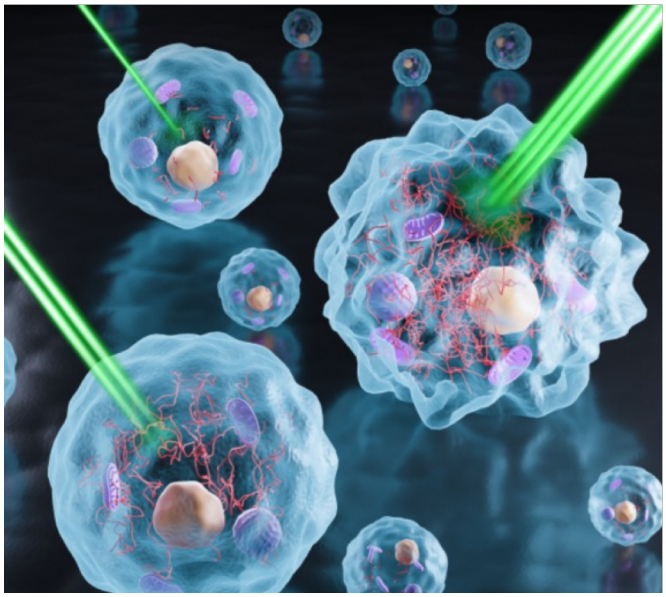


Figure 1. Bioresponsive caged peptide monomers enter living cells and undergo chemical transformations initiated by light and form supramolecular peptide nanofibers that can control cellular processes (Y. Ren et al. Nature Synthesis 2025).

.

Short Bio

Gonçalo Bernardes is Professor of Chemical Biology at the University of Cambridge. He completed his D.Phil. at the University of Oxford in 2008, followed by postdoctoral research at the Max Planck Institute of Colloids and Interfaces and at ETH Zürich. He began his independent research career at the University of Cambridge in 2013 as a Royal Society University Research Fellow. He was appointed University Lecturer in 2018, promoted to Reader in 2019, and to Full Professor in 2022.

Professor Bernardes is the recipient of three European Research Council grants and has received numerous distinctions, including the 2024 Corday–Morgan Prize for Chemistry from the Royal Society of Chemistry. His research focuses on applying chemical principles to generate new biological insights and to develop targeted therapeutics. He has co-founded several companies based on technologies developed in his laboratory and is a Senior Fellow at Flagship Pioneering, the world's largest global venture creation firm. He is a first-generation high-school and university graduate.

Translational Chemical Biology

Gonçalo Bernardes[1,2]

[1] *Yusuf Hamied Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, United Kingdom.*
[2] *Translational Chemical Biology Group, Spanish National Cancer Research Centre 26 (CNIO), Madrid 28029, Spain.*
E-mail: gb453@cam.ac.uk

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

1. methods for site-selective chemical modification of proteins and antibodies;
2. bioorthogonal cleavage reactions for targeted drug activation in cells;
3. small molecule RNA degraders, that when in proximity can irreversibly degrade RNA, akin to ribonucleases.

Short Bio

Mariola Tortosa obtained her PhD at the Organic Chemistry Institute (CSIC, Madrid, Spain) in 2005. Then, she moved to The Scripps Research Institute in Florida (USA) to work as a Postdoctoral Fellow with Prof. William R. Roush. In 2008 she returned to the Organic Chemistry Institute (Madrid, Spain) and in 2011 she started her independent career at the Universidad Autónoma de Madrid (UAM) as a Ramón y Cajal Fellow. In 2013 she received an ERC-Starting Grant awarded by the European Research Council to work on the project "Design and Applications of Unconventional Borylation Reactions". More recently (2020), she was awarded with an ERC-Consolidator grant to work on the project "Selective pathways for carbon-nitrogen bond cleavage". She has received several awards including the Young Investigator Award from the Royal Society of Chemistry of Spain (2014), the Young Spanish Investigator Eli Lilly Award (2014), and the Barluenga Medal (2021).
Biologically active compounds are a continuous inspiration for her research which is focused on the development of novel catalytic transformations to build molecular complexity in a sustainable way.

Catalysis to increase complexity: stereoselective synthesis of sp³-rich building blocks

Mariola Tortosa

Universidad Autónoma de Madrid, Organic Chemistry Department
Campus de Cantoblanco, Madrid 28049, Spain
E-mail: mariola.tortosa@uam.es

Transition-metal catalysis is at the core of modern chemistry and has become increasingly important for the pharmaceutical industry. As the pharmaceutical industry is shifting from compounds with a strong sp^2 character to libraries of compounds with enlarged three-dimensionality, the need to develop catalytic methods to provide compounds with an increased sp^3 character becomes apparent. In our group, we have recently focused on the development of catalytic enantioselective and stereospecific transformations for the preparation of sp^3-rich building blocks, providing tools for stereodefined carbon-boron bond formation, synthesis of benzene bioisosteres and selective carbon-nitrogen bond cleavage. These methods have allowed us to prepare a broad variety of useful synthetic intermediates, with special emphasis on the synthesis of functionalized strained-rings.[1] Some of these transformations will be presented in this talk.

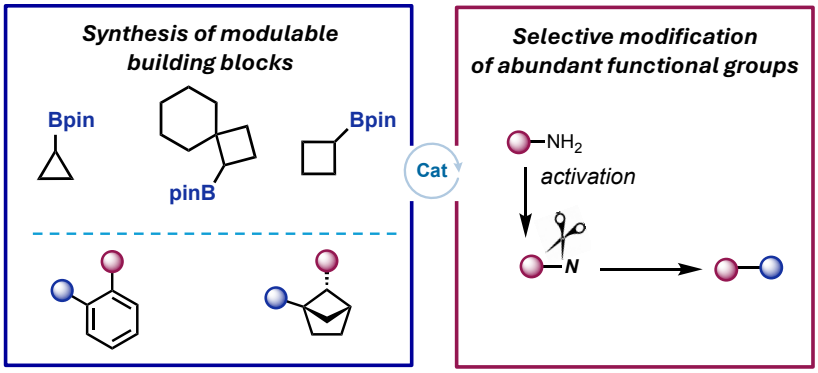


Figure 1. Synthesis of sp^3-rich building blocks

References

[1] **Selected references**: (a) Garrido-García, P.; Quirós, I.; Milán-Rois, P.; Ortega-Gutiérrez, S.; Martín-Fontecha, M.; Campos, L. A.; Somoza, A.; Fernández, I.; Rigotti, T.*; Tortosa, M.* *Nat. Chem.* **2025**, https://doi.org/10.1038/s41557-025-01746-7. (b) Quirós, I.; Martín, M.; Gomez-Mendoza, M.; Cabrera-Afonso, M. J.; Liras, M.; Fernández, I.; Nóvoa, L.; Tortosa, M. *Angew. Chem. Int. Ed.* **2024**, e202317683. https://doi.org/10.1002/anie.202317683. (c) Nóvoa, L.; Trulli, L.; Parra, A.; Tortosa, M. *Angew. Chem. Int. Ed.* **2021**, *60*, 11763. (d) Amenós, L.; Trulli, L.; Nóvoa, L.; Parra, A.; Tortosa, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 3188.

Short Bio

Rui Moreira completed his master degree in Pharmaceutical Sciences at the Faculty of Pharmacy, University of Lisbon, and obtained his PhD in Pharmacy under supervision of Professors Eduarda Rosa (University of Lisbon) and Jim Iley (The Open University, UK). After a postdoctoral stay in the UK, where he worked on prodrug chemistry from a physical organic chemistry point of view, Rui started his career as an independent scientist at the Faculty of Pharmacy, University of Lisbon. He was promoted to Full Professor of Medicinal Chemistry in 2006. Rui's research is focused on chemical tools to study the underlying mechanisms in infectious diseases, cancer and neurodegenerative disorders. His current research interests cover the development of anti-infectious agents, prodrug chemistry and targeted drug delivery systems, design of covalent inhibitors, and design of chemical probes for activity- and photoaffinity-based protein profiling. He has published over 150 papers (SCOPUS AUTHOR ID 71025540 and ORCID ID 0000-0003-0727-9852) and supervised/co-supervised more than 20 PhD students. Rui was co-founder of the Medicinal Chemistry Division of the Portuguese Chemical Society, and as served EFMC as Council member in 2008-2015 and as Executive Committee member since 2015. He is the current EFMC President.

Chemical Modalities and Precision Medicine. New tools for targeted drug release and targeted degradation of challenging proteins

Rui Moreira

Faculty of Pharmacy, University of Lisbon, Av. Professor Gama Pinto, 1649-003, Lisboa, Lisboa, Portugal
E-mail: rmoreira@ff.ulisboa.pt

While the human genome project helped to validate critical disease-relevant targets, including many previously considered difficult to drug or “undruggable”, many conditions remain unaddressed. This gap underscores the need for a deeper understanding of biological pathways, their connections to human disease, and new ways to interrogate challenging targets using chemical modalities beyond traditional small molecules, including novel strategies for drug delivery.
This communication will report the development of chemical tools that can pave the way for precision medicine. We will highlight how endoperoxide chemistry can be tailored to the target iron metabolism dysregulation and achieve highly selective release of cytotoxic payloads inside cancer cells. In addition, we will address the design of bifunctional molecules to promote the targeted degradation of poorly druggable proteins involved in cancer and neurodegenerative diseases.

Acknowledgments
We thank the support of FCT (projects UID/04138/2025 and 2022.07857.PTDC)

INVITED LECTURES

Bridging organic chemistry and functional nanomaterials

Carlos Baleizão

Centro de Química Estrutural and Institute of Molecular Sciences, Department of Chemical Engineering, Instituto Superior Técnico, Portugal

E-mail: carlos.baleizao@tecnico.ulisboa.pt

Developing functional nanomaterials requires a multidisciplinary approach that combines strategies and methodologies from organic chemistry, inorganic chemistry and materials chemistry. The challenges are transversal and independent of the type of nanomaterial (organic, inorganic or hybrid-based). However, it is using organic chemical transformations that we can empower nanomaterials with new functions to address the societal challenges of the 21st century. Conversion, selectivity and yield quantification are challenging when an organic transformation is performed on the surface of a nanoparticle or in a large polymeric vector. The characterization strategies and techniques typically used in organic chemistry reactions must be adapted for use with solid, and sometimes insoluble, materials.

The ability of some molecules and nanomaterials to interact with and respond to light is key to the development of fluorescent imaging agents, optical sensors and targeted nanocontainers. The most efficient strategy for combining fluorescent molecules with nanomaterials is to covalently bind the molecules to a specific site instead of simply entrapping them, to avoid leaching and improve photostability. Perylenediimides (PDIs, Figure 1) started to be used as industrial pigments for fabrics and paints (1910s-1980s), but recently they have been extensively studied as fluorescent solar collectors, in organic photovoltaics, or as imaging agents. The synthesis of PDIs derivatives, starting from the commercially available perylene-3,4,9,10-tetracarboxylic acid dianhydride, allows the selective introduction of substituents in the imide group or in the bay region (Figure 1).

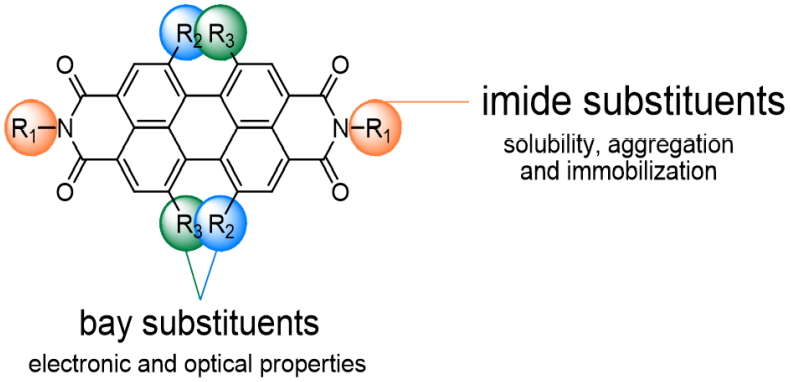


Figure 1: PDIs general structure and influence of the different substituents position.

In this communication, I will discuss the challenges of carrying out organic reactions with/in nanomaterials, focusing on silica nanoparticles and polymer vectors. I will also cover strategies for tuning the structure of perylenediimides to obtain the desired optical properties and further incorporation into nanomaterials.

Acknowledgements: Fundação para a Ciência e a Tecnologia for the financial support (DOI:10.54499/UID/00100/2025, DOI:10.54499/UID/PRR/100/2025, DOI:10.54499/LA/P/0056/2020, and DOI:10.54499/2022.05950.PTDC).

Glycan recognition as chemical biology strategy in cancer therapy

Filipa Marcelo[1,2]

[1]Applied Molecular Biosciences Unit, NOVA School of Science and Technology, 2829-516 Caparica, Portugal; [2]Associate Laboratory i4HB, Institute for Health and Bioeconomy, NOVA School of Science and Technology, 2829-516 Caparica, Portugal

E-mail: filipa.marcelo@fct.unl.pt

Decoding how lectins interpret tumour associated glycans is essential for advancing chemically driven strategies in cancer biology and therapeutics. The macrophage galactose type lectin (MGL) expressed by antigen-presenting cells such as macrophages and dendritic cells, recognizes N-acetylgalactosamine (αGalNAc) residues found in the tumour-associated antigens, hallmark features of malignant transformation [1,2].

Through an integrative chemical biology approach combining NMR, calorimetry, molecular dynamics, glycoengineered cell models, and mucin-based arrays, we have elucidated the structural and dynamic determinants governing MGL's recognition of Tn, STn, and TF tumour-associated antigens [3]. These studies reveal a clear preference for short tumour associated O glycans, highlight the critical influence of glycan and lectin presentation, and support the emerging concept of MGL as a universal receptor for truncated cancer glycans.

Building on these mechanistic insights, we engineered a chemically defined MGL based drug conjugate (mMGL vcMMAE) via site selective conjugation to a cytotoxic payload. The construct preserves native αGalNAc specificity, selectively binds colorectal cancer tissues, and enhances tumour cell cytotoxicity while reducing off target toxicity relative to free drug [4]

Together, the lecture will showcase how structural glycochemistry and chemical biology converge to transform fundamental glycan recognition principles into innovative glycan directed strategies for selective cancer targeting.

Funding: Fundação para a Ciência e Tecnologia (FCT-Portugal) for the funding: MGL4Life project (10.54499/PTDC/QUI-OUT/2586/2020), UCIBIO project UID/04378 and i4HB project 10.54499/LA/P/0140/2020). F.M. thanks FCT-Portugal for the CEEC contract CEECINST/00042/2021/CP1773/CT0011. Lisbon Regional Programme, in the ERDF component through European Union, and by the FCT-Portugal, through national funds (PIDDAC) (Operation n.º 17044, Funds operation code LISBOA2030-FEDER-00833700 and national funds code 10.54499/2023.18377.ICDT). European Union for the GLYCOTwinning project (No. 101079417) funded under the Horizon Europe program

References

[1] F. Marcelo, et al. J Biol Chem., 2019, 294, 1300-1311.
[2] A. Gabba, et al Biochemistry 2021, 60, 1327-1336.
[3] A. S. Grosso et al. JACS Au 2025. https://doi.org/10.1021/jacsau.5c00905.
[4] C. D. L. Lima et al. J Med Chem 2026 submitted

Computational methods to capture pH effects in biomolecules

Miguel Machuqueiro

BioISI: Biosystems and Integrative Sciences Institute, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal

E-mail: machuque@ciencias.ulisboa.pt

Constant-pH molecular dynamics (CpHMD) simulations are powerful computational tools that couple the conformational space of biomolecules to pH, by allowing the protonation states of ionizable sites to change dynamically in response to the environment [1]. This is a significant improvement over traditional MD simulations, which use fixed protonation states, as it provides a more realistic representation of pH effects on molecular structure, function, and binding. In inhomogeneous media, this representation becomes more challenging to capture accurately using these state-of-the-art computational methodologies [2]. Recent advances have focused on enhancing the accuracy and efficiency of these methods, thereby expanding their application to larger and more complex systems, such as protein-drug complexes and membrane proteins. We will present our most recent methodological developments, including the coupling of CpHMD with enhanced sampling schemes [3] to investigate the effects of pH on various biomolecules. However, many challenges remain, including high computational cost, the need for more accurate force fields, and the need to ensure adequate conformational sampling. This presentation will focus on many of those challenges... the success stories are already in the papers!

Funding: We acknowledge financial support from FCT through the project UID/04046/2025.

References

[1] Gomes, A. M. M., Costa, P. J., Machuqueiro, M. (2023) BBA Advances, 4, 100099.
[2] Teixeira, V. H., Vila-Viçosa, D., Reis, P. B. P. S., Machuqueiro, M. (2016) J. Chem. Theory Comput., 12, 930-934.
[3] Oliveira, N. F. B., Machuqueiro, M. (2022) J. Chem. Inf. Model., 62, 2550.

.

Rational design of proline derivatives for the assembly of bioactive peptides targeting neurological disorders

Ivo E. Sampaio-Dias[1,*], Xavier C. Correia[1], Hugo F. Costa-Almeida[1], Sara C. Silva-Reis[1], Beatriz L. Pires-Lima[1], Xerardo García-Mera[2], José E. Rodríguez-Borges[1]

[1]LAQV/REQUIMTE, Department of Chemistry and Biochemistry, Faculty of Sciences, University of Porto, 4169-007, Porto, Portugal; [2]Department of Organic Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, Santiago de Compostela, Spain.

** E-mail: ivdias@fc.up.pt*

The design and synthesis of tailored amino acid derivatives are central to modern peptide chemistry, playing a pivotal role in drug discovery and chemical biology.[1] Among the proteinogenic amino acids, proline occupies a privileged position due to its distinctive cyclic structure, which enables exceptional control over peptide conformation, dynamics, and biological function.[1,2] This lecture explores advanced strategies for the efficient synthesis of proline derivatives, with a particular emphasis on sustainable methodologies that reduce hazardous reagents, improve atom economy, and enhance overall synthetic efficiency.[2,3]

Special attention is given to rational functionalization strategies, including stereoselective modifications and the introduction of structurally diverse chemical motifs, aimed at fine-tuning peptide stability, conformational preferences, and interactions with biological targets. These approaches provide versatile molecular tools to expand the functional landscape of peptides.[1-3]

This lecture focuses on the application of proline derivatives as building blocks in the context of neuroscience research. Selected case studies will illustrate how these tailored amino acids can be incorporated into peptides with neuroactive, neuromodulatory, or receptor-targeting properties, leading to improved bioactivity, enhanced target selectivity, and favorable pharmacokinetic profiles relevant to biomedical applications targeting the central nervous system.

Funding: This work received financial support from PT national funds (FCT/MCTES, Fundação para a Ciência e a Tecnologia and Ministério da Ciência, Tecnologia e Ensino Superior) through project 2023.14440.PEX (DOI: 10.54499/2023.14440.PEX).

Acknowledgements: FCT is also acknowledged for supporting the project UID/50006/2025 DOI 10.54499/UID/50006/2025 - Laboratório Associado para a Química Verde - Tecnologias e Processos Limpos. I.E.S.-D. thanks FCT for funding through the Individual Call to Scientific Employment Stimulus with reference 2020.02311.CEECIND/CP1596/CT0004 (DOI: 10.54499/2020.02311.CEECIND/CP1596/CT0004). X.C.C., H.F.C.-A., and B.L.P.-L. thank FCT for the Ph.D. grants 2024.02245.BD, UI/BD/154888/2023 (DOI: 10.54499/UI/BD/154888/2023), and 2022.14060.BD (DOI: 10.54499/2022.14060.BD), respectively. S.C.S.-R. thanks REQUIMTE for the post-doc contract with reference REQUIMTE 2025-43.

References

[1] Sampaio-Dias, I.E.; Reis-Mendes, A.; Costa, V.M.; García-Mera, X.; Brea, J.; Loza, M.I.; Pires-Lima, B.L.; Alcoholado, C.; Algarra, M.; Rodríguez-Borges, J.E. J. Med. Chem. 2021, 64, 6209-6220.

[2] Sampaio-Dias, I.E.; Pinto da Silva, L.; Silva, S.G.; García-Mera, X.; Rodríguez-Borges, Green Chem. 2020, 22, 3584-3596.

[3] Sampaio-Dias, I.E.; Silva-Reis, S.C.; Correia, X.C.; Costa-Almeida, H.F.; Pires-Lima, B.L.; García-Mera, X. ACS Sustainable Chem. Eng. 2024, 12, 16986-16998.

Synthesis of novel glycosylated quinolone and acridone scaffolds and evaluation of their cytotoxic activity

Vera L. M. Silva[1,*], Pedro M. O. Gomes[1,2], Romeu A. Videira[2], Artur M. S. Silva[1], Paula B. Andrade[2]

[1]LAQV-REQUIMTE and Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal
[2]LAQV-REQUIMTE, Laboratório de Farmacognosia, Departamento de Química, Faculdade de Farmácia, Universidade do Porto, Rua Jorge Viterbo Ferreira, nº 228, 4050-313 Porto, Portugal.
** E-mail: verasilva@ua.pt*

The search for novel chemotherapeutic agents remains a critical priority in addressing drug resistance. In this context, quinolones and acridones, two historically distinct families of heterocyclic compounds, have emerged as versatile platforms for the discovery of novel anticancer agents [1,2]. While quinolones are widely recognized for their antibacterial origins and acridones for their rich photophysical properties and DNA-intercalating ability, recent advances in medicinal chemistry and molecular oncology have revealed their unexploited potential in targeting cancer-relevant pathways [3]. In particular, for glycosylated derivatives, the sugar unit can act as a solubility enhancer, but it can also critically influence activity, selectivity, and pharmacokinetic behaviour.

In this work, the synthesis and biological evaluation of novel glycosylated quinolone- and acridone-based scaffolds were carried out, aiming to assess their cytotoxicity and potential as anticancer agents. The cytotoxic activity of these compounds was screened against a panel of distinct human cancer cell lines, including lung (A549), neuroblastoma (SH-SY5Y), and colorectal (Caco-2) cells. Some compounds exhibited significant cytotoxic profiles (**Figure 1**).

Overall, these findings highlight glycosylated quinolone and acridone scaffolds as valuable platforms for the development of next-generation anticancer agents and provide a foundation for further structural optimization.

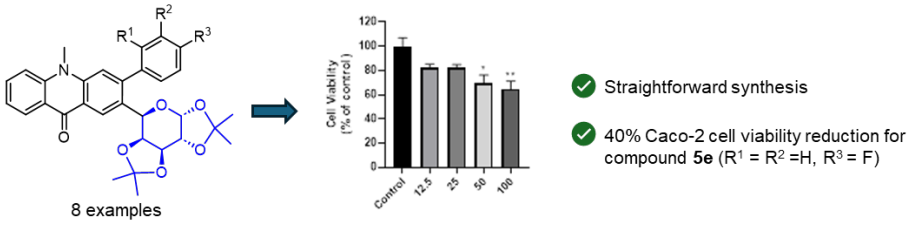


Figure 1. Structure of novel *C*-glycosylacridones and cytotoxic activity of derivative **5e** against Caco-2 cell lines.

Funding: This work received financial support from PT national funds (FCT/MCTES, Fundação para a Ciência e Tecnologia and Ministério da Ciência, Tecnologia e Ensino Superior) through the project units UIDB/50006/2020 and UIDP/50006/2020 (LAQV/REQUIMTE), DOI identifier https://doi.org/10.54499/UIDP/50006/2020). Pedro M. O Gomes thanks FCT/MCTES and ESF (European Social Fund) through NORTE 2020 (Programa Operacional Região Norte) for the financial support of his PhD grant 2020.04972.BD. Romeu A. Videira thanks FCT for funding through CEECINST/00136/2021/CP2820/CT0001, DOI 10.54499/CEECINST/00136/2021/CP2820/CT0001.

Acknowledgements: Thanks are due to the University of Aveiro and FCT (Fundação para a Ciência e a Tecnologia), the European Union, QREN, FEDER, and COMPETE for funding the LAQV-REQUIMTE (UIDB/50006/2020+ UIDP/50006/2020).

References

[1] Bisacchi, G.S.; Hale, M.R. Curr Med Chem. 2016, 23, 520-577.
[2] Yadav, T.T.; Murahari, M.; Peters, G.J.; Yc M. Eur J Med Chem. 2022, 239, 114527.
[3] Marques, T.J.S.; Salvador, D.; Oliveira, H.; Serra, V.V.; Paradis, N.; Wu, C.; Silva, V.L.M., Ramos, C.I.V. RSC Med Chem. 2025, 16, 2785-2807.

Hybrid molecules for neuroprotection: translating design into therapeutic potential

Maria J. Matos[1,*]

[1]*Department of Organic Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain*

* *E-mail:mariajoao.correiapinto@usc.es*

Selective drug design and delivery to the central nervous system remain major challenges in medicinal chemistry. Despite the growing global impact of neurodegenerative diseases, therapeutic options are limited and often exhibit modest efficacy. Advances in understanding the molecular mechanisms underlying these complex and multifactorial disorders have highlighted the need for innovative chemical strategies capable of modulating key biological targets. In this context, scientific creativity has driven the development of molecular hybrids and fragment-based compounds as promising alternatives to conventional therapies.

Our research group has been focused on the design of hybrid molecules that integrate distinct chemical features of biologically active agents within a single structure, with the aim of preserving the pharmacological properties of each component while enhancing pharmacokinetic performance [1,2]. Computer-assisted drug design, combined with efficient synthetic methodologies, novel diseases models and the development of drug delivery systems [3], has expanded the range of possibilities for therapeutic innovation. By drawing on insights into the biochemical pathways involved in patients' neurodegeneration and moving toward the use of phenotypic assays [4], these approaches offer the potential for treatments that are both more effective and less toxic than traditional strategies.

Here it is presented an overview of our research, highlighting diverse design approaches and their successful application in the pursuit of improved therapies for neurodegenerative diseases.

Funding: This work is supported by a Xunta de Galicia Grant (ED431B 2025/15). One of the projects that contributed to the presented results received support from a PhD fellowship awarded by Fundación Ramón Areces to Manuel Novás González.

References

[1] Matos, M.J.; Novo, P.; Mayán, L.; Torres, I.; Uriarte, E.; Yáñez, M.; Fontenla, J.A.; Ortuso, F.; Alcaro, S.; Procopio, F.; Rodríguez-Franco, M.I.; Val, C.; Loza, M.I.; Brea, J.; Borges, F.; Viña, D. Eur. J. Med. Chem. 2023, 248, 115091.

[2] Novás, M.; Matos, M.J. Molecules 2025, 30(14), 3009.

[3] Fernandes, C.; Martins, C.; Fonseca, A.; Nunes, R.; Matos, M.J.; Silva, R.; Garrido, J.; Sarmento, B.; Remião, F.; Espinar-Otero, F.; Uriarte, E.; Borges, F. ACS Appl. Mater. Interfaces 2018, 10(46), 39557–39569.

[4] Barro-Fernández, M. Santiago de Compostela: Serv. Publicac. Interc. Cient. 2025. Available at: https://hdl.handle.net/10347/41595.

KEYNOTES

Ultra-high-pressure enables electrocyclization reactions

Rafael F. A. Gomes[1,*], Tiago Santos[1], Sabrina Cabral[1], Lidia Cavaca[1], Carlos A. M. Afonso[1]

[1]*Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisbon, Portugal*

** E-mail: rafael.gomes@campus.ul.pt*

The control of chemical reactivity has traditionally relied on the fine-tuning of temperature, solvents, and catalysts. In parallel, ultra-high-pressure (UHP) reactors have emerged as a versatile tool capable of achieving reaction conditions up to several thousand atmospheres.[1] Originally applied in areas such as food preservation, UHP has found broad applications in organic synthesis, polymer chemistry, and enzymatic transformations. The effect of high pressure on chemical reactions is closely linked to the volume of activation (Δ‡V), with reactions exhibiting negative Δ‡V accelerating under UHP. This mechanistic sensitivity enables selective control over reaction pathways, enhancing both yield and regio- or enantioselectivity in cycloadditions, condensations, and domino reactions, even for sterically hindered or electronically deactivated substrates.[2] Among the reactions most impacted by UHP are intramolecular and hetero-Diels–Alder cycloadditions. Pressures above 10 kbar facilitate transformations that are otherwise challenging under ambient conditions, allowing the formation of complex cyclic scaffolds under milder temperatures and shorter reaction times.

In this work we show that UHP promotes the formation of cylcopentenones from furanic scaffolds, thus enabling the use of electron-poor and hindered amines, as well as the use of poorly reactive dienophiles in Diels-Alder reactions (**Figure 1**).[3]

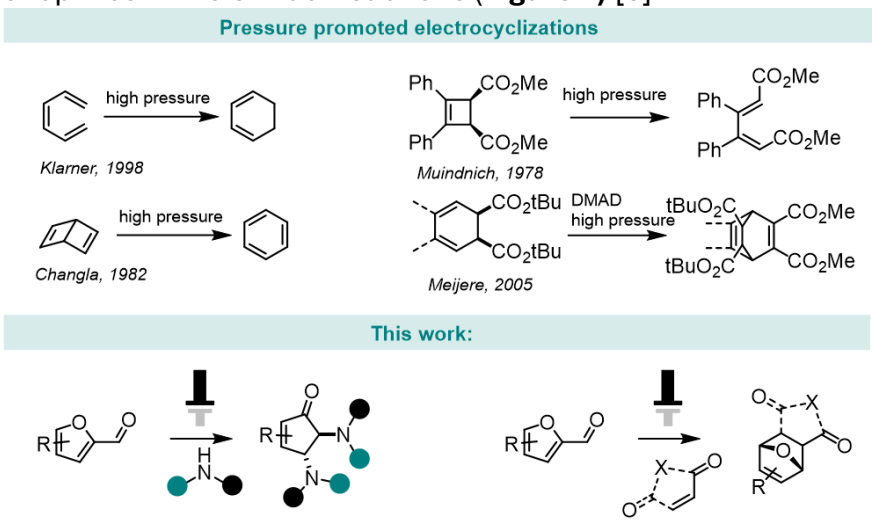


Figure 1. UHP promoted electrocyclization, including the ones explored in this work.

Acknowledgements: We thank the Fundação para a Ciência e Tecnologia for financial support (2023.11341.PEX, UIDB/04138/2025 - Instituto de Investigação do Medicamento.)

References

[1] B. Chen, R. Hoffmann, R. Cammi, *Angew. Chem. Int. Ed.*, **2017**, 56, 11126-11142.
[2] A. Yu. Rulev, F. I. Zubkov, *Org. Biomol. Chem.*, **2022**, 20, 2320.
[3] L. A. S. Cavaca, J. M. J. M. Ravasco, R. F. A. Gomes and C. A. M. Afonso, *J. Org Chem*, **2024**, 89, 6677-6683.

Small molecules to reclaim tumor suppressor p53 function in cancer

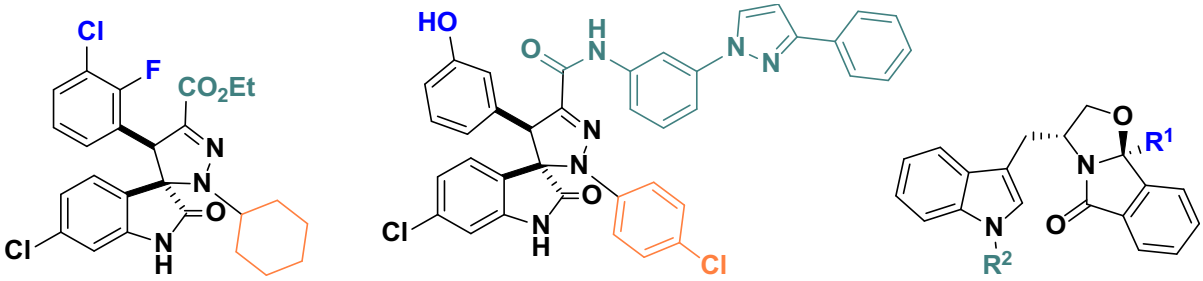
Maria M. M. Santos[1,*]

[1]*Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Lisboa, Portugal*

** E-mail: mariasantos@ff.ulisboa.pt*

p53, a protein encoded by the most frequently mutated gene in cancer, *TP53*, represents a promising target for innovative cancer treatments. Strategies to reactivate p53 include blocking its key negative regulators (MDM2 and MDM4) or restoring the wild-type functions to p53 mutants. Several small-molecule MDM2 inhibitors, as well as a small molecule that rescues p53 Y220C mutant, have advanced to clinical trials showing encouraging results as p53 activators [1]. However, the development of small molecules with dual MDM2/MDM4 inhibitory activity or the ability to rescue poorly studied p53 mutants remains a key priority in cancer drug discovery.

In this keynote, I will present our efforts to optimize an initial MDM2 inhibitor into a potent dual inhibitor of p53–MDM2/MDM4 protein–protein interactions [2]. Additionally, I will share our latest findings on the optimization of tryptophanol-derived compounds as activators of both wild-type p53 and clinically relevant mutants, including the p53 DNA contact R273H and R280K mutants (**Figure 1**) [2].



p53-MDM2/4 inhibitor
p53-MDM2 18 nM
p53-MDM4 15 nM

SELECTIVE p53-MDM2 inhibitor
p53-MDM2 26 nM
p53-MDM4 219 nM

wt and mut p53 activators
1 covalent binder to wild-type p53
18 stabilizers of R273H p53 mutant
24 stabilizers of R280K p53 mutant

Figure 1. p53 small molecule reactivators developed in our research group.

Funding: Fundação para a Ciência e a Tecnologia through iMed.ULisboa (UID/04138/2025, https://doi.org/10.54499/UID/04138/2025), projects PTDC/QUI-QOR/1304/2020 and 16199 – LISBOA2030-FEDER-00735600.

Acknowledgements: I would like to thank all collaborators and PhD students whose contribution was key for the presented results.

References

[1] a) Wiman, K.G. et al; Nat. Rev. Clin. Oncol. 2024, 21, 106–120. b) Vu, B.T. et al; ACS Med. Chem. Lett. 2025, 16, 34–39.

[2] a) Santos, M.M.M. et al; ChemMedChem 2021, 16, 250-258. b) Santos, M.M.M. et al; Eur. J. Med. Chem. 2022, 241, 114637c) Antunes, A.M.M.; Santos, M.M.M. et al; ACS Pharmacol. Transl. Sci. 2025, 8, 1726-1740.

Visible-light-activatable molecules: porphyrins and related compounds

João P. C. Tomé

Centro de Química Estrutural & Institute of Molecular Sciences & Departamento de Engenharia Química, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, Lisboa, Portugal
E-mail: jtome@tecnico.ulisboa.pt

Light has attracted sustained interest across a broad range of scientific disciplines and is now exploited in practically all areas of science [1]. For instance, light-driven processes play a central role in modern chemistry, motivating the development of photoactive molecules and materials with tunable physicochemical properties. Among these, porphyrins (Pors) and related chromophores are well-established systems that have been extensively investigated in light-based chemical technologies [2]. Their structural versatility enables systematic functionalization with diverse (bio)motifs and coordination with a wide range of metal ions, allowing precise modulation of their photophysical, redox, and chemical properties [3].

Porphyrin-based (bio)conjugates developed by our group have been explored in several chemically relevant applications, including: i) bioimaging [4]; ii) molecularly targeted photodynamic therapy (PDT) [5]; and iii) (chemo)sensing [6].

This presentation highlights recent advances from our group in the synthesis, functionalization and application of porphyrin-based (bio)conjugates and hybrid materials.

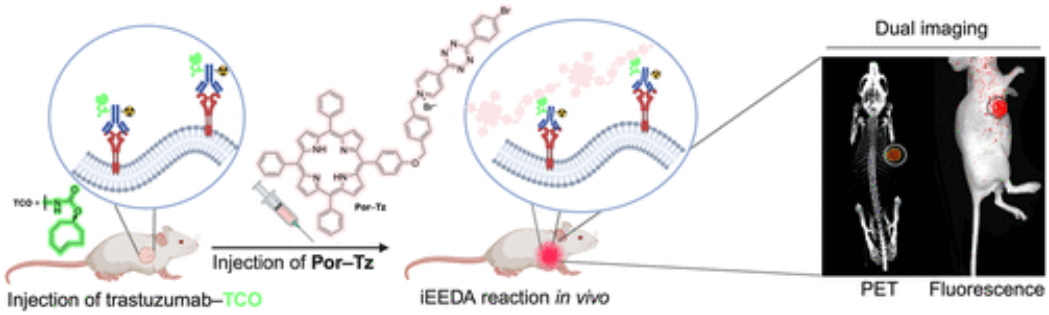


Figure 1. Pretargeted approach for dual PET and optical imaging of HER2-expressing tumors.

Acknowledgements: Thanks are due to FCT Portugal for the financial support to CQE research unit (UID/00100/2025 and UID/PRR/100/2025) and IMS Associate Lab (LA/P/0056/2020) through national funds and where applicable cofinanced by the FEDER, within the PT2020 Partnership Agreement

References

[1] Diogo Gonçalves *et al. Anal. Chim. Acta,* **2026**, 1384 (22), 344982.
[2] Sandra Beirão *et al. Eur. J. Med. Chem.*, **2025**, 117105.
[3] Sara Gamelas *et al. J. Photochem. Photobiol. A-Chem.,* **2024**, 454, 115742.
[4] Sara Gamelas *et al. Bioconjug. Chem.*, **2025**, 36 (5), 1013–1020.
[5] a) Leandro Lourenço *et al. J. Photochem. Photobiol. A-Chem.,* ***2023****, 442,* 114768; b) Sara Fernandes *et al., J. Photochem. Photobiol. B-Biol*, ***2023****, 243,* 112716.
[6] a) Guilherme Costa *et al. Microchem. J.,* **2026**, 220, 116307; b) Flávio Figueira*, Dyes Pigments*, **2025**, 112535.

Unlocking the potential of the diterpenoids for the treatment of infection

Vânia M. Moreira[1,2,3*]

[1]Faculty of Pharmacy, University of Coimbra, Pólo das Ciências da Saúde, Azinhaga de Santa Comba, 3000-548 Coimbra, Portugal; [2]Centre for Innovative Biomedicine and Biotechnology (CIBB), University of Coimbra, 3000-548 Coimbra, Portugal; [3]Drug Research Program, Division of Pharmaceutical Chemistry and Technology, Faculty of Pharmacy, University of Helsinki, 00014 Helsinki, Finland.
**E-mail: vmoreira@ff.uc.pt*

In 2019 alone, infectious diseases were responsible for 24.2% of global mortality, causing 13.7 million deaths, especially in low-income countries that bore a disproportionate burden in the global picture [1,2]. Remarkably, among the deaths that could be attributed to a single causative agent, bacterial infections accounted for 64.8% of the infectious disease mortality globally, followed by viruses (6.1%), fungi (2.4%) and parasites (1.0%). Despite the tremendous impact of the introduction of antimicrobials into the clinics on human quality of life and life expectancy, at present, the number and type of this class of drugs in clinical development is clearly insufficient, as stated by the WHO [3], due to the emergence of antimicrobial resistance (AMR) and a stagnated discovery pipeline. If nothing is done to address AMR, there will be an estimated increase in the number of deaths of the growing global population from roughly 1.3 million to up to 10 million annually, in the upcoming years [4]. Strikingly, AMR will kill more people than cancer in this new paradigm, by 2050. Thus, in the light of this scenario, the design and discovery of new classes of antimicrobial agents with innovative modes of action, is currency for survival.

Terpenoids have rendered significant contributes as anti-infective drugs [2]. Examples are the diterpenoids pleuromutilins (retapamulin and lefamulin), inhibitors of bacterial protein synthesis with broad spectrum of action against Gram-positive and -negative bacteria, and with a low potential for the development of resistance. Our research is devoted to the exploration of structure-activity relationships among small cyclic terpenoids. Using this strategy, we have successfully identified several novel compounds with relevant activities in the context of infection [6,7], cancer [8] and neuroinflammation [9]. This lecture will entail the story of the chemical derivatization and optimization of the antimicrobial properties of diterpenoids of the abietane-type [6, 7, 10].

Acknowledgments: VMM acknowledges Business Finland (former TEKES, project 1297/31/2016), the Academy of Finland (project decisions 264020 and 265481) and the Magnus Ehrnrooth Foundation (ME2012n44) for financial support. EU-funded COST action 1307 CM1307 (Targeted chemotherapy towards diseases caused by endo parasites) is also acknowledged.

References

[1] G.B.D.A.R. collaborators, Lancet, 400 (2022) 2221-2248.
[2]. O. Antoniuk, A. Maranha, Jorge A. R. Salvador, N. Empadinhas, Vânia M. Moreira, Natural Product Reports, 41 (2024), 1858-1894.
[3] World Health Organization, (2022). 2021 Antibacterial agents in clinical and preclinical development: an overview and analysis. https://www.who.int/publications/i/item/9789240047655 (accessed April 2024).
[5] G.B.D.A.R. collaborators, Lancet, 399 (2022), 629-655.
[6] S. Manner, M. Vahermo, M. E. Skogman, S. Krogerus, P. M. Vuorela, J. Yli-Kauhaluoma, A. Fallarero, V. M. Moreira, European Journal of Medicinal Chemistry, 102 (2015) 68-79.
[7] M. Pirttimaa, A. Nasereddin, D. Kopelyanskiy, M. Kaiser, J. Yli-Kauhaluoma, K.-M. Oksman-Caldentey, R. Brun, C. L. Jaffe, V. M. Moreira, S. Alakurtti, Journal of Natural Products 79 (2016) 362-368.
[8] L. E. Kolsi, Leael, A. S., J. Yli-Kauhaluoma, K. T. Liby, V. M. Moreira, Scientific Reports 8 (2018) 15923
[9] T. J. Ahonen, C. P. Ng, B. Farinha, B. Almeida, B. Victor, C. Reynolds, E. Kalso, J. Yli-Kauhaluoma, J. Greaves, V. M. Moreira, ACS Medicinal Chemistry Letters 14 (2023) 1404-1410.
[10] Moreira, V.M., Vahermo, M., Fallarero, A., Yli-Kauhaluoma, J., Vuorela, P." Abietane-type diterpenoids, WO 2016/051013 A1, Apr. 7th, 2016; PCT/FI2015/050495, Jul 9th, 2015; FI20145858, Oct. 2nd, 2014.

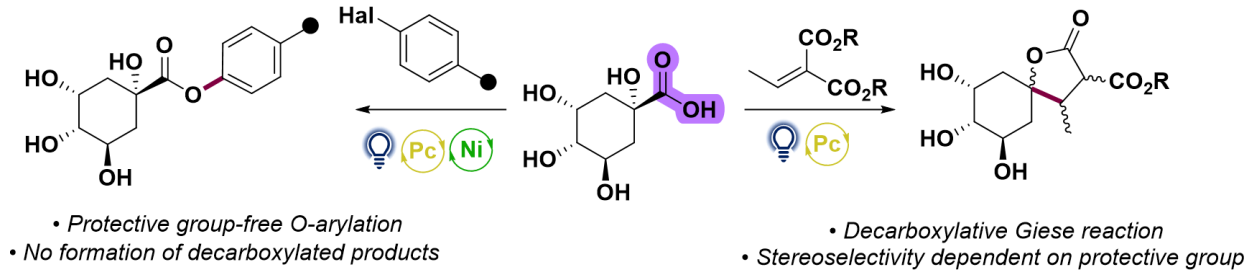
Exploring the carbon-centred radical chemical space: from quinic acid to peroxysilanes

Nuno R. Candeias

LAQV-REQUIMTE, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal
E-mail: ncandeias@ua.pt

The realm of carbon-centred radicals continues to expand thanks to breakthroughs in radical generation, persistent–transient radical coupling, and photoredox methodologies. Photoredox catalysis[1] has emerged as a versatile platform for controlled radical generation under mild visible light conditions, enabling both carbon-centred and heteroatom-centred radical formation with excellent scope and functional group tolerance [2]. By integrating stable radical design, photoredox activation, and catalytic cross-over approaches, new regions of the carbon-centred radical chemical space are now reachable.

Herein, we present the modification of quinic acid through the application of photoredox catalytic systems (**Scheme 1**). This approach enables the preparation of quinic acid-derived esters via photocatalyzed O-arylation with haloarenes [3], offering a streamlined route to functionalized derivatives. In stark contrast, the same photoredox principles facilitate the construction of highly intricate spiro-lactam architectures, underscoring the versatility of radical-mediated transformations in accessing both simple and complex molecular frameworks. Recent advances in the use of peroxysilanes [4] as alkylating agents will also be discussed, emphasizing their role in radical-mediated transformations.



Scheme 1. Photoredox modifications of quinic acid

Acknowledgements and Funding: This work received support and funding from PT national funds (FCT/MCTES) through the projects UID/50006/2025-Laboratório Associado para a Química Verde - Tecnologias e Processos Limpos, PTDC/QUI-QOR/1131/2020 and 2023.17015.ICDT (COMPETE2030-FEDER-00753500), also from COMPETE2030 and Portugal2030.

References

[1] Scaiano, J.C.; *Chem. Soc. Rev.* **2023**, *52*, 6330-6343.
[2] Huang, C.Y.; Li, J.; Li, C.J.;, *Chem. Sci.* **2022**, *13*, 5465-5504.
[3] Bárbara, M.A:; Candeias, N.R.; Veiros, L.F.; Menezes, F.; Gualandi, A.; Cozzi, P.G.; Afonso, C.A.M.; *Tetrahedron Green Chem.* **2025**, *5,* 100070.
[4] Alexandrov, Y. A., *J. Organometallic Chem.,***1982**, *238*, 1-78.

Unlocking the potential of ruthenium(II)-based compounds as anticancer chemotherapeutic and targeted agents

Tânia S. Morais[1, 2, *]

[1]Centro de Química Estrutural, Institute of Molecular Sciences, and Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal; [2]Associação do Instituto Superior Técnico para a Investigação e Desenvolvimento (IST-ID), Avenida António José de Almeida, 12, Lisboa, 1000-043, Portugal

** E-mail: tania.morais@tecnico.ulisboa.pt*

Ruthenium(II)-based compounds are emerging as promising anticancer agents due to their unique chemical properties and their potential for selective tumor targeting. Recent studies have highlighted their ability to modulate the tumor microenvironment, enhancing therapeutic efficacy while minimizing off-target effects [1]. In this talk, I will present an overview of research conducted in my laboratory over the past years on the anticancer activity of organometallic Ru(II)-based compounds, investigated in vitro and in vivo [2].

Within this context, targeted strategies are a cornerstone of personalized medicine and are expected to play an important role in advancing the translational potential of metal-based chemotherapeutics in oncology. I will also describe site-specific bioconjugation strategies developed in my group to improve the safe delivery and tumor-targeting capabilities of ruthenium(II) compounds [3,4]. This approach involves the development of smart metallodrug delivery systems (SMDS), in which cytotoxic Ru(II) complexes are linked to tumor-targeting peptides through stimulus-responsive linkers. These systems allow the drug to be released precisely at the tumor site, increasing therapeutic effectiveness while reducing off-target toxicity. The focus of this presentation will be on the structure, drug release profiles, and selective cytotoxicity of ruthenium SMDS, highlighting their potential as precision-targeted anticancer therapeutics for the treatment of primary and metastatic disease.

Acknowledgements: This work was funded by the Fundação para a Ciência e Tecnologia (FCT), I.P./MCTES for the financial support through the projects UID/00100/2025, UID/PRR/100/20250 (CQE), and LA/P/ 0056/2020 (IMS, DOI 10.54499/LA/P/0056/2020). T.S. Morais acknowledges the support of FCT through the Scientific Employment Stimulus – FCT-Tenure, and the Plano de Recuperação e Resiliência (PRR) n.º 02/C06-i06/2024.

References

[1] Lu, Y.; Zhu, D.; Le, Q.; Wang, Y.; Wang, W.; Nanoscale, 2022, 14, 16339-16375

[2] Valente, A.; Morais, T.S.; Teixeira, R.G.; Matos, C.P.; Tomaz, A.I.; Garcia, M.H.; Ruthenium and iron metallodrugs: New inorganic and organometallic complexes as prospective anticancer agents. In Book Synthetic Inorganic Chemistry: New Perspectives; EditorHamilton, E.J.M.; Elsevier, 2021, Chapter 6, pp. 223-276.

[3] Machado, J.F.; Machuqueiro, M.; Marques, F.; Robalo, M.P.; Piedade, M.F.M.; Garcia, M.H.; Correia, J.D.G.; Morais, T.S.; Dalton Trans. 2020, 49, 5974-5987.

[4] Machado, J.F.; Sá, M.; Pires, I.; Silva, M.; Marques, F.; Coelho, J.A.S.; Mendes, F.; Piedade, M.F.M.; Machuqueiro, M.; Jiménez, M.A.; Garcia, M.H.; Correia, J.D.G.; Morais, T.S.; Dalton Trans. 2024, 53, 7682-7693.

Liquid–liquid phase separation of dehydropeptides: from molecular design to functional assemblies

Paula M.T. Ferreira[1,*], Carolina Amorim[1], José A. Martins[1]
[1] *Chemistry Centre of the University of Minho (CQ-UM), Campus de Gualtar, Braga, Portugal*
** E-mail: pmf@quimica.uminho.pt*

Liquid–liquid phase separation (LLPS) has transformed our understanding of how simple molecular building blocks can self-organise into dynamic, membraneless compartments with functions reminiscent of living cells [1]. Peptide-based condensates are particularly attractive in this context, as short sequences can encode complex interaction networks while retaining chemical precision and modularity. However, a central challenge remains their limited stability, as peptide droplets frequently evolve into gels or ordered aggregates, restricting their practical use in biomaterials and protocell design [2,3].

Recently a minimalist design strategy to stabilise peptide-based condensates by combining natural aromatic amino acids with α,β-dehydroamino acids within short molecular architectures has been developed. The incorporation of dehydroamino acids introduces conformational restriction and backbone rigidity, suppressing ordered hydrogen-bonding motifs and structural ageing, while the aromatic amino acid component promotes dynamic, reversible interactions. This balance enables access to condensates that remain fluid while resisting conversion into solid aggregates (Figure 1). Beyond molecular design, solvent modulation is introduced as an external handle to control phase behaviour and stability. Transient liquid droplets formed under specific solvent conditions can be converted into robust microspherical assemblies that preserve morphology and can encapsulate cargo upon transfer to aqueous environments. These assemblies display efficient cellular internalisation, highlighting their potential for delivery and bioimaging applications.

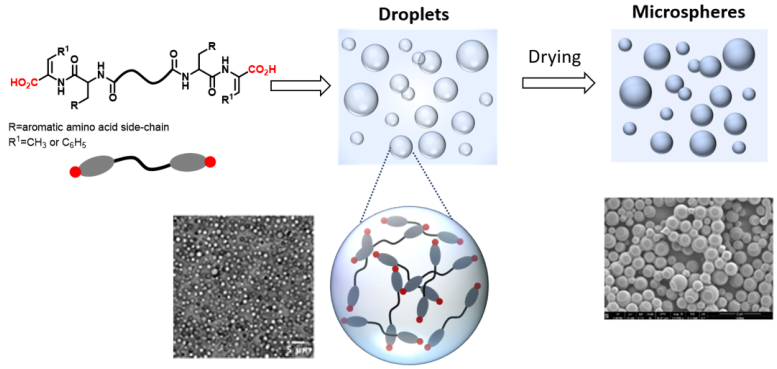


Figure 1. Molecular design and droplet formation from dehydropeptide based constructs.

Funding: This work was supported by the Portuguese Foundation for Science and Technology (FCT) in the framework of the Strategic Funding UID/00686: Centro de Química da Universidade do Minho (CQ-UM/UM)
Acknowledgements: Carolina Amorim acknowledges FCT for PhD grant 2021.07135.BD.

References

[1] Yuan, J.W.; Yang, Y.F.; Dai, K. ; Fakhrullin, R.; Li, H.; Zhou, P.; Yuan, C.Q.; Yan, X.H. ACS Applied Materials & Interfaces 2025, 17, 27697-27712.
[2] Bao, Y.S.; Xia, J., J. Am. Chem. Soc. AU, 2025, 5, 5267-5285.
[3] Abbas, M.; Lipinski, W.P.; Nakashima, K.K.; Huck, W.T.S.; Spruijt, E. Nature Chemistry 2021, 13, 1046-1054.

Why membranes matter: lipid bilayers and 3D drug descriptors in PK/PD prediction

Maria João Moreno[1,*]

[1] *Coimbra Chemistry Center, Institute of Molecular Sciences (CQC-IMS), Department of Chemistry, Faculty of Sciences and Technology, University of Coimbra, 3004-535 Coimbra, Portugal*
** E-mail: mmoreno@ci.uc.pt*

The ability to predict drug pharmacokinetics (PK) and pharmacodynamics (PD) from *in vitro* and *in silico* studies is a central challenge in modern drug design, as it directly impacts the success of translation to *in vivo* studies and clinical trials. Current molecular descriptors are largely based on overall physicochemical properties and frequently rely on Lipinski's Rule of Five to assess drug-likeness. In addition, drug–membrane affinity is often approximated from partitioning between water and nonpolar solvents. However, such bulk phases fail to capture the highly heterogeneous, anisotropic, and interfacial nature of biological membranes.

Lipid bilayers present steep polarity gradients, charged interfaces, and distinct hydrogen-bonding environments over nanometer length scales—features that strongly influence drug location, orientation, ionization state, and interactions with membrane proteins. These properties cannot be reproduced by conventional solvent models but are essential for understanding both drug distribution (PK) and drug–target interactions in membrane environments (PD).

This presentation will discuss the key structural and physicochemical characteristics of lipid bilayers that govern drug–membrane interactions and provide an overview of experimental and computational methods used to quantify membrane association. Particular emphasis will be placed on three-dimensional molecular descriptors that account for anisotropic solvation, charge distribution, and molecular orientation within membranes, together with approaches for their quantification. The goal is to provide a framework that integrates membrane affinity into medicinal chemistry workflows, improving the predictive power of PK/PD models and supporting more rational drug design.

Funding: This work has been funded by muitiple projects over the years, and more recently through projects UIDB/00313/2023 and UIDP/ 00313/2023, by FEDER funds through the program COMPETE – Programa Operacional Factores de Competitividade, and by national funds through FCT.

INVITED ORAL COMMUNICATIONS

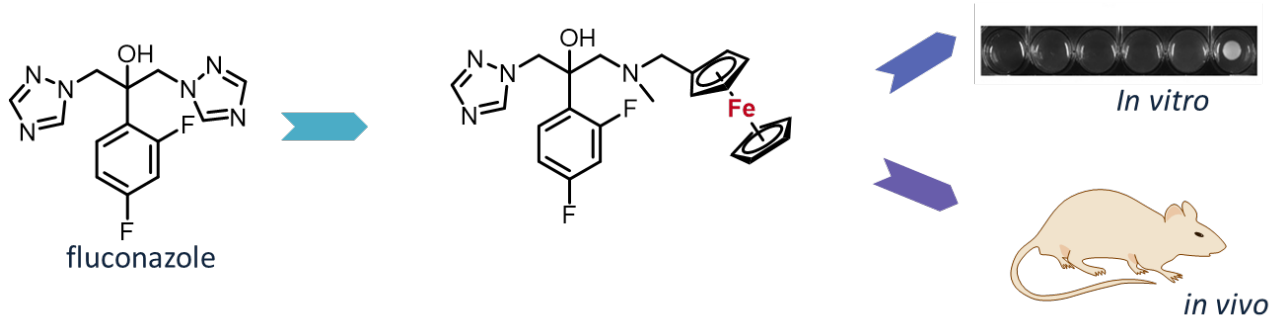
Organometallic derivatization of drugs for promising antiparasitic and antifungal treatments

Kevin Cariou[1,*]

[1]*Chimie ParisTech, PSL University, CNRS, Institute of Chemistry for Life and Health Sciences, Laboratory for Inorganic Chemical Biology, 75005 Paris, France.*

** E-mail: kevin.cariou@chimieparistech.psl.eu*

The advent and globalization of modern anti-infectious therapies in the XXth century has led to the emergence of resistance phenomena, which have become increasingly difficult to overcome. This includes fungal pathogenes, for which the WHO has recently published a list of critical strains. Metal-based drugs constitute an ever-growing class of therapeutic agents, with a wide array of modes of actions, that can allow to overcome such therapeutic dead ends. In this context, we systematically study the incorporation of organometallic-moieties into anti-infectious drug-frameworks to improve their therapeutic profile. During this talk we will present our latest results on several series antimycotic compounds based on various conazole scaffolds that incorporate a metallocene moiety and have given extremely promising results on critical strains such as FCZ-resistant Candida sp. including in in vivo murine models.[1-3]



Scheme. Organometallic derivatization of conazole drugs for antifungal evaluation *in vitro* and *in vivo*.

References

[1] S. Zhong, A. Kalamatianou, G. Scalese, C. O'Beirne, M. Redrado, O. Blacque, C. Tomasoni, C. Logé, M. Albassier, I. Ourlac-Garnier, F. Pagniez, P. Le Pape, L. Pérez-Díaz, D. Gambino, M.A. Comini, K. Cariou,* and G. Gasser,* *Inorg. Chem.*, **2025**, *64*, 16192.

[2] Y. Lin, G. Scalese, C.A. Bulman, R. Vinck, O. Blacque, M. Paulino, A. Ballesteros-Casallas, L. Pérez Díaz, G. Salinas, M. Mitreva,* T. Weil,* K. Cariou,* J.A. Sakanari,* D. Gambino,* and G. Gasser,* *ACS Infect. Dis.*, **2024**, *10*, 938.

[3] Y. Lin, H. Jung, C.A. Bulman, J. Ng, R. Vinck, C. O'Beirne, S. Zhong, M.S. Moser, N. Tricoche, R. Peguero, R. Li, J.F. Urban Jr, P. Le Pape, F. Pagniez, M. Moretto, T. Weil,* S. Lustigman,* K. Cariou,* M. Mitreva,* J.A. Sakanari* and G. Gasser,* *J. Med. Chem.*, **2023**, *6*, 15867.

Liquid–liquid phase separation-driven peptide microreactors as minimal hubs for emergent catalysis

Ana S. Pina[1]

[1]*Instituto de Tecnologia Quimica e Biológica António Xavier, Universidade Nova de Lisboa, Av. da República, 2780-157 Oeiras, Portugal.*

** E-mail: ana.pina@itqb.unl.pt*

Enzymes are among nature's finest creations, refined over billions of years to carry out essential chemical reactions with exceptional accuracy and selectivity. They are thought to have arisen from simpler, more flexible peptide building blocks, hinting that short peptides themselves can also act as catalysts [1,2]. Yet using peptides as catalysts in water is still very challenging, because their natural disorder and conformational flexibility are usually seen as drawbacks. As a result, most design strategies of catalytic peptides have relied on imposing rigid architectures that mimic traditional enzymes [2]. Living cells, however, show a different strategy: through liquid–liquid phase separation (LLPS), they create fluid, membrane-free compartments, also known as coacervates, in which flexibility and disorder enable sophisticated control over biochemical reactions [3,4].Learning how to reproduce this interplay between phase separation and catalysis in simple synthetic peptide systems is a largely unexplored opportunity that could open new possibilities for sustainable catalysis, synthetic biology, etc.

Our lab designs minimal peptide-based platforms in which LLPS is harnessed to create catalytic microcompartments and programmable functional materials [5]. By integrating supramolecular peptide design with LLPS, we uncover how sequence-encoded disorder, phase transitions and structural organization can be exploited to tune catalysis, molecular recognition and emergent behaviours of direct relevance to both biology and prebiotic chemistry. Using flexible catalytic peptides as model systems, we demonstrate that disordered peptide sequences can undergo a conformational switch to form coacervate-generating peptides with structured domains [6]. These coacervate-based microreactors display remarkable 15,000-fold enhancement in catalytic efficiency relative to soluble peptides, while selectively sequestering phosphotyrosine-containing substrates [6]. Together, these findings position LLPS as a fundamental mechanism in the evolution of chemical function, enabling the control of conformational flexibility and offering new insights into how enzyme-like activity and catalysis could have emerged.

References

[1] Frenkel-Pinter, M.; Samanta, M.; Ashkenasy, G.; Leman, .L.J.; Chem Rev 2020, 120, 4707–65.
[2] Carvalho, S.; Peralta Reis, D.Q.; Pereira, S.V.; Kalafatovic, D.; Pina,A.S.; Isr J Chem 2022, 62, e202200029.
[3] Reis, D.Q.P.; Calvário, J.; Chibeles, I.; Kumar, M.; Pina, A.S.; ChemSystemsChem 2025, 7, e00089.
[4] O'Flynn, B.G.; Mittag, T.; Curr Opin Cell Biol 2021, 69, 70–9.
[5] Calvário, J.; Antunes, D.; Cipriano, R.; Kalafatovic, D.;Mauša, G.;Pina, A.S.; Biomacromolecules 2025, 26, 7247–64.
[6] Reis, D.Q.P.; Pereira, S.; Ramos, A.P.; Pereira, P.M.; Morgado, L.; Calvário, J.; Henriques, A. O.; Serrano, M.; Pina, A.S.; Nat Commun 2024, 15, 9368.

.

DNA-inspired supramolecular hydrogels assembled by combining non-covalent and covalent strategies

João Borges[1,*], Vera Sousa[1], Rita Sobreiro-Almeida[1], João F. Mano[1]

[1]*CICECO – Aveiro Institute of Materials, Department of Chemistry, University of Aveiro, Campus Universitário de Santiago, 3810-193 Aveiro, Portugal*

** E-mail: joaoborges@ua.pt*

Supramolecular self-assembly is ubiquitous in nature, relying on the spontaneous non-covalent-driven self-organization of the fundamental building blocks of life into fascinating self-assembled structures. These include G-quadruplexes – non-canonical four-stranded self-assembled structures formed in guanine-rich DNA and RNA sequences within living cells – which have inspired the development of bioinspired supramolecular systems for bioapplications owing to their unique self-assembled structures and multiple biological roles [1,2]. However, the G-quadruplex structures have shown to undergo irreversible disassembly mainly due to their hydrophilic nature [3], which is a major limitation hampering their use in biomedical applications.

In this work, dynamic and stable G-quadruplex-derived supramolecular hydrogels were successfully developed through the multicomponent self-assembly of guanosine, 2-formylphenylboronic acid, and gelatin in the presence of K^+. The stability of the G-quadruplex structures was accomplished by the synergistic action of supramolecular self-assembly, macromolecular crowding, and transglutaminase-mediated covalent crosslinking. The hydrogels were characterized for their chemical and rheological properties, and printability, revealing optimal viscosity, yield stress, shear-thinning properties, and enabling 3D printing. The hydrogels revealed to be cytocompatible towards primary human mesenchymal stem cells. The high versatility imparted by the supramolecular hydrogels was shown by their readily availability as an 'off-the-shelf' biomaterial product, and ability to fabricate highly complex and tunable 3D structures, being suitable to recreate virtually any kind of damaged tissue and be used in advanced tissue engineering and regenerative medicine strategies.

Funding: This work was funded by the European Union's Horizon Europe research and innovation programme under the grant agreement no. 101079482 ("SUPRALIFE"), and by FEDER - Fundo Europeu de Desenvolvimento Regional funds through the COMPETE 2030 in the framework of the project COMPETE2030-FEDER-00874400 ("SUPRANEURO"). The financial support by FCT through the individual PhD grant (DOI 10.54499/2020.06771.BD – V.S.), and individual Junior (2022.04605.CEECIND – R.S.-A.) and Assistant Researcher contracts (DOI 10.54499/2020.00758.CEECIND/CP1589/CT0007 – J.B.) is gratefully acknowledged. This work was developed within the scope of the project CICECO - Aveiro Institute of Materials, UID/50011/2025 (DOI 10.54499/UID/50011/2025) & LA/P/0006/2020 (DOI 10.54499/LA/P/0006/2020), financed by national funds through the FCT/MCTES (PIDDAC)..

References

[1] Monsen, R.C.; Trent, J.O.; Chaires, J.B. ; *Acc. Chem. Res.* **2022**, *55*, 3242–3252.

[2] Varshney, D.; Spiegel, J.; Zyner, K; Tannahill, D.; Balasubramanian, S.; *Nat. Rev. Mol. Cell Biol.* **2020**, *21*, 459–474.

[3] Sousa, V.; Amaral, A.J.R.; Castanheira, E.J.; Marques, I.; Rodrigues, J.M.M.; Félix, V.; Borges, J.; Mano, J.F. *Biomacromolecules* **2023**, *24*, 3380–3396.

A bispecific small molecule mediates armed antibodies targeting of bone mineral matrix

Alberto Dal Corso,[1]* Cassandra Spinosa,[1] Mattia Mason,[1] Cristina Visentin,[2] Stefano Ricagno,[2] Beatrice Rocutto,[3] Marco Gobbi,[3] Massimo Zucchetti,[3] Roberta Frapolli[3] Claudia Nastasi[3]

[1]*Department of Chemistry, Università degli Studi di Milano, Via C. Golgi 19, 20133 Milan, Italy*
[2]*Department of Biosciences, Università degli Studi di Milano, Via G. Celoria 26, 20133 Milan, Italy*
[3]*Istituto di Ricerche Farmacologiche Mario Negri, IRCCS, Via Mario Negri, 2, 20156 Milan, Italy*
** E-mail: alberto.dalcorso@unimi.it*

Pre-targeting strategies within antibody research traditionally exploit specific small molecules (SM) as on/off switches of the biologic's pharmacological activity. In contrast to these approaches, we propose a new pre-targeting strategy in which a bispecific SM adaptor is used to drive the mAb binding to the bone mineral matrix (hydroxyapatite, HA), i.e., a clinically-relevant receptor so far inaccessible to mAb-based therapeutics.

This SM exploits the exquisite affinity of alendronate (ALN) for HA to selectively bind the bone matrix and install an artificial receptor (R), which can be reversibly targeted by a mAb, loaded with a suitable payload of interest.

The selected ALN-R adaptor showed long-lasting binding to HA both *in vitro* and *in vivo*. Competitive SPR experiments and confocal microscopy studies confirmed the R unit recognition by an anti-R mAb fragment. Finally, ALN-R induced the HA accumulation of the mAb armed with a cytotoxic payload, inducing apoptosis of neighbouring cancer cells *in vitro*.

These findings demonstrate the feasibility of an ALN-based pre-targeting system for recruiting therapeutic antibodies to bone lesions, with potential applications against bone metastases of solid tumours and in other bone-related diseases.

Acknowledgements: We thank Fondazione Beppe and Nuccy Angiolini Onlus for financial support. M.M. thanks the University of Milan for a PhD fellowship.

References

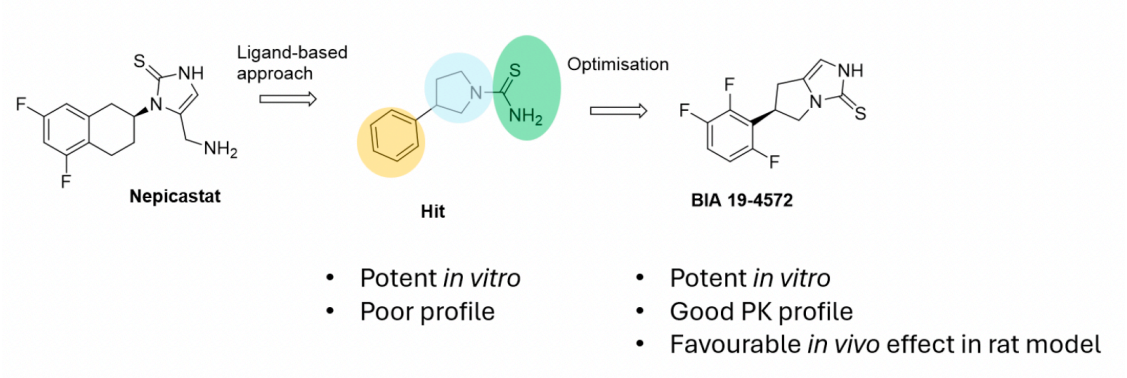
[1] M. Steiner, D. Neri, Clin. Cancer Res. 2011, 17, 6406-6416.
[2] D. A. Campbell, B. Gong, L. M. Kochersperger, S. Yonkovich, M. A. Gallop, P.G. Schultz, J. Am. Chem. Soc. 1994, 116, 2165-2166.
[3] R. Rossin, R. M.Versteegen, J. Wu, A. Khasanov, H. J. Wessels, E. J. Steenbergen,W. ten Hoeve, H. M. Janssen, A. H. A. M. van Onzen, P. J.Hudson, M. S. Robillard, Nat. Commun. 2018, 9, 1484.
[4] G. Rotta, E. Gilardoni, D. Ravazza, J. Mock, F. Seehusen, A. Elsayed, E. Puca, R. De Luca, C. Pellegrino, T. Look, T. Weiss, M. G Manz, C. Halin, D. Neri, S. Dakhel Plaza, EMBO Mol Med. 2024, 16, 904-926.
[5] Y. G. Lee, H. Chu, Y. Lu, C. P. Leamon, M. Srinivasarao, K. S. Putt, P.S. Low, Nat. Commun. 2019, 10, 2681.
[6] A. Q. Zhang, A. Hostetler, L. E. Chen, V. Mukkamala, W. Abraham, L. T. Padilla, A. N. Wolff1,4, L. Maiorino, C. M. Backlund, A. Aung, M. Melo, N. Li, S. Wu, D. J. Irvine, Nat. Biomed. Eng. 2023, 7, 1113-1128.
[7] C. Pellegrino, N. Favalli, M. Sandholzer, L. Volta, G. Bassi, J. Millul, S. Cazzamalli, M. Matasci, A. Villa, R. Myburgh, M. G. Manz, D. Neri, Bioconjugate Chem. 2020, 31, 1775-1783.

Identification of a brain penetrant DβH inhibitor for the treatment of panic and anxiety disorders

Jessica Baiget

BIAL, Coronado (S. Romão e S. Mamede) 4745-457, Trofa, Portugal
E-mail: jessica.baiget@bial.com

DβH inhibitors have therapeutic potential for the treatment of panic and anxiety disorders by reducing norepinephrine synthesis and, modulating dopamine levels, thereby attenuating the noradrenergic hyperactivity implicated in these conditions.
This presentation will outline the discovery of BIA 19-4572, a brain penetrant DβH inhibitor. The initial hit, a thiourea-based scaffold, was identified through a ligand-based approach but displayed a limited drug-like profile. Through targeted medicinal chemistry optimisation, BIA 19-4572 successfully addressed the shortcomings of the original series. The compound also demonstrated favorable pharmacodynamic properties and produced a robust anxiolytic response in animal models.



.

Regiodivergent cation sampling for distal Csp³-functionalization

Miloš Vavrík[1], Philipp Spieß[1], Jakob Frey[1], Uroš Vezonik[1], Daniel Kaiser[1], Nuno Maulide[1,*]

[1]*Department of Organic Chemistry, University of Vienna, Währinger Straße 38, 1090 Vienna, Austria*

** E-mail: nuno.maulide@univie.ac.at*

Despite notable progress in catalytic olefin isomerization processes enabling distal Csp³–H functionalization, most methods depend on complex metal-based catalytic systems and face inherent challenges in achieving regiodivergent outcomes [1–5].

In this work, we report a conceptually distinct approach in which we leverage acid-mediated olefin isomerization for regiodivergent Csp³–H functionalization, wherein the selectivity results from a ketone-assisted process we term *cation sampling* (**Figure 1**). This method enables site-selective, on-demand regiodivergent functionalization of Csp³ carbons, allowing the formation of C–heteroatom bonds in challenging positions and unlocking access to products that were previously unattainable through metal-based methodologies [3,6]. Remarkably, this platform is not limited to olefinic substrates, also offering a versatile framework for *alcohol transposition* reactions, a formal *migratory Appel reaction*, and an effective solution for *resolving regioisomeric bromohydrin mixtures* [7].

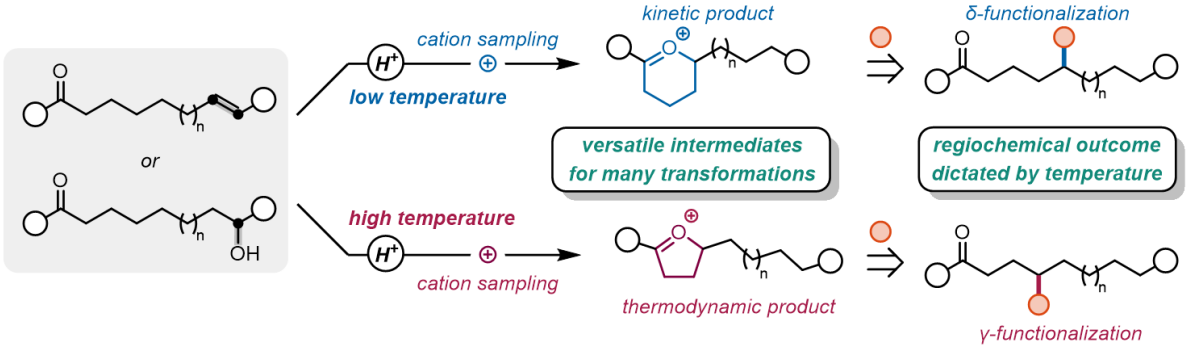


Figure 1. Cation sampling enables the regiodivergent generation of δ- and γ-oxocarbenium ions from alkenyl or hydroxy ketones upon treatment with an acid. The regioselectivity of these transformations is controlled solely by the reaction temperature, providing an operationally simple platform for selective δ- and γ-functionalization of ketones.

Funding: Funded by the European Union (ERC, C-HANCE, 101142915 to N.M.) and by the Austrian Science Fund (FWF, 10.55776/P37182 to N.M.).

Acknowledgements: We thank the Core Facility Crystal Structure Analysis and the NMR Center of the Faculty of Chemistry for their valuable support. We are grateful for the University of Vienna's continued and generous support of our research programs.

References

[1] Sommer, H.; Juliá-Hernández, F.; Martin, R.; Marek, I.; ACS Cent. Sci. 2018, 4, 153–165.
[2] Romano, C.; Martin, R.; Nat. Rev. Chem. 2024, 8, 833–850.
[3] Janssen-Müller, D.; Sahoo, B.; Sun, S.-Z.; Martin, R.; Isr. J. Chem. 2020, 60, 195–206.
[4] Vasseur, A.; Bruffaerts, J.; Marek, I.; Nat. Chem. 2016, 8, 209–219.
[5] Wang, J.-W.; Liu, D.-G.; Chang, Z.; Li, Z.; Fu, Y.; Lu, X.; Angew. Chem. Int. Ed. 2022, 61, e202205537.
[6] Fan, C.; Dhawa, U.; Qian, D.; Sakic, D.; Morel, J.; Hu, X.; Angew. Chem. Int. Ed. 2024, 63, e202406767.
[7] Spieß, P.; Vavrik, M.; Frey, J.; Vezonik, U.; Kaiser, D.; Maulide, N.; ChemRxiv 2025, ks4x0.

Micellar catalysis: enabling sustainable chemistry in water

João Sardinha

Hovione Farmaciência S.A., Loures, Portugal
E-mail: jsardinha@hovione.com

Micellar chemistry, often referred to as micellar catalysis, presents a greener alternative to traditional organic solvents. Although water can occasionally replace solvents effectively, its compatibility with organic reagents is not always ideal. Nevertheless, recent developments have led to the introduction of innovative additives, such as aqueous micelles that function as "nanoreactors". These nanospheres, formed by surfactant molecules create a unique environment that enables chemical transformations in aqueous media. This advancement represents a significant step forward in sustainable chemistry, reducing reliance on harmful solvents and promoting environmentally friendly practices in chemical synthesis.

At Hovione, we have been exploring the application of micellar chemistry in various types of reactions, namely amide bond formation, S_NAr, Suzuki couplings, nitro reductions among others. Some examples and comparison with traditional organic solvent methods will be presented. Additionally, a comparative study of an alkylation reaction in the synthesis of a Hovione API will be showcased, highlighting the superior efficiency, safety, and environmental benefits of micellar chemistry over the existing organic solvent process.

Synthesis laboratory in the agrochemical industry

Carlos M. Monteiro[1,*], J. A. S. Coelho[2], R. S. Gomes[2], D. B. Clemente[2], C. M. Catarino[2], M. B. T. Ferreira[1], A. M. R. Rocha[1], K. H. S. Andrade[1]

[1]ASCENZA Agro, S.A., Screening and Synthesis Laboratory, Setúbal, Portugal.;
[2]Centro de Química Estrutural, Institute of Molecular Sciences, Department of Chemistry and Biochemistry, Faculty of Sciences, University of Lisbon, Lisbon, Portugal
** E-mail: carlos.monteiro@ascenza.rovensa.com*

ASCENZA is a Portuguese agrochemical company dedicated to the development, registration, production, and commercialization of crop protection solutions. Innovation, quality, and regulatory excellence are core pillars of its activity, with product safety being a central commitment. ASCENZA integrates advanced chemical research with industrial development to support sustainable agriculture.

The development of agrochemicals requires a comprehensive assessment of the safety profile of active ingredients, including the evaluation of toxicity and the determination of the physicochemical properties of their metabolites and impurities. The sustainable and efficient synthesis, isolation, and full characterization of these compounds constitute the primary mission of the Synthesis & Screening Laboratory.

This presentation will focus on synthetic strategies for the preparation of impurities and metabolites of agrochemical active ingredients, their isolation and structural characterization, and the role of close collaborations with academic partners in addressing complex challenges in agrochemical research and development.

Funding: FCT (PTDC/QUI-QOR/1786/2021, UID/00100/2025, UID/PRR/100/2025 and LA/P/0056/2020) and Fundação Calouste Gulbenkian (Novos Talentos 2024 Nº 328964).

Abietane diterpenoids: natural scaffolds for antitumor drugs

Patrícia Rijo[1,2,3*]

[1]CBIOS Lusófona's Research Center for Biosciences and Health Technologies, Campo Grande 376, 1749-024 Lisbon, Portugal; [2]Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal; [3]Centro de Química Estrutural, Institute of Molecular Sciences, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal

** E-mail: patricia.rijo@ulusofona.pt*

Natural products play a central role in anticancer drug development, exemplified by several clinically used agents such as paclitaxel, vincristine and doxorubicin. Among the most promising sources, the *Plectranthus* genus provides abietane diterpenoids with notable antitumor activity. However, challenges such as low solubility, poor stability and limited bioavailability often restrict their direct therapeutic application [1].

In this work, bioactive diterpenoids from *Plectranthus*, including 7α-acetoxy-6β-hydroxyroyleanone (Roy) from *P. grandidentatus* Gürke (Lamiaceae) or the derivative RoyBz [2], as well as newly synthesized derivatives, were explored as potential anticancer leads. Molecular modelling guided the selection of structural modifications predicted to enhance interactions with PKC-α. The resulting derivatives displayed improved antiproliferative activity in breast cancer cell lines and reduced cytotoxicity in non-tumoral fibroblasts. Functional studies further confirmed their ability to modulate PKC-α and influence biological pathways relevant to tumor progression.

To address pharmacokinetic limitations, two nanotechnology-based delivery strategies were investigated: gold nanoparticles and self-assembled nanoparticles derived from lipid or terpenoid conjugates. These systems enhanced solubility, improved stability and enabled more controlled release of the diterpenoids [3].

Overall, this study highlights the potential of *Plectranthus* abietane diterpenoids and their derivatives as innovative antitumor candidates and underlines the value of nanotechnology—particularly gold and self-assembled nanoparticles—as supportive strategies to optimize their therapeutic application.

Funding: This work was supported by FCT (Portugal) through the projects with reference UID/04567/2025

References

[1] Bangay, G.; Brauning, F.Z.; Rosatella, A.; Díaz-Lanza, A.M.; Domínguez-Martín, E.M.; Gonçalves, B.; Hussein, A.A.; Efferth, T.; Rijo, P. Phytomedicine 2024, 129, 155634.

[2] Bessa, C.; Soares, J.; Raimundo, L.; Loureiro, J.B.; Gomes, C.; Reis, F.; Soares, M.L.; Santos, D.; Dureja, C.; Chaudhuri, S.R.; Lopez-Haber, C.; Kazanietz, M.G.; Gonçalves, J.; Simões, M.F.; Rijo, P.; Saraiva, L. Cell Death Dis. 2018, 9, 15.

[3] Bangay, G.; Isca, V.M.S.; Morais, J.; Fernández Alarcón, J.; Viana, A.S.; Reis, C.P.; Pereira-Leite, C.; Díaz-Lanza, A.M.; Saraiva, L.; Fornaguera, C.; Rijo, P. *J. Drug Deliv. Sci. Technol.* 2025, 114 (Part A), 107389.

ORAL COMMUNICATIONS

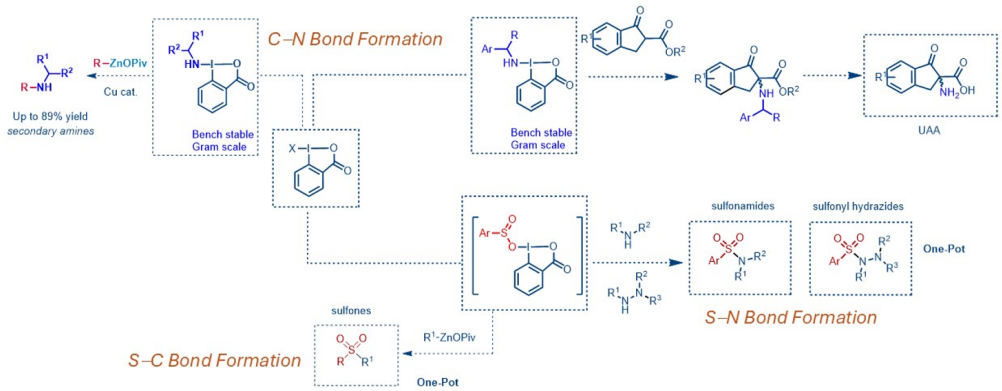
Next-generation cyclic iodine(III) reagents driving new frontiers in bond-forming chemistry

Maria Manuel B. Marques[1]

[1]*LAQV-REQUIMTE, Department of Chemistry, NOVA School of Science and Technology, Universidade Nova de Lisboa, 2829-516 Caparica, Portugal*

* *E-mail: mmbmarques@fct.unl.pt*

Cyclic hypervalent iodine reagents (HIR) have become powerful tools in modern organic synthesis, offering a rare combination of stability, tunable reactivity, and sustainable reaction conditions [1]. Their unique features open previously inaccessible disconnections, boosting synthetic efficiency and expanding the landscape of functional-group interconversion. We have developed a new generation of benziodoxolone-derived reagents that unlock unprecedented reactivity in key bond-forming transformations. By merging HI chemistry with sulfinate salts, we established highly selective sulfonyl-transfer reactions for amines, anilines, hydrazines, and most recently C-based nucleophiles—providing a sustainable route to valuable sulfonyl motifs [2]. In parallel, we designed BBX reagents that deliver primary amines to β-keto esters via oxidative amination, streamlining access to α-amino carbonyl compounds, and have now extended this platform to secondary-amine synthesis using BBX with aryl- and alkylzinc reagents [3]. Together, these methodologies enable efficient construction of pharmacologically relevant scaffolds and highlight the versatility of HI in late-stage functionalization and medicinal chemistry. Collectively, our findings showcase the expanding power of HIRs as practical, selective, and sustainable tools for modern synthetic innovation (**Scheme 1**).



Scheme 1. Benziodoxolone-mediated C–N and N–S bond formation.

Acknowledgements: We thank FC&T project funding (2022.04623.PTDC), the Laboratory for Green Chemistry-LAQV which is financed by national funds from FCT/MCTES (UID/QUI/50006/2019) and co-financed by the ERDF under the PT2020 Partnership Agreement (POCI-01-0145-FEDER - 007265).

References

[1] Macara, J.; Caldeira, C.; Poeira, D. L. ; Marques, M. M. B. *Eur. J. Org. Chem.* **2023**, e202300109.

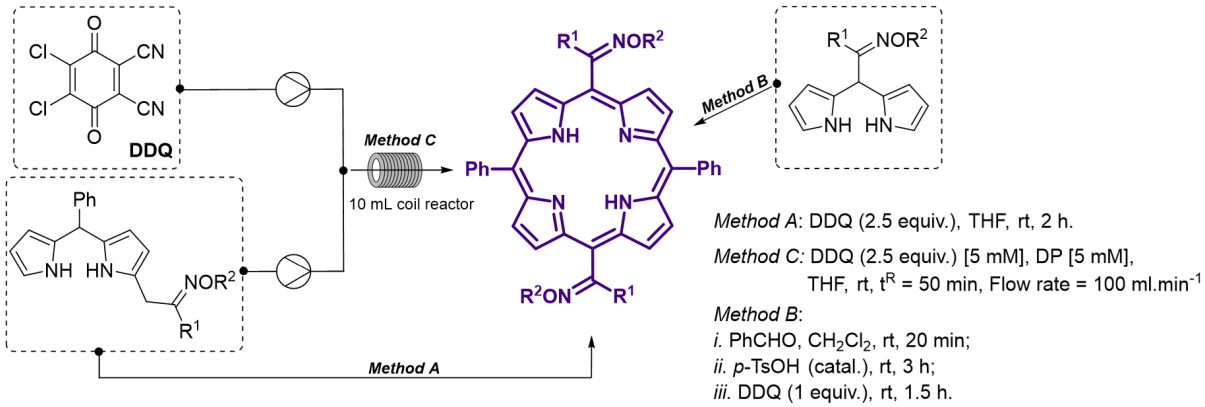
[2] a) Poeira, D. L.; Macara, J.; Faustino, H.; Coelho, J. A. S.; Gois, P. M. P.; Marques, M. M. B. *Eur. J. Org. Chem.* **2019**, *15*, 2695-2701; b) Macara, J.; Poeira, D. L.; Coelho, J. A. S.; Marques, M. M. B. *Synlett* **2021**, *32*, 1730-1734; c) Macara, J.; Caldeira, C.; Cunha, J.; Coelho, J. A. S.; Silva, M. J.; Krämer, K.; Gratwhol, C.; Bräse, S.; Marques, M. M. B. *Org. Biomol. Chem.* **2023**, *15*, 2695-2126.

[3] a) Poeira, D. L.; Negrão, A. C.; Faustino, H.; Gomes, C.; Coelho, J. A. S; Gois, P. M. P.; Marques, M. M. B. *Org. Lett.* **2022**, *24*, 776-781; b) Negrão, A. C.; Dedeiras, B.; Cunha, J.; Carvalho, D. F; Santos, F.; Gomes, C.; Coelho, J. A. S.; Gois, P. M. P.; KNochel, P.; Marques, M. M. B. *Org. Lett.* **2025**, *27*, 9914-9919.

A novel synthetic pathway to *trans*-A_2B_2-porphyrins: from serendipitous discovery to controlled macrocyclization

João C. S. Simões[1,*], Bruna D. P. Costa[1], Ana Clara B. Rodrigues[1], Susana M. M. Lopes[1], J. Sérgio Seixas de Melo[1], Marta Pineiro[1], Teresa M. V. D. Pinho e Melo[1]
[1]*University of Coimbra, Coimbra Chemistry Centre-Institute of Molecular Sciences (CQC-IMS) and Department of Chemistry, 3004-535 Coimbra, Portugal*
** E-mail: joao95simoes@gmail.com*

We report an unprecedented strategy for the synthesis of *trans*-A_2B_2 porphyrins starting from *α*-oxime-substituted dipyrromethanes. Initially observed serendipitously during attempts to prepare oxime-functionalized BODIPYs, the reaction was found to proceed through a DDQ-mediated sequence of intermolecular and intramolecular metal-free C(sp^3)–C(sp^2) cross-coupling steps, giving rise to the porphyrin macrocycle under mild conditions. In parallel, the classical [2+2] condensation between *meso*-oxime-functionalized dipyrromethanes and aldehydes was also evaluated, providing access to the same *trans*-A_2B_2 porphyrins, albeit in lower yields and with more challenging purification. Mechanistic studies, including the use of radical initiators and TEMPO inhibition, strongly support a radical-driven pathway. The methodology was further expanded under continuous-flow conditions, improving sustainability and scalability while maintaining comparable yields. Photophysical characterization revealed that the resulting porphyrins display high singlet-oxygen quantum yields (up to 86%), highlighting their potential as photosensitizers for photodynamic therapy. This work demonstrates a novel, efficient, and versatile approach to porphyrin construction, opening avenues for the synthesis of other functional macrocyclic systems.



Scheme1. Porphyrin Synthesis via three different synthetic methods.

Funding: This work was supported by Project PTDC/QUI-QOR/0103/2021, which is funded by the Fundação para a Ciência e a Tecnologia (FCT), I.P./MCTES, by national funds (PIDDAC; DOI: 10.54499/PTDC/QUI-QOR/0103/2021). We acknowledge funding from the Coimbra Chemistry Centre – Institute of Molecular Sciences (CQC-IMS)which is supported by the Fundação para a Ciência e a Tecnologia (FCT), Portuguese Agency for Scientific Research. CQC is funded by FCT through projects UID/PRR/00313/2025 (https://doi.org/10.54499/UID/PRR/00313/2025) and UID/00313/2025 (https://doi.org/10.54499/UID/00313/2025) and IMS through special complementary funds provided by FCT (project LA/P/0056/2020 https://doi.org/10.54499/LA/P/0056/2020).
Acknowledgements: The authors also acknowledge the UC-NMR facility for the NMR data (www.nmrccc.uc.pt).
References: João C. S. Simões, Bruna D. P. Costa, Ana Clara B. Rodrigues, Susana M. M. Lopes, J. Sérgio Seixas de Melo, Marta Pineiro, and Teresa M. V. D. Pinho e Melo.; J. Org. Chem. 2025, 90, 45, 16060–16069.

In vitro evaluation of innovative peptides towards breast cancer metastization

Ana Estrela[1,2], Marco Cavaco[1,3], Miguel A.R.B. Castanho[1,3]

[1]*Fundação GIMM - Gulbenkian Institute for Molecular Medicine, Av. Professor Egas Moniz, Lisboa, Portugal;* [2]*Faculdade de Ciências, Universidade de Lisboa, Campo Grande, Lisboa, Portugal;* [3]*Faculdade de Medicina, Universidade de Lisboa, Av. Professor Egas Moniz, Lisboa, Portugal*

** E-mail: ana.estrela@gimm.pt*

Triple-negative breast cancer (TNBC) is the most aggressive breast cancer subtype, associated with poor clinical outcomes. The lack of estrogen, progesterone, and HER2 receptors limits approved targeted therapies, underscoring the need for selective molecular strategies [1]. In this context, the Wnt/β-catenin pathway, driven by Frizzled-7 (FZD7) overexpression, emerges as a critical driver of TNBC tumorigenesis, metastatic dissemination, and resistance to therapy [2]. To selectively target FZD7, we engineered linear peptides derived from the complementary-determining regions (CDRs) of an anti-FZD7 antibody, preserving high-affinity receptor recognition while mitigating limitations associated with full-length antibodies [3]. Given their strong preclinical performance, these peptides form the foundation for a subsequent optimization phase, in which stapling strategies will be applied to enhance chemical stability and pharmacological performance (manuscript in preparation), yielding a more advanced generation of anti-FZD7 candidates [4]. Stapling introduces intramolecular covalent crosslinks, such as bridges between Lys and Asp side chains, that constrain peptide conformation into bioactive α-helices, which are expected to translate into higher binding affinity for FZD7 [5]. Several stapled variants and N-terminally labelled analogues (Quasar 670 or biotin) were synthesized for mechanistic and localization studies.

Both linear and stapled anti-FZD7 peptides demonstrated cytotoxic effects in TNBC cells under conventional 2D cell culture and more physiologically relevant 3D spheroid models, with stapled peptides retaining substantial, though slightly reduced, activity compared with the parent linear sequence. Ongoing and future work will include comprehensive peptide characterization, quantitative analysis of cell binding kinetics, biodistribution and pharmacokinetics in vivo using zebrafish models, and functional assessment of FZD7 signalling inhibition. Collectively, these efforts bridge peptide chemistry and tumour biology to support stapled anti-FZD7 peptides as a promising targeted agent for TNBC.

Funding: This research was funded by “la Caixa” Foundation (ID 100010434) and FCT, I.P under the agreement LCF/PR/HP21/52310015.

References

[1] Waks, A.G.; Winer, E.P. Breast Cancer Treatment: A Review. JAMA 2019, 321, 288–300.
[2] Yang, L.; Wu, X.; Wang, Y.; Zhang, K.; Wu, J.; Yuan, Y.; et al. FZD7 Has a Critical Role in Cell Proliferation in Triple-Negative Breast Cancer. Oncogene 2011, 30, 4437–4446.
[3] Afonso, A.L.; Cavaleiro, C.T.; Castanho, M.A.R.B.; Neves, V.; Cavaco, M. The Potential of Peptide-Based Inhibitors in Disrupting Protein–Protein Interactions for Targeted Cancer Therapy. Cancers 2024, 16, 461.
[4] Afonso, A.L.L. Characterization of Peptide-Based Inhibitors to Tackle Triple-Negative Breast Cancer (TNBC). Master’s Thesis, NOVA Medical School, NOVA University Lisbon, Portugal, 2023.
[5] Kim, D.H.; Kang, S.M. Stapled Peptides: An Innovative and Ultimate Future Drug Offering a Highly Powerful and Potent Therapeutic Alternative. Biomimetics 2024, 9, 537.

Machine learning-guided target identification and optimization of a scorpion-venom alkaloid

Ana Laura Dias[1,*], Carlos M. M. Afonso[2,3], Gonçalo J. L. Bernardes[4,5], Tiago Rodrigues[1]

[1]*Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, University of Lisbon, Portugal;*
[2]*Centro Interdisciplinar de Investigação Marinha e Ambiental (CIIMAR/CIMAR), Porto, Portugal;*
[3]*Laboratório de Química Orgânica e Farmacêutica, Faculty of Pharmacy, University of Porto, Portugal;*
[4]*The Gulbenkian Institute for Molecular Medicine (GIMM), Faculty of Medicine, University of Lisbon, Lisbon, Portugal;* [5]*Department of Chemistry, University of Cambridge, Cambridge, UK.*
** E-mail: ana.laura.dias@edu.ulisboa.pt*

Animal venoms are highly complex mixtures of bioactive molecules with significant medicinal potential [1,2]. Despite this, their chemical diversity is often underexplored, mostly due to challenges in elucidating their mode of action and identifying molecular targets by conventional chemoproteomics.

In this study, we aimed to de-orphanize an unexplored scorpion venom-derived alkaloid [3] by leveraging machine learning (ML) algorithms. Our workflow (Fig. 1) combined supervised and unsupervised ML models trained on curated ChEMBL datasets. Through this integrated approach, we predicted a likely GPCR target, which we subsequently validated *in vitro*. The alkaloid displayed micromolar affinity in a radioligand binding assay (IC_{50} = 10 μM) and potent agonist activity in a cAMP functional assay (EC_{50} = 0.125 μM). Guided by these results, computer-aided drug design allowed the synthesis of a focused library of analogues also active against the identified GPCR. Follow-up biological studies are planned to assess its potential anti-cancer activity in neuroendocrine tumor models.

In conclusion, our ML-driven target identification strategy enabled the systematic exploration of a previously unexplored venom-derived natural product. This work resulted in a novel small-molecule library active against the identified target and provided deeper insights into its biological mode of action. This study highlights the powerful role of machine learning in medicinal chemistry, allowing for data-driven discovery and innovation.

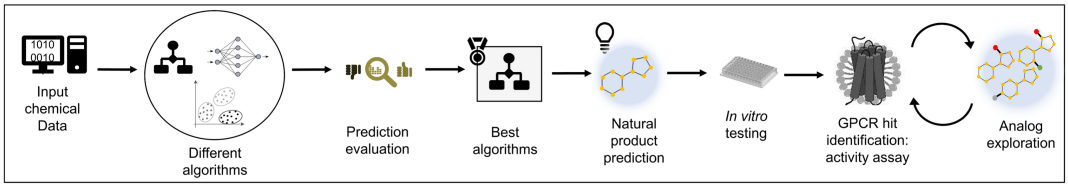


Figure 1. Workflow followed to discover a novel protein target for an unexplored alkaloid natural product isolated from a scorpion venom.

Funding: This work was supported by Fragment-Screen (101094131) and FCT (UID/04138/2025). Ana Laura Dias acknowledges the FCT for the financial support from the PhD studentship 2022.09827.BD.

References

[1] A. McDermott, *PNAS* **2020**, *117*, 10100-10104.
[2] M. Holford, M. Daly, G. F. King, R. S. Norton, *Science* **2018**, *361*, 842-844.
[3] S. Banerjee, E. Gnanamani, S. R. Lynch, F. Z. Zuñiga, J. M. Jiménez-Vargas, L. D. Possani, R. N. Zare, *J. Nat. Prod.* **2018**, *81*, 1899-1904.

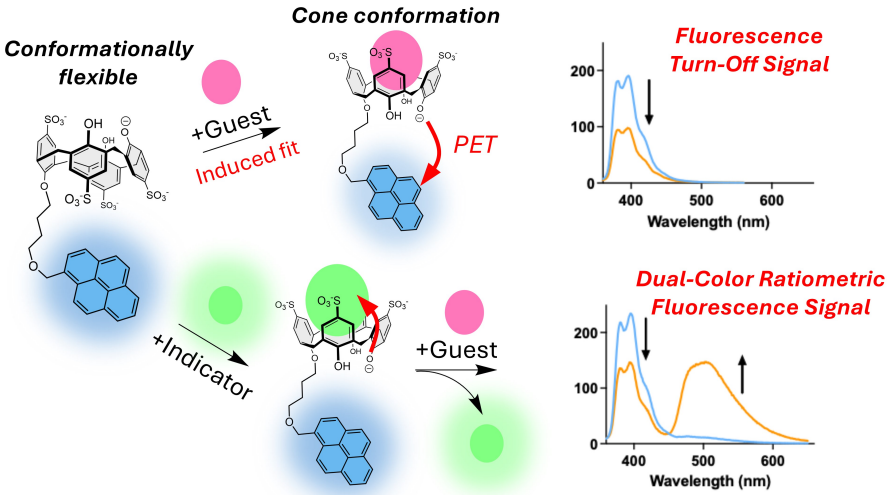
Calixarene–pyrene conjugates for induced-fit recognition and dual-wavelength fluorescence sensing in water

Nuno Basílio[1,*], Joana N.Martins[1], João Carlos Lima

[1] *Laboratório Associado para a Química Verde (LAQV), Rede de Química e Tecnologia (REQUIMTE), Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade NOVA de Lisboa 2829-516 Caparica, Portugal*

** E-mail: nuno.basilio@fct.unl.pt*

The discovery of fluorescence receptors that selectively bind small molecules with high affinity in aqueous media is critical for the development of new sensing and bioimaging assays. In this presentation, I will introduce new fluorescence receptor-dye chemosensors based on the monofunctionalization of *p*-sulfonatocalix[4]arene (SC4) receptor with pyrene dyes (SC4-Py). The SC4-Py conjugates were found to retain the exceptional binding properties of SC4, allowing the high-affinity recognition of neurotransmitters, amino acids, and biogenic amines in aqueous solution and their optical detection. The SC4-Py chemosensor operates through a photoinduced electron transfer (PET) mechanism triggered by conformational changes in the calixarene structure upon binding, allowing single-wavelength fluorescence detection of target analytes and its expansion into a dual-wavelength ratiometric indicator displacement assay (IDA) that relies on competitive PET between the pyrene and non-covalently bound lucigenin dye (see **Scheme 1**).



Scheme 1. A sulfonatocalix[4]arene–pyrene conjugate functions as a fluorescence chemosensor for the optical detection of biorelevant analytes in water. Photoinduced electron transfer (PET) response is triggered by an induced-fit recognition mechanism. Noncovalent assembly with an additional dye affords dual-color ratiometric signaling via competitive PET.

Funding: This work was financed by national funds from FCT - Fundação para a Ciência e a Tecnologia, I.P., under the scope of the project UID/50006/2023 of the Associate Laboratory for Green Chemistry- LAQV REQUIMTE. FCT is also acknowledged for the project 2023.16144.ICDT; cofinanced by FEDER through COMPETE 2023 with reference COMPETE2030-FEDER-00899900. J. N. M. acknowledges FCT for the PhD grant (2021.06296.BD).

Dendrimer-induced biofilm disruption is accompanied by a global shift in *Listeria monocytogenes* gene expression

Laura Pereira[1], Maria Carvalho[1,2], Adriana Cruz[1], Ana Godinho-Santos[3], José M. Andrade[4], Marta M. Alves[5], Vasco D.B. Bonifácio[1], Sandra N. Pinto[1]*,

[1]*Institute for Bioengineering and Biosciences (iBB), Instituto Superior Técnico, Universidade de Lisboa, Lisbon, Portugal;* [2]*Global Health and Tropical Medicine (GHTM), Instituto de Higiene e Medicina Tropical (IHMT), Universidade Nova de Lisboa, Lisbon, Portugal;* [3]Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, 1649-003 Lisboa, Portugal; [4]Instituto de Tecnologia Química Biológica António Xavier, Universidade NOVA de Lisboa, Portugal; [5]*Centro de Química Estrutural (CQE), Instituto Superior Técnico, Lisbon, Portugal.*
** E-mail: sandrapinto@ist.utl.pt*

*Listeria monocytog*enes is a foodborne pathogen whose biofilm-forming ability enhances its persistence in food processing environments and compromises treatment. The ineffectiveness of conventional antimicrobials against biofilms necessitates novel therapeutic strategies. Thus, this study evaluates the efficacy of synthetic cationic polyurea dendrimers in disrupting and eradicating *L. monocytogenes* biofilms.

Here we used two cationic polyurea dendrimers, $PURE_{G4}$-$OCEI_{24}$ and $PURE_{G4}$-OEI_{48}, were synthesized and first evaluated for their membrane selectivity using giant unilamellar vesicles (GUVs) mimicking bacterial membranes. The more promising dendrimer was then selected for comprehensive anti-biofilm assessment. We determined minimum inhibitory and bactericidal concentrations (MIC/MBC), performed live-dead assays via spectral flow cytometry, quantified biofilm inhibition and eradication, and analyzed the dendrimer's impact on the expression of key virulence and biofilm-related genes.

Our results showed that $PURE_{G4}$-OEI_{48} exhibited a higher zeta potential (+43.52 mV) and greater selectivity for bacterial membrane mimics than $PURE_{G4}$-OEI_{24} and due to this result we proceeded our study with $PURE_{G4}$-OEI_{48}. This dendrimer demonstrated potent bactericidal activity against *L. monocytogenes* (MIC = MBC = 0.78 µM). The dendrimer significantly inhibited biofilm adhesion and disrupted pre-formed biofilms, even under a high bacterial load (10^8 CFU/mL). Mechanistic studies revealed that $PURE_{G4}$-OEI_{48} treatment suppressed critical virulence pathways, including quorum sensing and biofilm formation genes. Furthermore, it restored normal cytoskeletal labeling in host cells, indicating impaired bacterial recruitment of host components for spread. In conclusion, the cationic polyurea dendrimer $PURE_{G4}$-OEI_{48} is a highly promising anti-biofilm agent against *L. monocytogenes*. Its dual mechanism of action, direct bacterial membrane disruption and downregulation of quorum sensing and biofilm formation genes, potentiates its efficacy. These findings position cationic dendrimers as an innovative strategy to prevent and treat recalcitrant Listeria biofilms.

Funding: This work funded by Fundação para a Ciência e a Tecnologia, Ministério da Ciência, Tecnologia e Ensino Superior (FCT/MCTES, Portugal) through projets Dendricare (2022.036627.PTD) and DREAM (PTDC/MEC-ONC/29327/2017). This work was also financed by national funds from FC&T in the scope of the projects UIDB/04565/2020 and UIDP/04565/2020 from the Research Unit iBB-Institute for Bioengineering and LA/P/0140/2020 from the Associate Laboratory i4HB-Institute for Health and Bioeconomy. This work was partially supported by PPBI - Portuguese Platform of BioImaging (PPBI-POCI-01-0145-FEDER-022122) co-funded by national funds from OE - "Orçamento de Estado" and by european funds from FEDER - "Fundo Europeu de Desenvolvimento Regional".

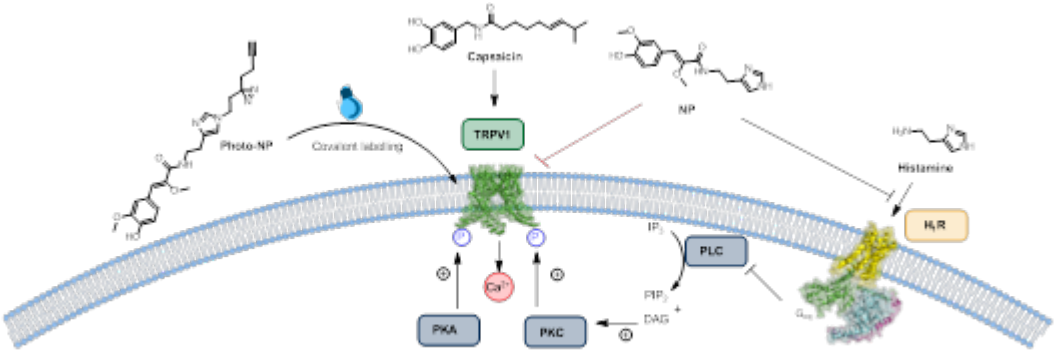
A scorpion venom derived natural product as a TRPV1 antagonist for the treatment of neuropathic pain

Nicholas Bossons[1,2,*], A.L. Dias[1], R. Gomes[1], C. Tang[3], M. Marques[3], T. Rodrigues[1], A. Fernández-Carvajal[4], A. Ferrer-Montiel[4], P. Góis[1], G. Bernardes[2,5]

[1]iMed.ULisboa, FFUL, Av. Prof. Gama Pinto, 1649-003 Lisbon, Portugal; [2]Chemprecise Lda, 2560-247 Torres Vedras, Portugal; [3]GiMM, Av. Prof. Egas Moniz, 1649-028 Lisboa, Portugal; [4]IdiBE, Universidad Miguel Hernandez, Avda. Universidad s/n, 03202 Elche, Spain; [5]Yusuf Hamied Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, United Kingdom.

** E-mail: nbossons@edu.ulisboa.pt*

Natural products and their derivatives constitute nearly 35% of FDA-approved therapeutics, largely due to their privileged structures, scaffold complexity and broad coverage of chemical space [1]. We addressed the challenge of target identification of a novel, non-cytotoxic natural product derived from scorpion venom using machine learning and affinity-based proteomics. We synthesised the compound in 6 steps with an overall yield of 34%, alongside photoaffinity probes enabling covalent protein labelling and downstream quantitative proteomics [2]. Using these approaches, we identified the TRP family of ion channels, widely implicated in neuropathic pain, as potential therapeutic targets. Using computational methods, we predicted the natural product as a TRPV1 antagonist and confirmed this with in vitro calcium imaging assays. We also proved target engagement using photoaffinity probes to modify TRPV1. Additionally, the natural product was able to inhibit histamine induced TRPV1 sensitisation indicating its potential therapeutic use in pruritus (Scheme 1). Together, these findings highlight the power of integrating chemical biology with machine learning to accelerate natural product driven drug discovery.



Scheme 1: identification of scorpion alkaloid as a TRPV1 antagonist

Funding: This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie Actions grant agreement No 956477. We thank the Fundação para a Ciência e Tecnologia for financial support 2023.11341.PEX, UIDB/04138/2025 - Instituto de Investigação do Medicamento.

References

[1] Patridge, E.; Gareiss, P.; Kinch, M. S.; Hoyer, D. Drug Discov. Today 2016, 21, 204–207.
[2] Grant, E. K et al. Angew. Chem., Int. Ed. 2020, 59, 21096–21105.

Photocatalytic synthesis of indoles

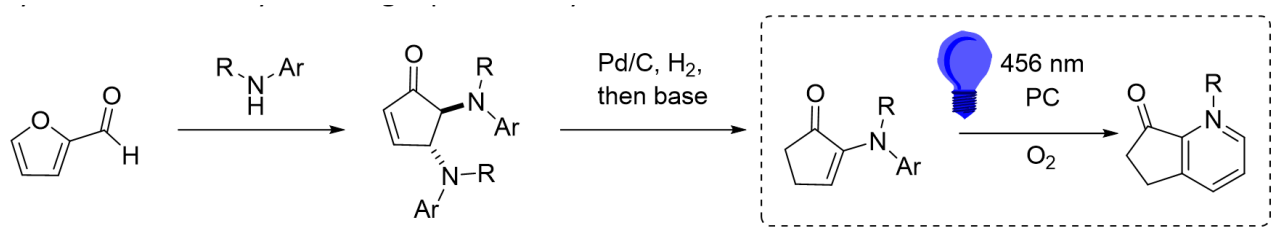
Gonçalo Vilela,[1] João R. Vale,[1*] Carlos. A. M. Afonso.[1]

[1]*Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisbon, Portugal*

**E-mail: jvale@edu.ulisboa.pt*

Indole derivatives are important motifs in natural products, pharmaceuticals, and agrochemicals,[1,2] which has driven interest in the development of new and more sustainable synthetic methodologies. Many classical approaches to indole synthesis such as Fischer, Bartoli and Madelung rely on harsh reaction conditions, toxic or expensive reagents, and display limited functional group tolerance. [3] In this context, visible-light photocatalysis has emerged as a powerful methodology, enabling mild and selective transformations aligned with green chemistry principles.[4]

At the outset of this work, we aimed to develop a photocatalytic strategy for the synthesis of indole derivatives starting from renewable feedstocks. Specifically, furfural, an industrial platform chemical readily obtained from biomass waste, was explored as a precursor. The complete synthetic sequence involves the conversion of furfural into trans-diaminocyclopentenones via Nazarov-type electrocyclization, followed by catalytic hydrogenation and β-amine elimination to afford α-enaminones as key precursors to the photocatalytic transformation (**Scheme 1**). These enaminones undergo an oxidative photocyclization of under blue light irradiation using the organic photocatalyst 3DPAFIPN in the presence of atmospheric oxygen. Under optimized conditions, a broad range of indole derivatives was obtained in moderate isolated yields (38–53%). Preliminary mechanistic investigations suggest an energy transfer-driven pathway rather than a single-electron transfer process. Overall, this work demonstrates a sustainable and biomass-derived approach to indole synthesis enabled by visible-light photocatalysis.



Scheme 1. Synthetic pathway for enaminones and their photocatalytic oxidation.

Funding: The authors gratefully acknowledge financial support from the Fundação para a Ciência e a Tecnologia (2023.11341.PEX, 2023.09224.CEECIND, UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025) Instituto de Investigação do Medicamento)

References

[1] Kumar, S.; Ritika. A.; Futur. J. Pharm. Sci. 2020, 6, 121.
[2] Singh, T. P.; Singh, O. M.; Mini Rev. Med. Chem. 2018, 18, 9-25.
[3] Chandra, A.; Yadav, S. C.; Cheekatla, S. R.; Kumar, A.; Org. Biomol. Chem., 2025, 23, 6853-6887.
[4] Michelin, C.; Hoffmann, N.; ACS Catal. 2018, 8,12046-12055.

Strategic synthetic approaches to push–pull porphyrin–carbazole derivatives

Melani J. A. Reis,[1] Maria G. P. M. S. Neves, [1] Nuno M. M. Moura[1,*]

[1] *LAQV-Requimte and Department of Chemistry, University of Aveiro, 3010-193 Aveiro, Portugal.*

** E-mail: nmoura@ua.pt*

Push–pull porphyrin derivatives have gained significant relevance due to their finely tunable electronic structures, which arise from the introduction of electron-donating (push) and electron-withdrawing (pull) substituents within the macrocycle. This strategically structural modulation enhances intramolecular charge-transfer (ICT) characteristics, enabling improved light-harvesting efficiency, red-shifted absorption, and enhanced photophysical or redox behaviour [1, 2]. These features, make push–pull porphyrins a powerful platform for developing advanced functional materials for applications in photodynamic therapy, photocatalysis, solar energy conversion, and molecular electronics [3].

In this communication, various synthetic approaches developed to prepare a new series of push-pull porphyrin-carbazole derivatives (**Figure 1**) will be presented and discussed. The strategies focused on the functionalization of the 5,15-diarylporphyrin with a carbazole electron-donating unit [4], and a carboxylic acid acceptor unit at the opposite *meso* position. The synthetic methodologies selected allowed fine-tuning of the spacer linking the porphyrin core to the carboxylic acid-type acceptor unit. These strategies were adapted to include a set of spacers with one or two double bonds, a triple bond, an additional aromatic ring, or a cyanoacrylic acid unit.

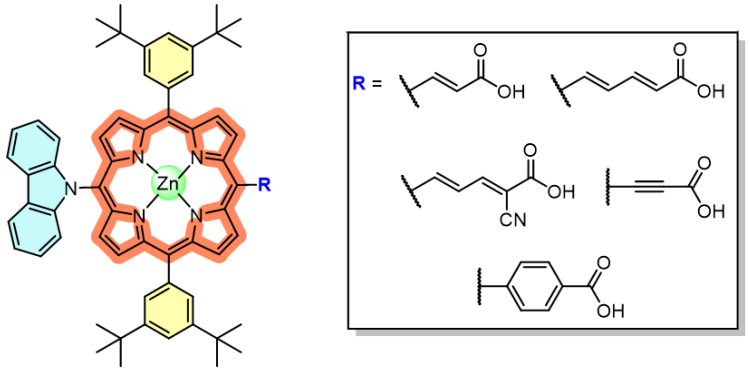


Figure 1. Structures of Zn(II) push-pull porphyrin-carbazole complexes.

Funding and Acknowledgements: This work was financed by national funds from FCT - Fundação para a Ciência e a Tecnologia, I.P., under the scope of the project UID/50006/2025 of the Associate Laboratory for Green Chemistry-LAQV REQUIMTE, and the Portuguese NMR Network. NMM Moura thanks FCT for funding his Assistant Research Position (2023.06495.CEECIND/CP2840/CT0031). MJA Reis thanks FCT for her PhD grant (2020.05838.BD).

References

[1] Zhang, Y.Z.; Higashino, T.; Imahori, H.; J, Mater Chem. C. 2023, 11, pp. 12659-12680.
[2] Lu, J.; Liu, S.; Wang, M.; Front. Chem. 2018, 6, 541.
[3] Hamza, J. R.; Sharma, K.; Karr, P.A.; Est, A.; D'Souza, F.; Poddutoori, P.K.; J. Am. Chem. Soc. 2024, 146, 25403-25408.
[4] Reis, M.J.A.; Nogueira, A.T.; Eulálio, A.; Moura, N.M.M.; Rodrigues, J.; Ivanou, D.; Abreu, P.E.; Correia, M.R.P.; Neves, M.G.P.M.S.; Pereira, A.M.V.M.; Mendes, A.; Dalton Trans. 2023, 52, 14762.

Solvent choice and decarboxylation as critical modulators of the antitumor activity of *Cannabis sativa* L. extracts

Rita Silva-Reis[1,2*], Joana L. C. Sousa[1], Catarina Cunha[3], Helena Oliveira[3], Artur M. S. Silva[1], Paula A. Oliveira[2,4], Susana M. Cardoso[1]

[1] LAQV-REQUIMTE, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal; [2] CITAB, Inov4Agro, University of Trás-os-Montes and Alto Douro, 5000-801 Vila Real, Portugal; [3] Department of Biology and CESAM, University of Aveiro, 3810-193 Aveiro, Portugal; [4] Clinical Academic Center of Trás-os-Montes and Alto Douro, University of Trás-os-Montes and Alto Douro, 5000-801 Vila Real, Portugal

** E-mail: reis.rita@ua.pt*

Cannabis sativa L. inflorescences are a complex reservoir of bioactive compounds such as cannabinoids, terpenes, and phenolic compounds, which have significant therapeutic potential, including in cancer [1]. However, current research often overlooks the impact of processing on the comprehensive chemical profile beyond cannabinoids. This study evaluated the impact of solvent polarity and thermal decarboxylation on the chemical composition and antitumor activity of *C. sativa* extracts against Caco-2 colorectal cancer cells.

The Extractions were performed using different solvents, namely EtOH, MeOH, hexane, and dichloromethane. Extracts were obtained by ultrasound-assisted extraction from untreated and thermally pretreated (120 °C, 1 h) material. GC-MS and LC-MS were used to identify volatile, semi-volatile, and pigment compounds [2]. Total phenolics and antioxidant activity were quantified by Folin Ciocalteu and DPPH radical scavenging assay, respectively. Cytotoxic effects on Caco-2 cells were assessed through the MTT assay and the intracellular ROS levels were measured using a fluorometric ROS detection kit, after 24–72h [3]. Seven families of metabolites were identified, with cannabinoids representing the largest fraction. Hexane and dichloromethane selectively extracted cannabinoids and terpenes, whereas MeOH favoured amino acids, sugars and alcohols. Thermal decarboxylation profoundly shifted the chemical profile, reducing THCA by 93–96% and increasing Δ^9-THC, and CBN by up to 54% and 48%, respectively. Terpenes generally decreased after heat treatment (*e.g.,* hexane extract dropped by 36.5%). Also, despite a reduction in phenolics after treatment in polar extracts, the antioxidant activity increased, possible due to the activation of cannabinoids. As for cytotoxic effects, the thermally pretreated hexane extract displayed the strongest antiproliferative effect, followed by pretreated MeOH extract (PTMeOH). Both extracts triggered significant, dose-dependent ROS accumulation, with PTMeOH acting as the strongest ROS inducer.

Overall, this study demonstrates that solvent polarity and decarboxylation are key factors shaping the chemical and functional profiles of *C. sativa* extracts. Combining the use of non-polar solvents with thermal activation maximize cannabinoid extraction and cytotoxic activity, whereas the use of polar solvents enhances ROS generation. Together, these findings provide mechanistic insight into how extraction parameters shape the anticancer potential of *C. sativa*.

Acknowledgements: We thank the financial support from PT national funds (FCT/MCTES, Fundação para a Ciência e Tecnologia and Ministério da Ciência, Tecnologia e Ensino Superior) through the projects UID/50006/2025-LAQV-REQUIMTE, and UID/04033/2025: CITAB and LA/P/0126/2020 (https://doi.org/10.54499/LA/P/0126/2020),to CESAM UID/50017/2025 (doi.org/10.54499/UID/50017/2025) and LA/P/0094/2020 (doi.org/10.54499/LA/P/0094/2020) by national funds through FCT. R.S.-R. thanks FCT/MCTES for the PhD grant ref. 2022.14518.BD. C.C. acknowledges BMRex project (funded by EU Horizon Europe Grant 101099528, supported by UK Innovation funding agency Grant 10062709) for the research Grant BI/UI88/11875/2024. Susana M. Cardoso thanks FCT/MCTES for the labour contract under the Scientific Employment Stimulus— Institutional Call.

References

[1] Silva-Reis, R. et al.; Biomolecules 2023, 13, 764. [2] Sónia S. Ferreira, et al.; Food Res. Int. 2020, 132, 109055. [3] Salvador, D. et al.; Int. J. Mol. Sci. 2022, 23, 35.

Discovery of new marine inspired therapeutic agents for topical treatment of inflammatory dermatological diseases

Márcia S. Martins[1,2], Sara Cravo[1,2], Katharina Simon[3], Davide Malfacini[3], Ana Jesus[4,5], Beatriz Rodrigues[6,7], Sónia A. Pinho[7], Artur M. S. Silva[8], Madalena M. M. Pinto[1,2], Girolamo Calò[3], Isabel F. Almeida[4,5], Maria T. Cruz[6,7], Emília Sousa[1,2*]

[1]Laboratório de Química Orgância e Farmacêutica, Faculdade de Farmácia, Universidade do Porto, Portugal, 4050-313; [2]CIIMAR–Centro Interdisciplinar de Investigação Marinha e Ambiental, Portugal, 4450-208; [3]Department of Pharmaceutical and Pharmacological Sciences, Section of Pharmacology, of Padova, Padova, Italy, 35131; [4]UCIBIO - Applied Molecular Biosciences Unit, Laboratory of Pharmaceutical Technology, Faculty of Pharmacy, University of Porto, Portugal, 4050-313; [5]Associate Laboratory i4HB, Faculty of Pharmacy, University of Porto, Portugal, 4050-313; [6]Faculty of Pharmacy, University of Coimbra, Portugal, 3000-548; [7]Centre for Innovative Biomedicine and Biotechnology and Center for Neuroscience and Cell Biology, Coimbra, Portugal, 3000-548; [8]LAQV-REQUIMTE & Department of Chemistry, University of Aveiro, Portugal, 3810-193.

** E-mail: esousa@ff.up.pt*

Inflammatory skin conditions, often accompanied by pruritus, impair patients' quality of life. Targeting the neurokinin-1 receptor (NK_1R), implicated in both processes, represents a promising therapeutic strategy [1]. This study aimed to identify novel NK_1R antagonists with anti-inflammatory potential based on fiscalin B (**Figure 1**), combining *in silico*, *in vitro,* and pre-formulation studies, together with synthesis. Docking studies (PDB ID: 6E59) evaluated the binding of an in-house fiscalin B library to NK_1R. Compounds with equal or higher affinity than fiscalin B and favourable skin permeation properties were tested *in vitro* in cytotoxicity and nitric oxide (NO) inhibition assays in skin-relevant cell lines. Derivatives containing an aromatic moiety displayed stronger NO inhibition, guiding the structure-based design of optimized hits. Thirteen new derivatives were synthesized (yields 8–25 %), showing low NK_1R inhibitory activity (IC_{50} = 5–6.7 μM) and selectivity. Most compounds reduced NO levels by approximately 50% at 12.5 μM, without compromising cell viability, an effect likely mediated through modulation of NF-κB and MAPK pathways. The compounds demonstrated low potential for skin sensitization and presented an adequate profile for topical application, regarding solubility, stability, and excipient compatibility. Although the modest NK_1R inhibition and selectivity, the compounds demonstrated consistent anti-inflammatory activity, supporting fiscalin B analogues as promising candidates for topical treatment of inflammatory skin conditions.

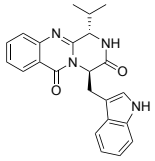


Figure 1. Chemical structure of the marine natural product, fiscalin B.

Funding: FCT–UIDP/04378/2020, UIDB/04378/2020, LA/P/0140/2020, UIDB/04423/2020, UIDP/04423/2020, UIDB/04539/2020, UIDP/04539/2020, LA/P/0058/2020, and 10.54499/2021.05964.B.

References

[1] Martins, M. S.; Almeida, I. F.; Cruz, M. T.; Sousa, E.; Biochem. Pharmacol. 2023, 212, 115568.

One-pot CuAAC strategies for 1,4-disubstituted 1,2,3-triazoles on (hetero)aromatics, including a green protocol in PEG_{400}

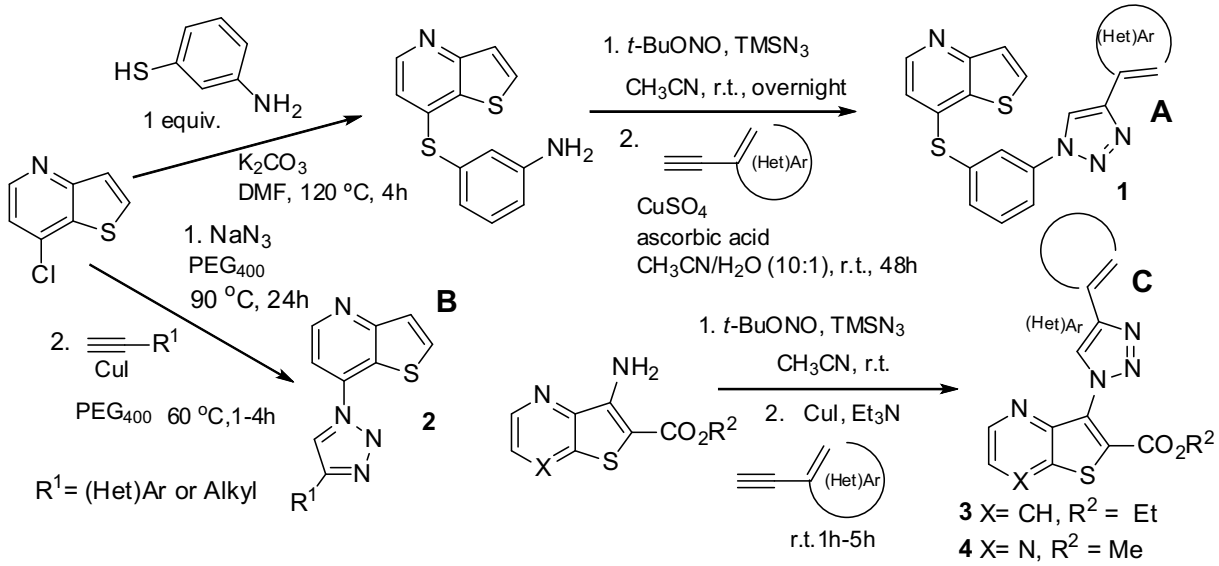
Maria-João R. P. Queiroz[1,*], Juliana Rodrigues[1], A. Patrícia Lourenço[1]

[1] *Centro de Química da Universidade do Minho (CQ-UM), Campus de Gualtar 4710-057 Braga, Portugal*

* *E-mail: mjrpq@quimica.uminho.pt*

Thienopyridines, thienopyrazines and 1,2,3-triazoles scaffolds are important bioactive cores [1–3].

Herein, we report a one-pot Cu(I)-catalyzed azide–alkyne cycloaddition reactions in which the corresponding intermediate azides are first generated *in situ* on the pyridine or thiophene rings of thieno[3,2-*b*]pyridines (**Scheme 1B** and **1C**), on an aryl ether derivative of thieno[3,2-*b*]pyridine (**Scheme 1A**), and on the thiophene ring of a thieno[2,3-*b*]pyrazine derivative (**Scheme 1C**). These azides, formed from chloro or amino precursors, were subsequently coupled with various (hetero)aryl or alkyl acetylenes in a one-pot, two-step procedure, including a green protocol using PEG-400 as the solvent. The 1,4-disubstituted 1,2,3-triazole derivatives **1**-**4** were obtained in good to high yields and fully characterized. Some of them exhibited promising antitumor activity, while others showed potential as anti-parasitic compounds.



Scheme 1A, B and C. Synthesis of several 1,4-disubstituted 1,2,3-triazoles on (hetero)aromatic systems.

Acknowledgements: To the FCT for financial support to CQ-UM (UID/0686).

References

[1] Lauria, A.; Delisi, R.; Mingoia, F.; Terenzi, A.; Martorana, A.; Barone, G.; Maria, A. *Eur. J. Org. Chem.* **2014**, 3289–3306.

[2] Rodrigues, J. M.; Calhelha, R. C.; Nogueira, A.; Ferreira , I. C. F. R.; Barros, L. and Queiroz, M.R.P. *Molecules* **2021**, *26*, 4823.

[3] Silva, B.R.; Rebelo, R.; Rodrigues, J.M.; Xavier, C.P.R.; Vasconcelos, M.H.; Queiroz, M.J.R.P. *Molecules* **2021**, *26*, 1594.

Mass spectrometry multi-omics reveals mortality biomarkers and ECMO-induced molecular stress in critical illness

Gonçalo C. Justino[1,*], Tiago A.H. Fonseca[2-4], Cristiana P. Von Rekowski[2-4], Rúben Araújo[2-4], M. Conceição Oliveira[1], Luís Bento[5,6], Cecília R.C. Calado[3,7]

[1]CQE-IMS, IST-UL, 1049-001 Lisbon, Portugal; [2]NOVA Medical School, FCM-UNL, 1169-056 Lisbon, Portugal; [3]ISEL-IPL, 1959-007 Lisbon, Portugal; [4]CHRC, UNL, 1150-082 Lisbon, Portugal; [5]Intensive Care Department, ULSSJ, 1150-199 Lisbon, Portugal; [6]Integrated Pathophysiological Mechanisms, CHRC, FCM-UNL, 1169-056 Lisbon, Portugal; [7]iBB/ i4HB, IST-UL, 1049-001 Lisbon, Portugal

** E-mail: goncalo.justino@tecnico.ulisboa.pt*

Critical illness requiring invasive mechanical ventilation (IMV), with or without extracorporeal membrane oxygenation (ECMO), is characterized by deep metabolic and immunological stress for which current clinical biomarkers offer limited mechanistic insight. To enable translation from molecular profiling to clinical support, analytical frameworks must be chemically rigorous, statistically transparent, and biologically interpretable.

We implemented a mass spectrometry-based omics strategy to identify serum mortality biomarkers and ECMO-associated molecular signatures in critically ill patients, using severe COVID-19 as a model cohort. Serum samples from 52 ICU patients under IMV, including a substantial ECMO subgroup, were analysed by high-resolution metabolomics and quantitative proteomics, enabling the simultaneous interrogation of lipids, small polar metabolites, stress hormones, and immune-related proteins.

Data were evaluated using a hypothesis-driven statistical workflow, with non-parametric screening and logistic regression guiding feature selection, followed by parsimonious multivariate models selected using AIC and ROC-AUC, with PCA used solely for interpretability.

This approach yielded high-performance yet mechanistically transparent mortality models, consistently implicating complement activation, Ca^{2+}-dependent proteolysis, and mitochondrial–carnitine metabolism, alongside protective markers of metabolic flexibility and inflammatory resolution. In parallel, modeling ECMO as a therapeutic perturbation revealed a reproducible molecular footprint marked by immune antigen-presentation remodeling, lipid and membrane stress, redox imbalance, and metabolic reprogramming, partially independent of outcome.

Notably, these signatures delineate orthogonal axes of risk and treatment-induced stress, enabling separation of disease-driven lethality from ECMO-associated molecular effects. Together, they define compact, biologically coherent marker panels with direct relevance for risk stratification, treatment monitoring, and translational validation in critical care settings. Although demonstrated in COVID-19, this chemistry-anchored framework is directly extensible to ARDS, sepsis, and ECMO-supported critical illness, supporting precision monitoring grounded in molecular mechanisms rather than algorithmic opacity.

Funding: Work funded through FCT grants UID/00100/2025, UID/PRR/100/2025, DSAIPA/DS/0117/2020, RNEM-LISBOA-01-0145-FEDER-022125, LA/P/0056/2020, 2024.02043.BD, 2023.01951.BD, 2021.05553.BD.

FLASH ORAL COMMUNICATIONS

Unanticipated reactivity towards nucleophilic attack in the synthesis of saccharyl-1,3,4-thiadiazolyl conjugates

Bruno C. Guerreiro[1*], Daniel Carvalho[2], Jaime Coelho[2], José A. Paixão[3], Luís M. T. Frija[2], Maria L. Cristiano[1]

[1]Center of Marine Sciences, CCMAR, and Faculty of Sciences and Technology, FCT, Department of Chemistry and Pharmacy, Gambelas Campus, University of Algarve, UAlg, 8005-139 Faro, Portugal; [2]Institute of Molecular Sciences (IMS), Centro de Química Estrutural (CQE), Faculty of Sciences, University of Lisbon, Campo Grande, 1749-016 Lisboa, Portugal; [3]CFisUC, Department of Physics, University of Coimbra, 3004-516 Coimbra, Portugal

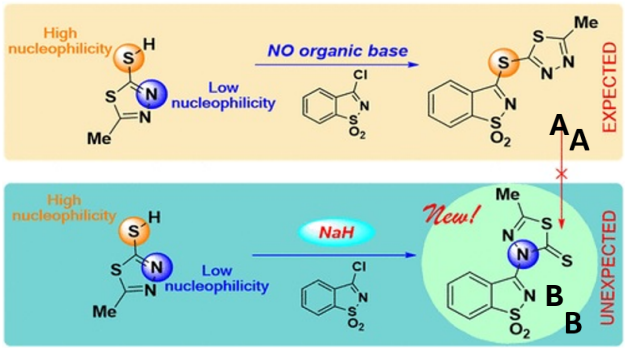
** E-mail: brunoecguerreiro@gmail.com*

Throughout the synthesis optimization of 3-[(5-methyl-1,3,4-thiadiazole-2-yl)sulfanyl]-1,2-benzothiazole 1,1-dioxide (MTSB), a selective copper chelator with potential interest in cancer chemotherapy [1], we isolated a novel compound, 3-(1,1-dioxidobenzo[d]isothiazol-3-yl)-5-methyl-1,3,4-thiadiazole-2(3H)-thione (BMTT), which evidenced an unpredictable reactivity of the starting 5-methyl-1,3,4-thiadiazole-2-thiol (5MTDT). [2]

To understand the reaction mechanisms, quantum chemical calculations were conducted and the crystal structures of MTSB and BMTT were investigated by X-ray crystallography.

The results conjecture the formation of BMTT from nucleophilic attack of the nitrogen at position 3 of the thiadiazole ring, involved in an S-to-N delocalized thiadiazole-2-thiolate structure, which is thermodynamically more favourable in the presence of Na^+. Experimental assays refute a plausible concerted 1,3-sigmatropic S- to N-rearrangement of MTSB to BMTT.

Contradicting the nucleophilicity indices of sulphur and nitrogen atoms of 5MTDT, it seems that an exotic nucleophilic attack by the nitrogen at 3-position of this reagent to the sp^2 carbon in position 3 of pseudo-saccharyl chloride take place (scheme 1).



Scheme 1. Reaction scheme for the synthesis of BMTT (A) and MTSB (B).

Acknowledgements: We thank FCT for financial assistance through projects contracts UID/04326/2025, UID/PRR/04326/2025 and LA/P/0101/2020 (DOI:10.54499/LA/P/0101/2020) (CCMAR/CIMAR LA); projects UIDB/00100/2020, UIDP/00100/2020 and LA/P/0056/2020 (CQE and IMS); projects UIDB/04564/2020 (DOI:10.54499/UIDB/04564/2020) and UIDP/04564/2020 (DOI:10.54499/UIDP/04564/2020) (CFisUC). L.M.T.F expresses gratitude to FCT for the contract 2023.07905.CEECIND/CP2830/CT0012 (Scientific Employment Stimulus, DOI:10.54499/2023.07905.CEECIND/CP2830/CT0012).

References

[1] L. Cabral, E. Brás, M. Henriques, C. Marques, L. Frija, L. Barreira, J.A. Paixão, R. Fausto, M.L.S. Cristiano, Chem. - A Eur. J. 2018, 24, 3251–326.

[2] Bruno E. C. Guerreiro, Daniel F. Carvalho, Jaime A. S. Coelho, José A. Paixão, Luís M. T. Frija, and Maria L. S. Cristiano, J. Org. Chem. 2025, 90 (46), 16301-16309

Synthesis of novel D-glucuronamide-based nucleos(t)ide analogs as promising anticancer and antibacterial hits

Domingos Morais Manuel[1,2,3*], Tânia Moreira[2], Gonçalo Almeida[1,2], Leonor Parente[2], Radek Jorda[4], Sérgio Filipe[5], Nuno M. Xavier[1,2]

[1]*Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal*

[2]*Centro de Química Estrutural - Institute of Molecular Sciences, Faculdade de Ciências,Universidade de Lisboa Ed. C8, 5° Piso, Campo Grande, 1749-016 Lisboa, Portugal*

[3]*Instituto Superior de Ciências da Educação da Huíla, Lubango-Huíla, Angola*

[4]*Departament of Experimental Biology, Faculty of Sience, Palacký University Olomouc, Šlechtitelů 27, 78371 Olomouc, Czech Republic*

[5]*UCIBIO-Applied Molecular Biosciences Unit, Department of Life Sciences, NOVA School of Science and Technology, NOVA FCT, Universidade NOVA de Lisboa, 2829-516, Caparica, Portugal*

** E-mail: moraisbwill@gmail.com*

The synthesis of D-glucuronamide-containing molecules has attracted considerable interest in the context of the search for new bioactive carbohydrate-based compounds, due to their biological profile reported for both natural and synthetic derivatives containing this glycosyl moiety [1]. In our ongoing interest in the synthesis of new, potentially bioactive D-glucuronamide-based compounds, including nucleoside analogs [2,3], we report herein on the synthesis of structurally new 6-chloropurine nucleos(t)ide analogs constructed on D-glucuronamide scaffolds, and containing 1,2,3-triazole, phosph(on)ate and/or phosphoramidate moieties. For access to the target compounds, D-glucofuranuronolactone was used as a starting material, and key synthetic steps included, among others, amidation, furanose to pyranose isomerization, anomeric azidation, azide-alkyne 1,3-dipolar cycloaddition, Staudinger-phosphite, and Arbuzov reaction. Biological evaluation revealed significant activities of some molecules against cancer cell lines and selective antibacterial effects against a *Streptococcus pneumoniae* clinical strain, turning them promising "hits" for further studies.

Acknowledgements: The authors thank FCT for funding:projects UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025, iMed-Ulisboa), UIDB/00100/2020, UIDP/00100/2020 (CQE) and LA/P/0056/2020 (IMS). D. M. Manuel also thank Instituto Nacional de Gestão de Bolsas de Estudos do Governo de Angola and Instituto Superior de Ciências de Educação da Huíla.

References:

[1] N. M. Xavier, A. Fortuna, Mol. Sci. and Chem. Eng (J. Reedijk, ed.), Elsevier, 2019, DOI: 10.1016/B978-0-12-409547-2.11098-4.

[2] N. M. Xavier, et al., Org. Biomol. Chem. 2017, 15, 4667.

[3] N. M. Xavier, et al., Pure Appl. Chem. 2019, 91, 1085.

"Mild modifications with major biological effects": *in vitro* efficacy of squaraine dyes as anticancer photodynamic agents

Eurico Lima[1,2*], Octávio Ferreira[2], Renato E. Boto[3], José R. Fernandes[1], Paulo Almeida[3], Samuel M. Silvestre[3], Adriana O. Santos[2], Lucinda V. Reis[1]

[1] CQ-VR – Chemistry Centre of Vila Real, University of Trás-os-Montes and Alto Douro, Quinta de Prados, 5001-801, Vila Real, Portugal; [2] RISE-Health, Faculty of Health Sciences, University of Beira Interior, Avenida Infante D. Henrique, 6201-506, Covilhã, Portugal; [3] RISE-Health, Faculty of Sciences, University of Beira Interior, Rua Marquês d'Avila e Bolama, 6201-001, Covilhã, Portugal

** E-mail: eurico_lima@icloud.com*

Designing efficient photosensitizers remains a key challenge in photodynamic therapy [1], and squaraine dyes offer a uniquely promising platform to address it. Squaraine dyes are polymethine chromophores whose strong absorption in the therapeutic window makes them attractive candidates for photodynamic therapy (PDT) [2]. Their photodynamic performance, however, is highly dependent on structural fine-tuning of the squaraine core [3].

In this communication, a series of squaraine dyes bearing different structural modifications on the four-membered central ring were synthesized. Benzothiazole-, indolenine-, and benz[e]indole-based squaraines were modified with γ-aminobutyric acid, a dansylpiperazino moiety, or a D-(+)-biotin derivative. Their photophysical and photochemical properties, including absorption, fluorescence, aggregation, photostability, and singlet oxygen generation, were systematically evaluated.

Photodynamic activity was investigated in several tumor (Caco-2, HeLa, MCF-7, PC-3) and non-tumor (NHDF) cell lines under dark and light conditions. The most promising compounds were further studied to elucidate their mechanism of action, including subcellular localization, ROS generation, genotoxicity, cell death pathways, and cell cycle effects.

Overall, this work demonstrates that subtle structural modifications in squaraine dyes decisively govern their photodynamic performance, enabling the identification of highly promising candidates for PDT. From a medicinal chemistry perspective, this work establishes a comprehensive structure–activity relationship framework, clarifying how targeted modifications of the squaraine core enhance photodynamic effects while deepening the understanding of their intracellular behavior and phototoxic mechanisms, thereby laying a solid foundation for future translational advances in PDT.

Acknowledgements: The authors acknowledge to Portuguese Foundation for Science and Technology (FCT) and European Regional Development Fund (FEDER) for financial support to the research centres CQVR (UIDB/00616/2020) and CICS-UBI (UIDB/0079/2020 and UIDP/00709/2020). The authors thank the technical support of the Fluorescence Microscopy Unit of RISE-Health, UBI, integrated in the national infrastructure PPBI - Portuguese Platform of Bioimaging. Eurico Lima gratefully acknowledges the doctoral fellowship grant (SFRH/BD/147645/2019) and the research fellowship grant (UIDP/00709/2020) financed by FCT. Octávio Ferreira extends his gratitude to FCT for supporting his doctoral studies through the fellowship grant SFRH/BD/141900/2018.

References

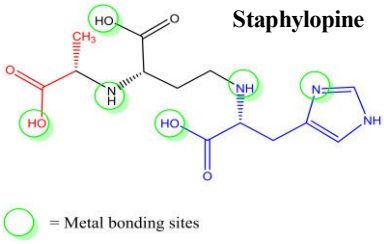
[1] Lima E, Reis LV. Molecules 2023;28:5092.
[2] Dereje DM, Pontremoli C, Moran Plata MJ, Visentin S, Barbero N. Photochem Photobiol Sci 2022.
[3] Lima E, Reis LV. Future Medicinal Chemistry 2022:fmc-2022-0112.

Bioinspired metallophore analogues: synthetic approaches and applications in infection diagnostics

Eduarda Ramos[1,*], Mariana Moreira[1], Samuel Silvestre[1], Sofia Gama[2],Paulo Almeida[1]

[1]RISE-Health, Department of Chemistry, Faculty of Sciences, University of Beira Interior, Rua Marquês de Ávila e Bolama, 6201-001 Covilhã, Portugal; [2]Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico, Universidade de Lisboa, Estrada Nacional 10 (km 139.7), 2695-066 Bobadela LRS, Portugal

** E-mail: m.eduarda.ramos@ubi.pt*



The growing threat of antimicrobial resistance has intensified the need for innovative therapeutic and diagnostic strategies. In this context, metallophores such as staphylopine, produced by the "superbug" *Staphylococcus aureus*, have attracted considerable attention due to their ability to chelate essential metal ions like Zn^{2+}, Cu^{2+} and Fe^{3+}[1,2]. This mechanism allows pathogenic bacteria to grow in metal-depleted environments by avoiding the host's nutritional immunity, thus contributing to enhanced bacterial virulence and resistance.

This work focuses on the total synthesis of novel staphylopine inspired metallophore analogues. Staphylopine is composed of three key building blocks, namely a D-lactate derivative, D-histidine, and L-homoserine[3]. For each precursor, both D- and L-stereoisomeric configurations are being explored. In the case of D-histidine, additional structural modifications are introduced, including replacement of the imidazole ring with structurally related moieties. These modifications aim to expand chemical diversity and improve synthetic accessibility, inspired by approaches in noncanonical amino acid design[4]. The structural alterations are intended to modulate and enhance the metal-chelating properties and selectivity of these analogues. The total synthesis involves multiple protection/deprotection steps using amino acid protecting groups such as Boc and Bn. A major synthetic challenge lies in the formation of C–N bonds to construct the pseudopeptidic scaffold. To overcome this, the Mitsunobu reaction was employed, enabling efficient and stereocontrolled coupling of the amino acid components.

On a later stage, the newly synthesized analogues will be evaluated as new differential diagnostic probes, when radiolabelled with ^{64}Cu, and as potential innovative antimicrobial agents.

Funding: This work was supported by national funds through the Portuguese funding agency, FCT – Fundação para a Ciência e a Tecnologia, and by the European Regional Development Fund (FEDER, "Regional Program of Lisbon") through the project LISBOA2030-FEDER-00786200, Programa de Apoio ao Desenvolvimento de Competências Científicas, Técnicas e Artísticas – UBI + Skills (Programa Impulso Jovens STEAM), Universidade da Beira Interior. The NMR spectrometers are part of the National NMR Facility supported by FCT-Portugal (ROTEIRO/0031/2013-PINFRA/22161/2016, cofinanced by FEDER through COMPETE 2020, POCI and PORL and FCT through PIDDAC). We thank the RISE-Health, Department of Chemistry, Faculty of Sciences, University of Beira Interior for financial support.

References

[1] Ghssein, G.; Ezzeddine, Z. The Key Element Role of Metallophores in the Pathogenicity and Virulence of Staphylococcus Aureus: A Review. Biology 2022 11(10), 1525.

[2] Nolan E. M. A metal shuttle keeps pathogens well fed. Science. 2016 352(6289), 1055-1056.

[3] Zhang, J.; Wang, S.; Bai, Y.; Guo, Q.; Zhou, J.; Lei, X. Total Syntheses of Natural Metallophores Staphylopine and Aspergillomarasmine A. J. Org. Chem. 2017, 82(24), 13643–13648.

[4] Trabocchi, A.; Scarpi, D.; Guarna, A. Structural Diversity of Bicyclic Amino Acids. Amino Acids 2007, 34(1), 1–24.

Molecular design of new organic emitters for light-emitting devices

Ana C. Amorim[1*], Filipa Pires[2], João P. Prates Ramalho[3], Paulo D. Nunes Barradas[1], Carla Cunha[1], Jorge Morgado[2], Susana M.M. Lopes[1], J. Sérgio Seixas de Melo[1], Luís C. Branco[4], and Anthony J. Burke[1,5]

[1]University of Coimbra, CQC-IMS, Department of Chemistry, 3004-535 Coimbra, Portugal. [2]Instituto de Telecomunicações (IT), Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisboa, Portugal. [3]Department of Chemistry and Biochemistry, School of Sciences and Technology, University of Évora, 7000-671 Évora, Portugal. [4]LAQVREQUIMTE, Department of Chemistry, NOVA School of Science and Technology, NOVA University of Lisbon, 2819-516 Caparica, Portugal. [5]Faculty Pharmacy, University of Coimbra, Pólo das Ciências da Saúde, Azinhaga de Santa Comba, 3000-548 Coimbra, Portugal.
** E-mail: anacatarina.amorim@hotmail.com*

Over the past two decades, OLED technology has seen remarkable progress in both academic research and industrial applications. Recognized for their efficiency and sustainability, OLEDs are steadily replacing traditional lighting and display systems. Continued advances in this field depend on the design of organic materials with tuned optoelectronic properties, which is a key step toward improving device performance and stability, while enabling the next generation of smart lighting and high-definition display technologies [1,2].

In this work, we explore new organic emitters by introducing a variety of substituents into conjugated cores to fine-tune essential properties, including electrochemical behaviour, photophysical response, thermal stability, and electroluminescence (**Figure 1**) [3]. Through this molecular tuning, our aim is to enhance material performance and contribute to the development of next-generation OLED emitters for high-efficiency applications.

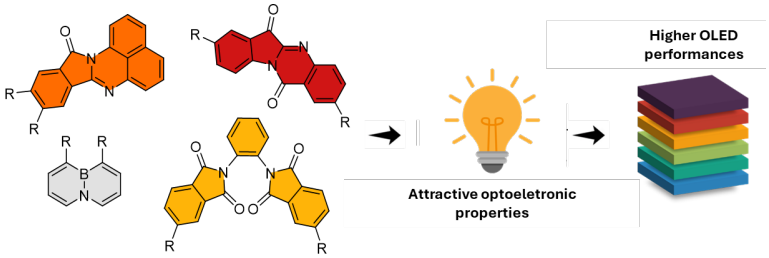


Figure 1. Strategic molecular core design for enhanced OLED performance.

Acknowledgements: We thank the Fundação para a Ciência e a Tecnologia (FCT) for funding through the project 2022.01391.PTDC (ConChiMOL). We also acknowledge funding from: CQC-IMS which is supported by the FCT, Portuguese Agency for Scientific Research. CQC is funded by FCT through projects UID/PRR/00313/2025 and UID/00313/2025 and IMS through special complementary funds provided by FCT (project LA/P/0056/2020); project UID/50008/2025 - Instituto de Telecomunicações; projects UIDP/04449/2020 and UIDB/04449/2020 - HERCULES Lab; FCT/MCTES (Portugal) through LAQV (LA/P/0008/2020, UIDP/50006/2020, and UIDB/50006/2020). We also thank the FCT for awarding a PhD grant (2021.04769.BD) to Ana Catarina Amorim.

References

[1] G. Hong, X. Gan, C. Leonhardt, Z. Zhang, J. Seibert, J.M. Busch, S. Bräse, *Advanced Materials*, 2021, 33, 2005630.
[2] J. Feng, X. Zhang, J. Shi, C. Zhang, Y. Chang, B. Hu, C. Redshaw, B. Chen, *Materials Chemistry Frontiers*, 2020, 4, 2293.
[3] A. C. de Melo Amorim, J. Morgado, J. P. Prates Ramalho, H. Cruz, C. Cunha, J. A. A. Paixão, J. S. Seixas de Melo, S. M. M. Lopes, L. C. Branco and A. J. Burke, *Materials Advances*, 2025, 6, 9556.

How click chemistry could enhance antimalarial drugs with antimicrobial ionic liquids

Ricardo Ferraz [1,2,3*], Guilherme Nixon[1], Ana Gomes [1], Paula Gomes[1]

[1]LAQV-REQUIMTE, Departamento de Química e Bioquímica, Faculdade de Ciências da Universidade do Porto, Porto, Portugal; [2] RISE-Health, Center for Translational Health and Medical Biotechnology Research (TBIO), ESS, Polytechnic of Porto, Porto, Portugal; [3] Chemical and Biomolecular Sciences, School of Health (ESS), Polytechnic Institute of Porto, 4200-072 Porto, Portugal

** E-mail: rferraz@ess.ipp.pt*

Malaria remains one of the most burdensome infectious diseases worldwide, particularly in tropical regions with limited access to healthcare [1]. Malaria incidence is particularly high in Africa, mainly where sanitation and healthcare systems are deficient. Although, significant progress has been made in the development of antimalarial agents, there is still an urgent need for therapeutic solutions that are more effective, stable, and affordable. New therapeutic aproches options should (i) concomitantly target multiple stages of parasite development, to increase therapeutic efficiency while reducing the chances of development of parasite resistance, and (ii) be cost-effective and chemically/thermally stable to become a real benefit for the settings where they are most needed.

Our group has long been involved in the rescuing of classical antimalarial drugs, as this is a worthy approach to decrease the overall cost of the drug development process [2]. Lately, our attention was drawn to conversion of antimalarial active pharmaceutical ingredients into ionic liquids (IL), with interesting results [3]. We are now chasing an alternative strategy: instead of converting antimalarials (primaquine and chloroquine) into IL, we want to link them covalently to antimicrobial IL through click chemistry [4]. Initial steps in this direction will be communicated.

Funding: This work received financial support from the PT national funds (FCT/MECI, Fundação para a Ciência e Tecnologia and Ministério da Educação, Ciência e Inovação) through the project UID/50006/2025 DOI 10.54499/UID/50006/2025 -Laboratório Associado para a Química Verde - Tecnologias e Processos Limpos.
Acknowledgements: Ana Gomes thanks FCT for CEEC contract (https://doi.org/10.54499/2022.08044.CEECIND/CP1724/CT0004).

References

[1] WHO, 2024: Geneva, Switzerland
[2] Silva, A.T., et al., RSC Medicinal Chemistry 2024, 15, 2657-2662.
[3] Silva, A.T., et al., International Journal of Molecular Sciences 2020, 21:5334.
[4] Gomes, A., et al., Microbiology Spectrum 2022, 10: e02291-21.

Ferroptosis-inducing PROTACs for targeted cancer therapy

Anastasiya Voloshchuk[1*], G. Torello[1], V. Branco[1], C. Martín[2], R. Godino[2], O. Geniloud[2], R. Moreira[1]

[1] *Research Institute for Medicines (iMed.Ulisboa), Faculty of Pharmacy, Universidade de Lisboa, Lisboa, Portugal,* [2]*Fundación Medina, Granada, Espanha*

* *E-mail: avoloshchuk@edulu.ulisboa.pt*

Iron is essential for enzymatic activity and redox homeostasis, and rapidly proliferating cancer cells display a marked "iron addiction" [1]. However, excess iron promotes Fenton chemistry, driving oxidative stress and lipid peroxidation that can trigger ferroptosis. To withstand this redox pressure, malignant cells upregulate antioxidant defences, particularly glutathione peroxidase 4 (GPX4) [2], a selenoenzyme that detoxifies lipid hydroperoxides (Figure 1). Despite its appeal as an anticancer target, GPX4 remains challenging to drug due to its shallow active site and the poor solubility, instability, and off-target reactivity of current electrophilic inhibitors [2,3]. To address these limitations, this project adopts a fragment-based PROTAC design strategy. Building on unexplored fragment-like allosteric GPX4 inhibitors [4], including TMT10, we designed and synthesized a CRBN-based degrader library of 11 compounds, including the parent inhibitor and fragment-derived warheads linked through PEG, alkyl, or short rigid spacers. All compounds were synthesized at FFUL with moderate to good yields, fully characterized, and their synthetic routes optimized. Biological evaluation in GPX4-expressing HT-1080 fibrosarcoma cells was performed at Fundación MEDINA using optimized MTT viability and high-content cytotoxicity imaging assays. Two fragment-based PROTACs bearing short rigid linkers, AV51 and AV55, emerged as the most potent degraders, with IC_{50} values of 9.5 µM and 9.97 µM at 48h, respectively, compared with 37.89 µM for the parent inhibitor. These results highlight fragment-driven PROTAC design as a promising strategy for GPX4 degradation and ferroptosis-based anticancer therapy.

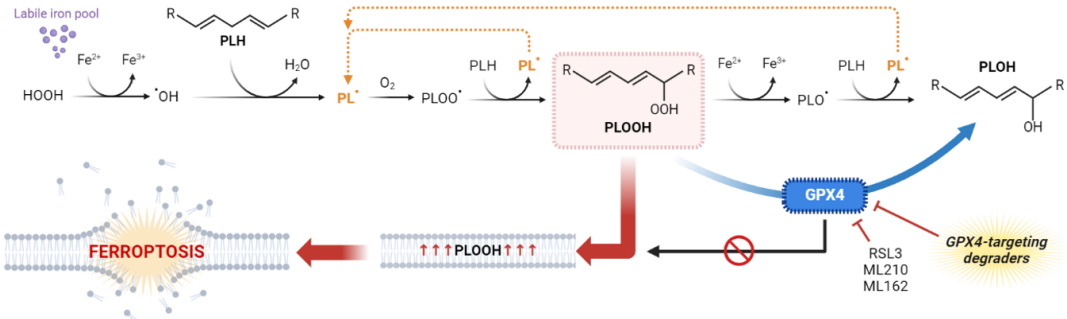


Figure 1. GPX4 detoxifies lipid hydroperoxides to prevent ferroptosis; its PROTAC-mediated degradation abolishes this defence, driving lipid peroxide accumulation and ferroptotic death in cancer cells.

Acknowledgements: UIDB/04138/2020, UIDP/04138/2025, 2024.02105.BD, EUOPENSCREEN Impulse Grant Agreement 101132028.

References

[1] Rodriguez, R., Schreiber, S. L. & Conrad, M.; Mol Cell, 2022, 82, 728–740
[2] Koeberle, S. C., Kipp, A. P., Stuppner, H. & Koeberle, A.; Med Res Rev, 2023, 43, 614–682.
[3] Sun, S., Shen, J., Jiang, J., Wang, F. & Min, J. t Target Ther, 2023, 8, 372.
[4] Liu, H. et al.; Cell Chem Biol, 2022, 29, 1680-1693.e9.

When light heals: flavylium derivatives as a new class of photosensitizers for photodynamic antimicrobial therapy

Patrícia Correia[1*], Nuno Mateus[1], Victor de Freitas[1], Joana Oliveira[1] and Iva Fernandes[1]

[1]*REQUIMTE/LAQV, Department of Chemistry and Biochemistry, Faculty of Sciences, 4169- 007 Porto, Portugal*

** E-mail: patricia.correia@fc.up.pt*

Antimicrobial resistance (AMR) is a critical global health challenge and projections estimate that it could cause up to 10 million deaths annually by 2050 [1]. This rising crisis accentuates the need for innovative, non-antibiotic therapeutic alternatives. Photodynamic therapy (PDT) has emerged as a promising strategy due to its minimal invasiveness, high selectivity and compatibility with modern therapeutic platforms. In this context, we recently investigated a series of amino-substituted flavylium dyes (absorption maxima between 550 and 650 nm), and proposed them as a new class of photosensitizers [2-4]. Substitutions at the C7 and C4' positions of the flavylium core with amino groups were found to play a key role in modulating light-induced cytotoxicity. Flavylium-derived molecules were able to inhibit the growth of *S. aureus* and *P. aeruginosa* under irradiation with a white LED panel (~4 J/cm^2). Notably, these compounds were especially effective against Gram-positive bacteria, achieving complete eradication at concentrations between 3 and 12 μM. They also exhibited remarkable photostability (≥90%) even at light doses exceeding those used during photoinactivation assays. Confocal microscopy confirmed rapid bacterial adsorption/internalization after 30 minutes of incubation, while atomic force microscopy revealed membrane disruption and leakage of intracellular contents. Singlet oxygen generation, measured indirectly using a chemical probe, was identified as a major contributor to the observed bactericidal activity. Overall, this work introduces a new family of light-responsive dyes as next-generation photosensitizers for photodisinfection applications.

Funding: This work received financial support from the PT national funds (FCT/MECI, Fundação para a Ciência e Tecnologia and Ministério da Educação, Ciência e Inovação) through the project UID/50006 -Laboratório Associado para a Química Verde - Tecnologias e Processos Limpos.

References

[1] Naghavi, M., et al.; The Lancet 2024, 404(10459), 1199-1226.
[2] Correia, P., et al.; Dyes and Pigments 2024, 224, 111975.
[3] Araújo, P., et al.; Dyes and Pigments 2025, 233, 112495.
[4] Correia, P., et al.; Sci Rep 2024. 14(1), 29535.

Bioactive recovery from tomato by-products: green chemical strategies for circular and sustainable food preservation

Raquel Nunes da Silva[1,2*], Bárbara Maurício[1,3], Ana Fernandes[1,2], Iva Fernandes[1,2], Nuno Mateus[1,2], Victor de Freitas[1,2]

[1]LAQV-REQUIMTE, Chemistry and Biochemistry Department, Faculty of Sciences, University of Porto, Rua do Campo Alegre 689, 4169-007 Porto, Portugal, [2]Chemistry and Biochemistry Department, Faculty of Sciences, University of Porto, Rua do Campo Alegre 689, 4169-007 Porto, Portugal; [3]Faculty of Engineering, University of Porto, s/n, R. Dr. Roberto Frias, 4200-465 Porto, Portugal

** E-mail: raq.silva@fc.up.pt*

The valorisation of by-products from the tomato processing industry represents a viable and needed strategy to address global sustainability challenges by reducing agro-industrial waste and recovering high-value bioactive compounds. Rich in polyphenols, carotenoids, and other functional molecules, tomato by-products offer a sustainable resource that aligns directly with circular economy principles and the development of natural food preservation technologies.
In collaboration with a multinational tomato processing company in Portugal, this study explored the chemical profile of pomace from standard and high-lycopene tomato varieties and assessed their future suitability for sustainable applications in food, nutraceutical, and antimicrobial systems. Extraction and quantification of polyphenols were optimized through colorimetric assays and HPLC-DAD, enabling the tentative identification of 25 polyphenols. Carotenoids were also extracted and quantified through chromatographic and spectrophotometric approaches. Antioxidant capacity was high across both varieties, supporting their potential as natural functional ingredients to control oxidative deterioration in food products [2]. Antimicrobial assays conducted with and without light exposure further demonstrated that both polyphenol and carotenoid extracts exhibit some inhibitory effects against tomato-spoiling bacteria. Irradiation enhanced antimicrobial activity of polyphenols, highlighting their potential as natural photosensitizers for photodynamic inactivation (PDI).
This work provides evidence that tomato by-products can be transformed into bioactive-rich, multifunctional ingredients suitable for sustainable food preservation and value-added applications. The optimized workflows contribute to the development of environmentally responsible solutions that simultaneously reduce waste, enhance resource efficiency, and support global efforts toward more resilient and circular food systems.

Funding: This work received financial support from the PT national funds (FCT/MECI, Fundação para a Ciência e Tecnologia and Ministério da Educação, Ciência e Inovação) through the project UID/50006/2025 -Laboratório Associado para a Química Verde - Tecnologias e Processos Limpos.

References

[1] Lu, Z.; Wang, J.; Gao, R.; Ye, F.; Zhao, G; Sustainable Valorisation of Tomato Pomace: A Comprehensive Review; Trends Food Sci. Technol.; 2019, 86, 172–187.
[2] Farinon, B.; Felli, M.; Sulli, M.; Diretto, G.; Savatin, D. V; Mazzucato, A.; Merendino, N.; Costantini, L. Tomato Pomace Food Waste from Different Variants as a High Antioxidant Potential Resource; Food Chem, 2024, 452, 139509.

Unlocking AIEgen potential via green multicomponent reactions

Mariana Peixoto[1*], André Marques[1], J. Sérgio Seixas de Melo[1], Marta Piñeiro[1]
[1]*CQC– IMS, Department of Chemistry, University of Coimbra, Portugal*
** E-mail: mariana.silva.fp@gmail.com*

Unlocking the potential of AIEgens is essential for creating advanced materials with unique photophysical properties. Expanding their structural diversity through sustainable multicomponent reactions (MCRs) offers high atom economy, operational simplicity, and reduced environmental impact. [1] This approach was selected for the development of 9,9-diphenyl-9*H*-fluorene (DPBF) derivatives, which have attracted significant attention due to their outstanding optical properties [2]. By enabling bottom-up strategies that align with green chemistry principles, multicomponent reactions will pave the way for the scalable and eco-friendly synthesis of next-generation AIEgens.

To achieve structural diversification, we explored the Biginelli, Strecker, and Hantzsch reactions, as well as the multicomponent synthesis of polysubstituted 2,6-dicyanoanilines (Wang synthesis). [3] All reactions were optimized using model reactions (benzaldehyde or 3,5-dimethoxybenzaldehyde). To prepare the DPBF derivative, the corresponding aldehyde was obtained from methyl-DPBF via a two-step, one-pot microwave-assisted synthesis (MAOS) strategy, achieving a high yield. The Biginelli and Hantzsch derivatives were synthesized via MAOS in just 10 minutes with good yields. The Strecker and Wang derivatives were produced using ball milling under solvent-free conditions, highlighting the versatility of mechanochemistry for sustainable synthesis.

In this presentation, we will discuss the rationale behind selecting MCRs, show how they facilitate the eco-friendly synthesis of DPBF derivatives, and present their optimization using MAOS and ball milling. We will also present the photophysical properties of the resulting AIEgens, focusing on their characteristic aggregation-induced emission behaviour.

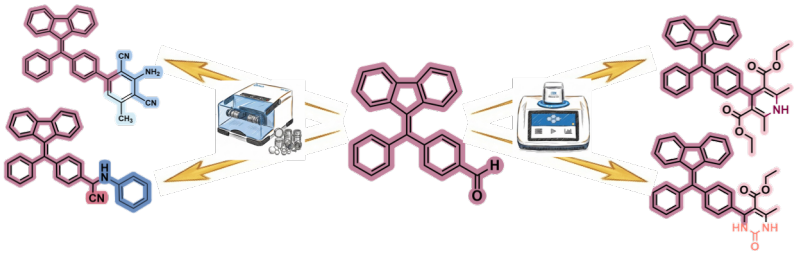


Figure 1. Multicomponent synthetic routes to DPBF derivatives using MAOS and mechanochemistry.

Acknowledgements: We acknowledge funding from the Coimbra Chemistry Centre – Institute of Molecular Sciences (CQC-IMS) which is supported by the Fundação para a Ciência e a Tecnologia (FCT), Portuguese Agency for Scientific Research. CQC is funded by FCT through projects UID/PRR/00313/2025 (https://doi.org/10.54499/UID/PRR/00313/2025) and UID/00313/2025 (https://doi.org/10.54499/UID/00313/2025) and IMS through special complementary funds provided by FCT (project LA/P/0056/2020 https://doi.org/10.54499/LA/P/0056/2020). The authors also acknowledge the UC-NMR facility for the NMR data (www.nmrccc.uc.pt). M. Peixoto thank FCT for PhD Grant, 2022.12812.BD.

References

[1] Brandão, P. B., Anthony J.; Piñeiro, Marta. QUÍMICA, 2020; 44, 264.
[2] Rodrigues, A. C. B.; Peixoto, M.; Gomes, C.; Pineiro, M.; Seixas de Melo, J. S. Chem – A Eur. J. 2022, 28 (7).
[3] S.-L. Cui, X.-F. Lin, Y.-G. Wang J. Org. Chem. 2005, 70, 2866.

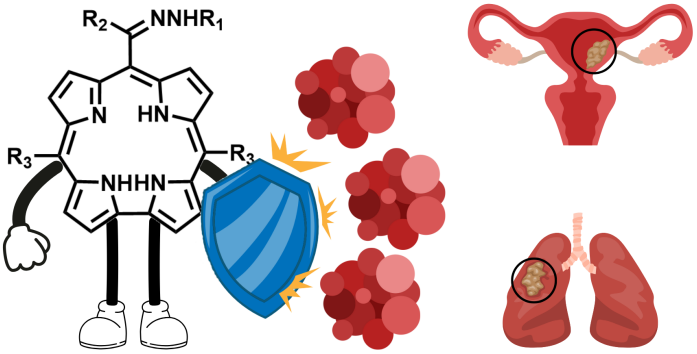
Photodynamic therapy of endometrial cancer using newly designed hydrazone-functionalized corroles

Bruna D. P. Costa[1*], Ana Clara B. Rodrigues[1], Marta Piñeiro[1], J. Sérgio Seixas de Melo[1], Maria F. Botelho[2,3,4], Susana M. M. Lopes[1], Mafalda Laranjo[2,3,4], Teresa M. V. D. Pinho e Melo[1]

[1] University of Coimbra, Coimbra Chemistry Centre-Institute of Molecular Sciences and Department of Chemistry, 3004-535 Coimbra, Portugal; [2] University of Coimbra, Coimbra Institute for Clinical and Biomedical Research (iCBR - CIMAGO), Biophysics Institute of Faculty of Medicine, Coimbra, Portugal. [3] University of Coimbra, Center for Innovative Biomedicine and Biotechnology (CIBB), Coimbra, Portugal. [4] Clinical Academic Center of Coimbra (CACC), Coimbra, Portugal.

** E-mail: brunacostaa97@gmail.com*

Endometrial cancer is the one of the most frequent gynaecological malignant diseases worldwide. The primary treatment for this cancer is total hysterectomy, highlighting the urgency to find efficient conservative therapies. Photodynamic Therapy (PDT) is considered a promising choice due to its easy access to the uterine cavity and minimal side effects.[1] Our group previously demonstrated the potent activity of hydrazone-functionalized corroles as photosensitizers for PDT in lung cancer cell lines, achieving IC_{50} values in the nanomolar range.[2] In here, we report the synthesis of a new series of hydrazone-functionalized corroles, exploring the chemistry of azoalkenes toward dipyrromethanes, followed by comprehensive characterization of these macrocycles as photosensitisers for PDT of endometrial cancer. Structural modifications were implemented to evaluate the impact of electron withdrawing groups on both the photophysical characteristics of the macrocycles and their biological activity.Overall, the photophysical features and encouraging *in vitro* results of these hydrazone-functionalized corroles indicate them as strong and promising candidates for PDT.



Acknowledgements: We acknowledge funding from the Coimbra Chemistry Centre – Institute of Molecular Sciences (CQC-IMS) which is supported by FCT, Portuguese Agency for Scientific Research. CQC is funded by FCT through projects UID/PRR/00313/2025 (https://doi.org/10.54499/UID/PRR/00313/2025) and UID/00313/2025 (https://doi.org/10.54499/UID/00313/2025) and IMS through special complementary funds provided by FCT (project LA/P/0056/2020 https://doi.org/10.54499/LA/P/0056/2020). Bruna D. P. Costa also thanks to the FCT for financial support (2022.12013.BD).

References [1] a) Obermair, A.; Baxter, E.; Brennan, D. J.; McAlpine, J. N.; Muellerer, J. J.; Amant, F.; van Gent, M. D. J. M.; Coleman, R. L.; Westin, S. N.; Yates, M. S.; Krakstad, C.; Janda, M., *Obstet. Gynecol. Sci.* **2020**, 63, 417–43. b) Won, S.; Kim, M. K.; Seong, S. *J., Clin. Exp. Reprod. Med.* **2020**, 47, 237–244.[2] Costa, B. D. P.; Simões, J. C. S.; Lopes, S. M. M.; Laranjo, M.; Rodrigues, A. C. B.; Gonçalves, A. C.; Seixas de Melo, J. S.; Botelho, M. F.; Pineiro, M.; Pinho e Melo, T. M. V. D., J. Med Chem. 2024, 67, 21934-21951.

Metal chelation mediated development of PET tracers based on *de novo* designed mini binders

Esther Calvino-Sanles[1,2*], Malamatenia Papavasileiou[1,2], Marta C. Marques[1,2], Pedro M. P. Gois[2], Rafael F. A. Gomes[2], Gonçalo J. L. Bernardes[3,4]

[1]Gulbenkian Institute for Molecular Medicine (GIMM), Edificio Egas Moniz, Av. Prof. Egas Moniz, Lisbon, Portugal; [2]Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, University of Lisbon, Avenida Professor Gama Pinto, Lisbon, Portugal; [3]Yusuf Hamied Department Chemistry, University of Cambridge, Lensfield Rd, Cambridge, United Kingdom; [4]Translational Chemical Biology Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain

** E-mail: esther.sanles@gimm.pt*

Molecular imaging techniques, such as positron emission tomography (PET) allow to visualize the expression of relevant biomarkers for cancer. The development of protein-based PET tracers would allow for tracers with a higher specificity and affinity, reducing background and improving sensitivity. However, one of the most used radioisotopes in PET imaging, fluorine-18, has a half-life incompatible with antibodies [1]. In this context, de novo designed protein mini binders appear as an alternative with compatible half-lives.

In this work, we have selectively incorporated chelating agents in protein mini binders relevant for cancer and achieved their late-stage cold labelling using reaction conditions compatible with fluorine-18 labelling (**Figure 1**). Importantly, the fluorination of the protein mini binders did not affect significantly their structure nor binding affinity and has shown to be stable under physiological conditions. Current efforts are focused on engineering the fluorinated proteins to reduce kidney uptake, a common issue faced with peptides and protein-based tracers, mainly related to proximal tubes reabsorption [2]. If successful, this work could significantly contribute to the progress of personalized medicine.

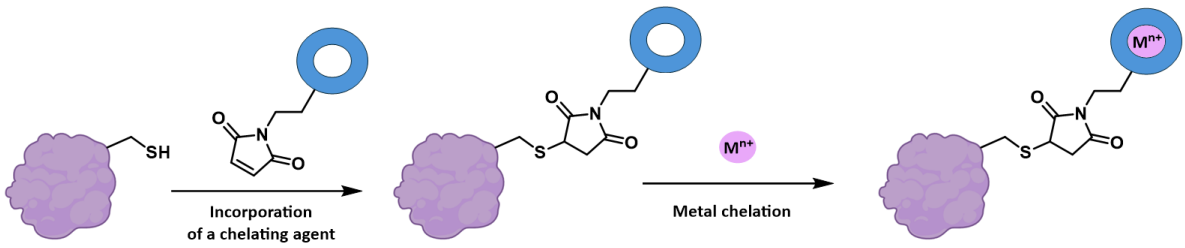


Figure 1. *Protein labelling strategy explored in this work*

Acknowledgements: The ISOBIOTICS project has received funding from the European Union Horizon Europe Research and Innovation Program under the Marie-Sklodowska Curie grant agreement 101072780. The authors also acknowledge Fundação para a Ciencia e Tecnologia (FCT) for financial support (2023.14078.PEX; 2023.11341.PEX; UID/04138/2025)

References

[1] Clark, J.; O'Hagan, D.; J. Fluor. Chem. 2017, 203, 31-46.
[2] Vegt, E.; de Jong, M.; Wetzels, J.F.M.; Masereeuw, R.; Melis, M.; Oyen, W.J.G; Gotthardt, M.; Boerman, O.C.; J Nucl Med 2010, 51,1049–1058.

Design and site-specific grafting of fluorescent probes onto cellulose via orthogonal coupling strategies

Ricardo Chagas[1,*], Luísa M. Ferreira[1], Meltem Avci-Adali[2], Emre Ergene[2]

[1]*LAQV REQUINTE, NOVA FCT, Campus da Caparica, Caparica, Portugal;*

[2]*Universitätsklinikum Tübingen, 72076 Tübingen, Germany*

** E-mail: r.chagas@fct.unl.pt*

Fluorescent and affinity probes are highly relevant for achieving unequivocal covalent or site-specific bonding of diverse molecules to cellulose, as they both report on and enforce the selectivity of the underlying conjugation chemistry. Using orthogonal reactive handles on cellulose (for example, carboxyl groups or click-chemistry motifs) and on the probe-bearing molecule enables highly controlled attachment of dyes, biomolecules, or functional ligands while minimizing nonspecific adsorption on the polysaccharide surface. Cellulose-binding modules can promote the immobilization of cellulose-based fluorescent probes that integrate the sensing unit into the polymer backbone, illustrating how robust, well-characterized coupling strategies yield materials with reproducible recognition and signalling performance. Here, we present the methodologies used to bind cellulose to a fluorescent probe in two steps (Figure 1), as well as the preparation of functionalized membranes.

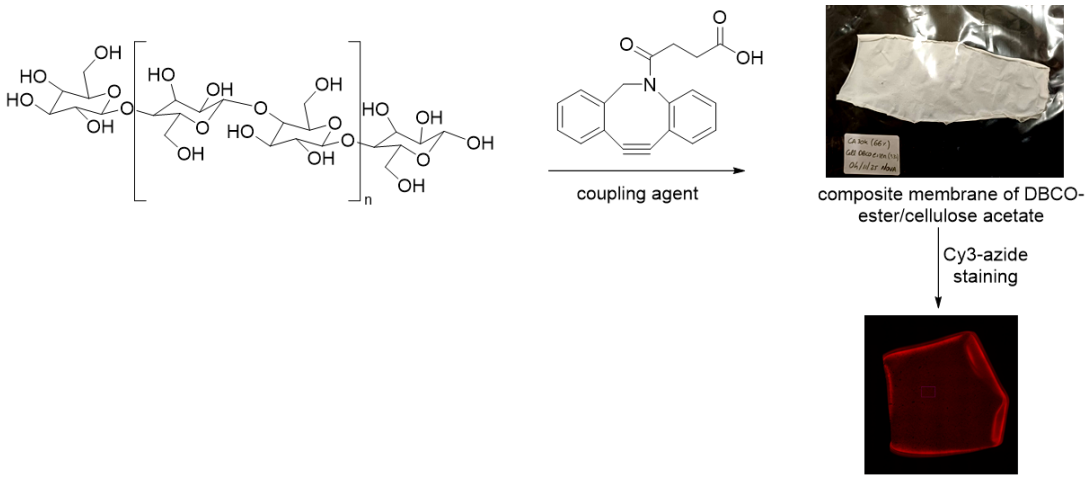


Figure 1. Synthesis of cellulose derivative with DBCO moiety and Cy3-azide stanning on the composite membrane of the DBCO-cellulose ester/cellulose acetate.

Funding: This work is funded by the European Union's EIC Pathfinder through the project CELLMEMBRANE (Grant Agreement ID 101130895) and by Fundação para a Ciência e a Tecnologia (FCT) under the researcher contract 2023.09397.CEECIND. This work was also financed by national funds from FCT - Fundação para a Ciência e a Tecnologia, I.P., under the scope of the project UID/50006/2023 of the Associate Laboratory for Green Chemistry - LAQV REQUIMTE.

References

[1] Bukharina D, Cauffiel K, Killingsworth LM, Brackenridge JA, Poliukhova V, Kim M, Brower J, Bernal-Chanchavac J, Stephanopoulos N, Tsukruk VV.; ACS Biomater Sci Eng. 2024, 10, 6155-6166.

[2] Navarro, J. R. G.; Conzatti, G.; Yu, Y.; Fall, A. B.; Mathew, R.; Edén, M.; Bergström, L.; Biomacromolecules 2015, 16 (4), 1293–1300.

In-situ derivatization and isolation strategy of marine natural products for bioactive analogue discovery

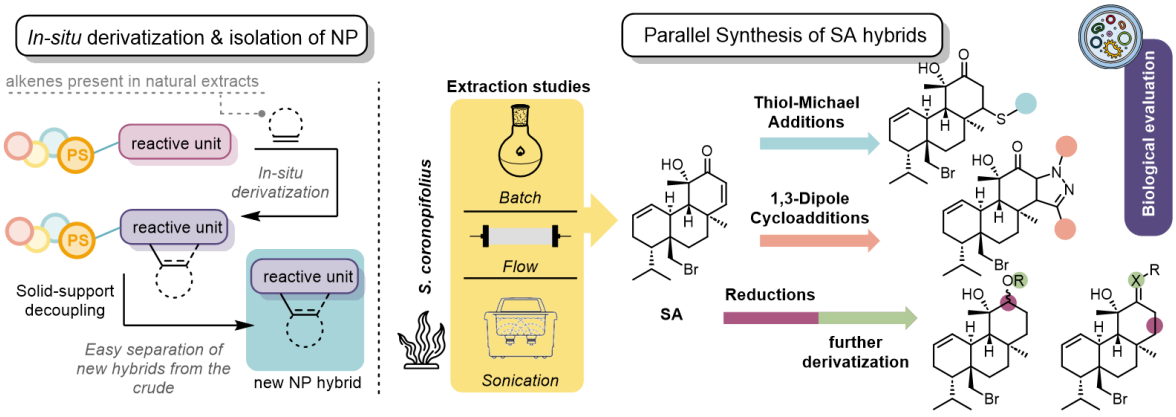
Milene A.G. Fortunato[1*], J. F. A. Martins[1], M. P. Alves[1], D. Sousa [2], J. Silva [2], C. Alves[2], J. Ferreira[1], J. Perdigão[1], A. Jordaan[3], D. F. Warner[3], F. Siopa[1], C. A. M. Afonso[1]

[1]*Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisbon, Portugal;* [2]*MARE—Marine and Environmental Sciences Centre/ARNET - Aquatic Research Network, ESTM, Politécnico de Leiria, 2520-614 Peniche, Portugal;* [3]*Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Rondebosch 7701, South Africa.*

** E-mail: milene.fortunato@edu.ulisboa.pt*

Natural products (NPs) are valued for their structural complexity and remain a key source of inspiration for new bioactive scaffolds. Creating NP hybrids to obtain complex, biologically active analogues is a central strategy in drug discovery. However, NP isolation is often labor-intensive, low-yield, and may require further synthetic modification [1].

We present an in-situ derivatization and isolation strategy targeting functional groups (e.g., activated olefins) within NP extracts. This method integrates photochemical, high-pressure, and conjugate addition reactions with simplified isolation technique such solid-phase synthesis (Scheme 1). As a proof of concept, we used an extract from the red seaweed *Sphaerococcus coronopifolius*, which contains Sphaerococcenol A (SA), a marine NP with reported antitumor, antimicrobial, and antimalarial activities [2]. By optimizing SA isolation through solvent screening and process variations (batch, flow, and sonication), we achieved a 1.8-fold yield improvement. This enabled the synthesis of 13 new analogues with moderate yields, currently under evaluation for cytotoxic, antibacterial, anti-tubercular, and neuroprotective properties, advancing the understanding of SA's structure–activity relationships (Scheme 1) [3].



Scheme 1. Strategy overview of the in-situ derivatization and isolation of NP and synthesis of SA hybrids.

Funding: We thank the Fundação para a Ciência e Tecnologia for financial support (2021.06598.BD; 2022.08851.PTDC; 2022.09196.PTDC; CEECINST/00060/2021/CP2799/CT0004; EAPA_0032/2022; UIDP/04292/2020; UID/04138/2025(https://doi.org/10.54499/UID/04138/2025))

References

[1] Atanasov, A. G.; Zotchev, S. B.; Dirsch, V. M.; Int Nat Prod Sci Taskforce; Supuran, C. T. Nat. Rev. Drug Discov. 2021, 20, 200.

[2] Alves, C.; Silva, J.; Afonso, M. B.; Guedes, R. A.; Guedes, R. C.; et al. Biomed. Pharmacother. 2022, 149, 112886.

[3] Sousa, D.; Fortunato, M. A. G.; Silva, J.; Pingo, M.; Martins, A.; Afonso, C. A. M.; Pedrosa, R.; Siopa, F.; Alves, C. Marine Drugs 2024, 22, 408.

Fluorescent 2-aminopurine derivatives: synthesis, photophysical properties and quantum chemical calculations

Jorge M. Gonçalves[1], Paulo J. G. Coutinho[2], Elisabete M. S. Castanheira[2], Alice M. Dias[1*]

[1]*Chemistry Centre of University of Minho (CQUM), Braga, Portugal;* [2]*Physics Centre of Minho and Porto Universities (CF-UM-UP) and Lab. of Physics for Materials and Emergent Technologies (LaPMET), Portugal*

** E-mail: ad@quimica.uminho.pt*

Fluorescence is one of the most sensitive, versatile, easily accessible, fast and straightforward technique for monitoring chemical interactions of biomolecules [1]. The use of fluorescent nucleobase analogues (FNAs) is an attractive strategy, yet the numerous analogues that have been synthesized showed absorption and emission spectra near the UV region [2,3]. Hence, the development of brighter fluorescent 2-aminopurine (2AP) analogues emitting at longer wavelengths, while maintaining their small size is an important milestone to fulfil. All these structural needs are difficult to achieve since efficient synthesis of purines remains challenging, being an even more demanding task the optimization of the photophysical properties of the purine scaffold.

In previous work, highly fluorescent 6-cyano-2-aminopurines were obtained [4], which exhibited absorption and emission bands in the visible region, and high fluorescent quantum yields and Stokes shifts. Recently, incorporation of more electron-withdrawing groups at the C-6 position through structural modifications on the cyano group was achieved, leading to improved photophysical properties. To gain some insight on the structural and electronic molecular properties of both ground state (S_0) and first excited state (S_1), TDDFT calculations [5] of electronic and vibrational structure were also performed.

In this work, the synthesis of new 2-aminopurines with different groups on C-6 position will be presented. The photophysical properties of the novel compounds in different media will be determined and compared with theoretical results obtained by TDDFT calculations in order to find out the best functional for this class of molecules.

Acknowledgements: This work was supported by the Portuguese Foundation for Science and Technology (FCT) in the framework of Strategic Funding UID/00686/2025 (CQUM) and UID/04650/2025 (CF-UM-UP). Jorge M. Gonçalves acknowledges FCT for a PhD fellowship (2024.01438.BD).

References

[1] Sinkeldam, R.W.; Greko, N.J.; Tor, Y.; Chem. Rev 2010, 110, 2579–2619.
[2] Saito, Y.; Koda, M.; Shinohara, Y.; Saito, I.; Tetrahedron Lett 2011, 52, 491-494.
[3] Xu, W.; Chan, K.M.; Kool, E.T.; Nat. Chem 2017, 9, 1043-1055.
[4] Gonçalves, J.M.; Gonçalves, J.N.D.; Pêra, A.S.; Senhorães, N.R.; Rodrigues, A.R.O.; Oliveira, R.; Coutinho, P.J.G.; Castanheira, E.M.S.; Dias, A.D.; Eur. J. Org. Chem 2023, 26, e202300176.
[5] Runge, E.; Gross, E.K.U.; Phys. Rev. Lett 1984, 52, 997-1000.

Targeting Gram-positive bacteria with tailored cationic diketopyrrolopyrroles as photosensitizers

Vasco M. S. Castanheira[1,*], Cátia S. S. Vieira[2], Maria. A. F. Faustino[1], Maria A. P. Almeida[2], Augusto C. Tomé[1]

[1]*LAQV-REQUIMTE, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal*

[2]*CESAM, Department of Biology, University of Aveiro, 3810-193 Aveiro, Portugal*

** E-mail: vasco.castanheira@ua.pt*

Diketopyrrolopyrroles (DPPs) are a versatile class of organic dyes widely studied for their outstanding optical and electronic properties, making them valuable in optoelectronic devices [1,2]. Recently, attention has shifted towards their potential in biological areas, including photodynamic inactivation (PDI) of microorganisms [3]. As antimicrobial resistance (AMR) is growing as a major health threat nowadays, PDI has special relevance as an alternative technique to eliminate microorganisms [4].

In this communication, we describe the synthesis of eight new cationic DPP derivatives, generated by reacting N-bromoalkyl DPPs with various nucleophiles. We further evaluate their photophysical properties, oxygen singlet generation and their photodynamic activity agaisnt methicillin-resistant *Staphylococcus aureus* (MRSA), a Gram-positive bacterium.

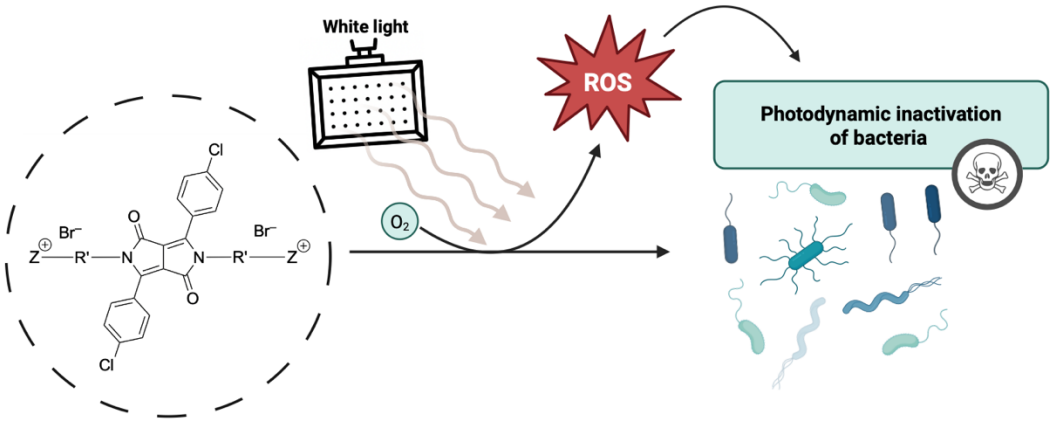


Figure 1. Illustration of the photodynamic process using cationic DPP derivatives as photosensitizers.

Acknowledgements: Thanks are due to the University of Aveiro and Fundação para a Ciência e a Tecnologia for the financial support to the UID/50006/2025 – Laboratório Associado para a Química Verde – Tecnologias e Processos Limpos and UID Centro de Estudos do Ambiente e Mar (CESAM) + LA/P/0094/2020. Thanks are also due to the Portuguese NMR and Mass networks.

References

[1] Meng, J.; Luo, N.; Zhang, G.; Shao, X.; Liu, Z.; Zhang, D. Chin. Chem. Lett., 2023, 34, 107687.
[2] Chandran D.; Lee, K. S. Macromol. Res., 2013, 21, 272-283.
[3] Costa, L. D.; Vieira, C.; Hackbarth, S.; Neves, M. G. P. M. S.; Almeida, A.; Faustino M. A. F.; Tomé, A. C. *Dyes Pigm.*, 2025, 244, 113101.
[4] Ndayishimiye, J.; Kumeria, T.; Popat, A.; Falconer, J.; Blaskovich, M. T. ACS Infect. Dis., 2022, 8, 693-712.

POSTER COMMUNICATIONS

Docking molecular and ADMET analysis of compounds derived from *Catharanthus roseus* against the E2 protein of CHIKV

Zayra V. B. da Silva[1*], Samuel H. B. da Silva[2], Pedro A. P. Pessôa[3], Fatima M. de S. Pereira[4]

[1,3,4] *Federal Institute of Education, Science, and Technology of Maranhão, Caxias, Maranhão, Brazil;*
[2] *Federal Institute of Education, Science, and Technology of Maranhão, São Luís, Maranhão, Brazil*
**E-mail: zayra.vitoria@acad.ifma.edu.br*

Chikungunya fever, caused by the CHIKV virus and transmitted by the mosquitoes Aedes aegypti and Aedes albopictus, still lacks specific antiviral treatment, which reinforces the need for new therapeutic approaches [1]. This study aimed to investigate in silico the potential of alkaloids from Catharanthus roseus (periwinkle) as inhibitors of the CHIKV E2 protein, using computational chemistry tools. Ligand structures were obtained from the ZINC database, prepared with ChimeraX and AutoDock Tools software, and submitted to molecular docking in AutoDock Vina [2]. Pharmacokinetic and toxicological analyses were performed on the SwissADME and ADMETlab 3.0 platforms [3]. Results indicated that Vincoside, Ajmalicine, Serpentine, and 19-S-vindolinine showed high affinity for the E2 protein, with binding energies between −8.2 and −9.2 kcal/mol. Serpentine stood out on E2 (ΔG = −9.2 kcal/mol; Ki ≈ 1.78×10^{-7} M).

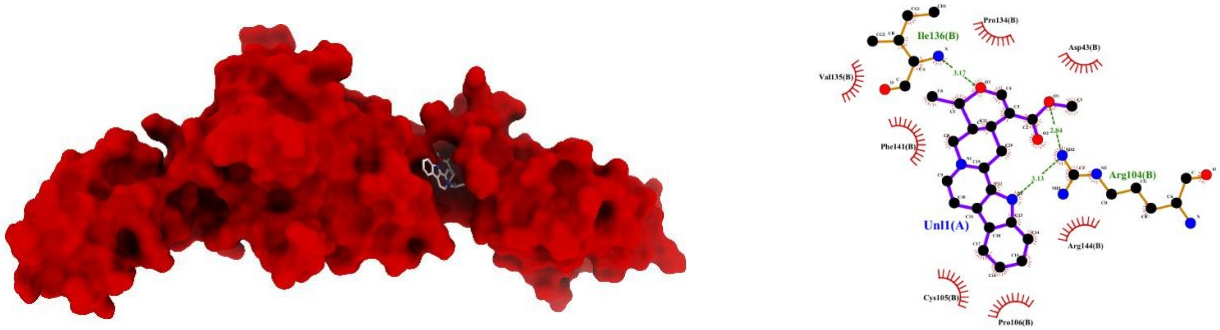


Figure 1. Complex: E2 (green surface) and Serpentine ligand (gray, red, and blue); LigPlot+ diagram showing hydrophobic and hydrogen bond interactions between Serpentine and the E2 active site.

Serpentine stood out on E2 (ΔG = −9.2 kcal/mol; Ki ≈ 1.78×10^{-7} M). Ajmalicine demonstrated the best ADMET profile, with high gastrointestinal absorption and no relevant toxic interactions, being the most promising compound. The findings suggest that alkaloids from C. roseus have potential for developing antiviral inhibitors against CHIKV, reinforcing the value of Maranhão biodiversity in pharmacological research and strengthening the local bioeconomy.

References

[1] Cunha MS, et al. Chikungunya virus: an emergent arbovirus to South America and a continuous threat to the world. Front Microbiol. 2020;11:1297. doi:10.3389/fmicb.2020.01297.
[2] Trott O, et al. AutoDock Vina: improving speed and accuracy of docking with a new scoring function, optimization, and multithreading. J Comput Chem. 2010;31(2):455-61. doi:10.1002/jcc.21334.
[3] Daina A, et al. SwissADME: free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep. 2017;7:42717. doi:10.1038/srep42717.

Targeting cancer with near-infrared activated prodrugs

João Vaz[1,*], Maria J. Perry[1], Rui Moreira[1], Luís G. Arnaut[2]

[1]*Research Institute for Medicines (iMed.ULisboa), Faculdade de Farmácia da Universidade de Lisboa, Av. Prof. Gama Pinto,1649-003 Lisboa, Portugal;* [2]*Chemistry Department, University of Coimbra, 3004-535 Coimbra, Portugal*

** E-mail: joaomvaz@edu.ulisboa.pt*

The severe side effects of chemotherapeutic agents remain a major limitation in the effective and safe treatment of cancer. Although targeted therapies have emerged, their clinical efficacy is still limited, highlighting the need for novel strategies [1]. Light offers a unique tool for precise drug delivery, enabling spatial and temporal control while reducing systemic toxicity. This control can be achieved using photopharmacological tools known as photocages, which release active drugs upon light activation. Focus has shifted focus toward near-infrared (NIR) light, which enables deeper tissue penetration and greater precision compared to traditional UV-triggered systems [2]. In this study, we report the design and synthesis of NIR-activated anticancer prodrugs aimed at minimizing off-target effects through controlled drug release. A series of known and novel *o*-hydroxycinnamate **(1, Figure 1)** and *o*-nitrophenethyl-based **(2, Figure 1)** photocages were synthesized to enhance photophysical and chemical performance. These were coupled to various anticancer drugs, yielding NIR-responsive prodrugs. The resulting compounds were evaluated for their photophysical and photochemical properties, stability, and photorelease under both UV and NIR irradiation. *In vitro* validation in cancer cell lines confirmed selective cytotoxicity only upon light activation. These findings underscore the potential of NIR-triggered photocaged prodrugs as a promising strategy for spatiotemporally controlled cancer therapy with reduced systemic toxicity.

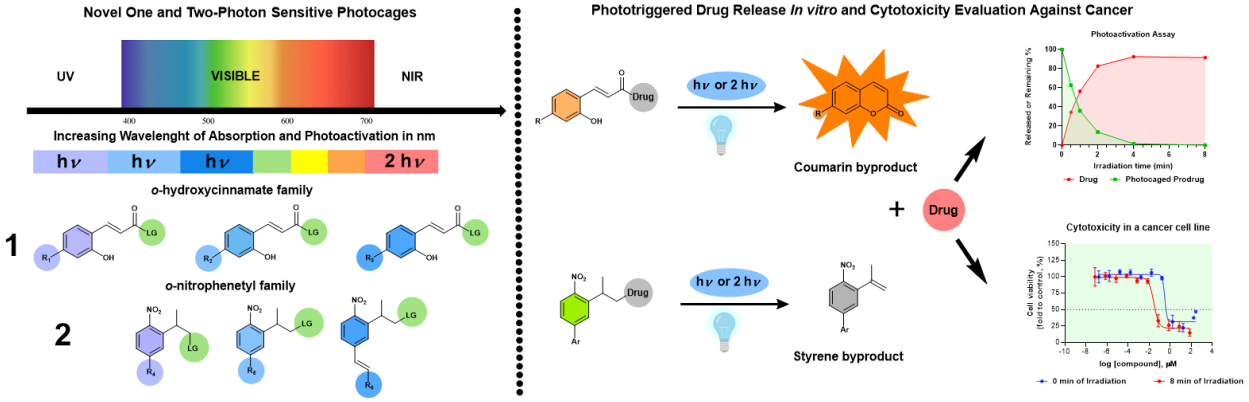


Figure 1. Overview of the Developed Work – Photocages, Mechanism of drug release and Results.

Funding: We thank Fundação para a Ciência e a Tecnologia for the support provided through UID/04138/2025, UID/00313/2025 and by the PhD Fellowship 2021.04705.BD (https://doi.org/10.54499/2021.04705.BD).

Acknowledgements: We thank the National NMR Network, supported by Infrastructure Project Nº022161 (co-financed by FEDER through COMPETE2020, POCI and PORL and FCT through PIDDAC), and the Portuguese MS Network, LISBOA-01-0145-FEDER-022125, supported by Lisboa2020, under the Portugal2020 Partnership Agreement, through the European Regional Development Fund.

References

[1] Dcona MM, Mitra K, Hartman MCT. Vol. 11, RSC Medicinal Chemistry; 2020. p. 982–1002.

[2] Josa-Culleré L, Llebaria A. ChemPhotoChem. 2021 Apr 22;5(4):296–314.

Design, screening and synthesis of new pyrrolo[4,3,2-*de*]quinolinone derivatives as new G4 targeting molecules

Bárbara Bahls[1,2,*], Paulo J. Costa[2], Alexandra Paulo[1]

*[1]Faculty of Pharmacy, Research Institute for Medicines (iMed.Ulisboa), Universidade de Lisboa, Av. Prof Gama Pinto, 1649-003 Lisbon, Portugal; [2]Faculty of Sciences, Biosystems and Integrative Sciences Institute (BioISI), Universidade de Lisboa, Campo Grande 016, 1749-016, Lisbon, Portugal; * E-mail: barbara.bruni@edu.ulisboa.pt*

G-quadruplexes (G4) are involved in several important cellular processes and are present in biologically relevant sequences, such as telomeres and proto-oncogenes. This makes G4s promising anti-cancer targets. Small molecules targeting these structures have been explored as therapeutical strategies [1-2] however they show toxicity and low efficiency issues. The pyrrolo[4,3,2-*de*]quinolinone (PQ) scaffold is found in several natural alkaloids that show different biological activities, such as cytotoxicity against cancer cells [3]. In this work, we aim to develop two libraries of PQ derivatives and comprehend their interaction with different G4s structures, looking for selectivity. Additionally, we seek to understand the correlation between docking scores and torsion angle of the aromatic substituents. Two libraries (**Figure 1**) were screened by molecular docking in two different PDB structures (5W77 and 3R6R) in previously identified binding sites. All compounds presented good binding energies, being promising G4 binders. The analysis of the binding energy and dihedral angle values showed that the torsion angles varied considerably and were not directly correlated with the docking scores. Library 1 was synthesized by Suzuki Coupling and library 2 by amidation. The binding affinities to G4 of all the compounds will be determined *in vitro*.

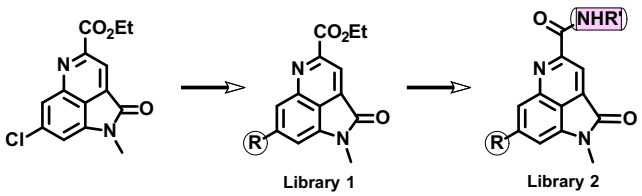


Figure 1. General scheme of libraries 1 and 2.

Fundings: Work supported UID/04046/2025 (BioISI), UID/04138/2025 (iMed) and 2022.06099.PTDC. PhD grant 2023.01798.BD (BB), European Union for TWIN2PIPSA, GA 101079147.

References

[1] Mendes, E.; Aljnadi, I.M.; Bahls, B.; Victor, B.L.; Paulo, A.; Pharmaceuticals 2022, 15, 300
[2] Dickerhoff, J., Warnecke, K. R., Wang, K., Deng, N., & Yang, D. Int. J. Mol. Sci. 2021, 22, 10801
[3] Delfourne, Med. Chem 2008; 8, 910-916

M SARS-CoV-2 M^{pro}-targeting PROTACs to bypass antiviral resistance

Francisca Almeida-Pinto[1,*], T. Rodrigues[1], H. Schwalbe[2], R. Moreira[1]

[1]*Research Institute for Medicines (iMed.Ulisboa), Faculty of Pharmacy, University of Lisbon, Portugal;*

[2]*Institut für Organische Chemie und Chemische Biologie, Johann Wolfgang Goethe Universität, Germany.*

** E-mail: francisca.pinto@edu.ulisboa.pt*

The rapid evolution of viral genomes limits the efficacy of occupancy-based inhibitors [1]. Recurrent coronaviruses outbreaks highlight the needs for antiviral strategies that remain effective despite viral mutations [2].

The SARS-CoV-2 Main Protease (M^{pro}) is a key therapeutic target, yet resistance to approved M^{pro} inhibitors has been reported. PROteolysis-TArgeting Chimeras (PROTACs) provide an alternative modality that may overcome resistance, as they rely on transient ternary-complex formation rather than high-affinity binding (Figure 1). However, current M^{pro}-Targeting PROTACs primarily focus on covalent warheads [2].

To broaden the understanding of whether PROTACs can circumvent resistance through weak yet productive target engagement, a first-generation of fragment-based M^{pro}-Targeting PROTACs were synthesized. To evaluate the activity of the synthesized PROTACs, thermal shift assays were performed to determine whether the fragment and fragment-based PROTACs bind SARS-CoV-2 M^{pro}. Enzymatic assays using a fluorogenic substrate were then carried out to further validate the PROTAC design. Ongoing studies aim to determine their ability to induce M^{pro} degradation.

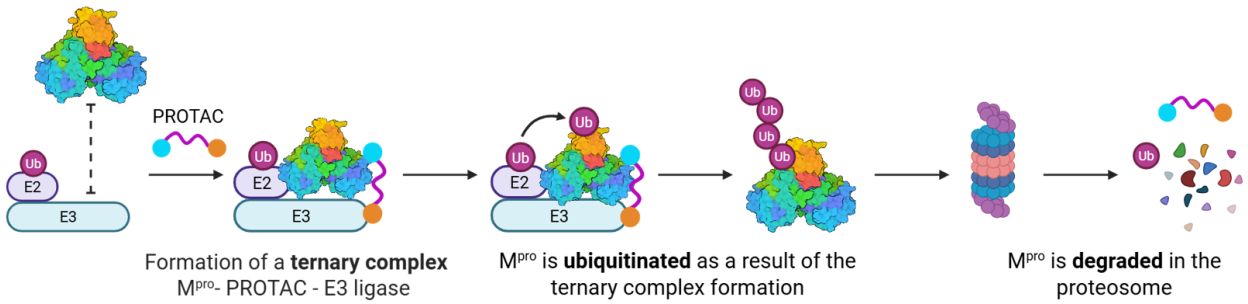


Figure 1. Mechanism of SARS-CoV-2 degradation via the Ubiquitin-Proteasome System mediated by the M^{pro}-Targeting PROTAC. Created with BioRender.com by Francisca Almeida-Pinto.

Funding: Support for this work was provided by UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025) and PhD Fellowship 2024.03409.BD from FCT, Portugal.

Acknowledgements: National NMR Network, supported by Infrastructure Project Nº022161 (co-financed by FEDER through COMPETE2020, POCI and PORL and FCT through PIDDAC), and the Portuguese MS Network, LISBOA-01-0145-FEDER-022125, supported by Lisboa2020, under the Portugal2020 Partnership Agreement, through the European Regional Development Fund.

References

[1] Almeida-Pinto F.; Pinto R.; Rocha J.; Infect. Dis. Ther. 2024, 13, 21-25

[2] Sang X.; Wang J.; Zhou J.; Xu Y.; An J.; Warshel A.; Huang Z.; J. Am. Chem. Soc. 2023, 145, 27248−2725

Anticancer potential of RuCp(II) complexes bearing (iso)nicotinic acid ligands

Bárbara Marques[1,2*], Diogo M. Engrácia[3], Jaime A. S. Coelho[4], Filipa Mendes[3], Tânia S. Morais[1,2]

[1]Centro de Química Estrutural, Institute of Molecular Sciences, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1, 1049-001 Lisboa, Portugal; [2]Associação do Instituto Superior Técnico para a Investigação e Desenvolvimento (IST-ID), Avenida António José de Almeida, 12, Lisboa, 1000-043, Portugal, [3]Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico, Universidade de Lisboa, 2695-066 Bobadela LRS, Portugal; [4]Centro de Química Estrutural, Institute of Molecular Sciences, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal;

** E-mail: barbara.marques@tecnico.ulisboa.pt*

More than 10 million cancer-related deaths were reported in 2022, and 1 in 5 people is estimated to develop cancer during their life. Moreover, current clinically available treatments still show limited efficacy and severe adverse effects, which urgently claims for novel therapeutic approaches to cancer treatment [1].

Organometallic ruthenium complexes have become highly promising candidates for cancer therapy, namely half-sandwich ruthenium(II)–arene complexes. Our group has developed several of these compounds containing the Ru(η^5-C_5H_5) (RuCp) moiety with strong anticancer and/or antimetastatic properties, both *in vitro* and *in vivo*. The most promising was the complex with the structure [RuCp(PPh_3)(bipy)][CF_3SO_3] (TM34), which has shown higher cytotoxicity than cisplatin in several cancer cell lines, including breast, ovarian, prostate, and leukemia [2]. This effect is linked to its distinct therapeutic target, the cell membrane.

To evaluate the influence of new bioactive ligands on this scaffold, we decided to incorporate nicotinic acid (vitamin B3) and isoniazid, which have garnered recent attention in cancer research, on the Cp ring [3]. Herein, we report the synthesis and full characterization of two new ruthenium(II) complexes with the general formula [Ru(η^5-$C_5H_4CCH_3$=R)(PPh_3)(bipy)][CF_3SO_3], where R = NNHCO(py-3-yl) (nicotinic acid derivative) or NNHCO(py-4-yl) (isoniazid derivative). The presence of *E/Z*-hydrazone isomerism was observed by spectroscopic techniques and confirmed by density functional theory calculations. Their stability in biological media was evaluated, and their cytotoxicity was determined *in vitro* in a panel of cancer cell lines: human melanoma (A375), human alveolar adenocarcinoma (A549), human epidermoid carcinoma (A431), and human breast cancer (MDA-MB 231).

Acknowledgements: We thank the Fundação para a Ciência e Tecnologia (FCT), I.P./MCTES for the financial support through the projects UID/100/2025, UIDB/00100/2020 (CQE, DOI 10.54499/UIDB/00100/2020), LA/P/0056/2020 (IMS, DOI 10.54499/LA/P/0056/2020) and UID/04349/2025 (C2TN). B. Marques and T. S. Morais thank FCT for the doctoral grant 2025.01871.BD and for support through the FCT Tenure program, respectively.

References

[1] Bray, F.; Laversanne, M.; Sung, H.; Ferlay, J.; Siegel, R. L.; Soerjomataram, I.; Jemal, A.; CA Cancer J. Clin. 2024, 74 (3), 229-263.

[2] Morais, T. S.; Valente, A.; Tomaz, A. I.; Marques, F.; Garcia, M. H.; Future Med. Chem. 2016, 8, 527-544.

[3] Marques, B.; Engrácia, D. M.; Machado, J. F.; Coelho, J. A. S.; Mendes, F.; Morais, T. S.; Pharmaceuticals 2025, 18 (1), 97.

Easy access to functionalized sparteine derivatives *via* electrochemical cyanation of quinolizidine alkaloids

Raquel M. Durão[1,2,*], Jaime A. S. Coelho[1], Svilen P. Simeonov[2], Carlos A. M. Afonso[2]

[1]*Centro de Química Estrutural, Institute of Molecular Sciences (CQE-IMS), Faculty of Sciences, University of Lisbon, Campo Grande, 1749-016, Lisbon, Portugal;* [2]*Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, University of Lisbon, Av. Prof. Gama Pinto, 1649-003, Lisbon, Portugal.*

** E-mail: raquel-durao@edu.ulisboa.pt*

Quinolizidine alkaloids (QA) are largely abundant in the Leguminosae family, especially in the genera Lupinus [1]. Maulide and Afonso's groups developed processes for the extraction of lupanine from Lupinus albus seeds wastewater and preparation of (+)- and (−)- sparteine [2]. These natural products are known for their pharmacological activities (e.g, antimicrobial, effects on the central nervous system) and use in asymmetric organic synthesis [3]. Motivated by the potential added value of novel QA derivatives, we explored the selective C–H functionalization of QA using electrochemistry. Over the past years, continuous flow processes have emerged due to their ability to enhance product quality and safety while reducing environmental impact, surpassing traditional batch syntheses [4]. As an attempt to improve the existing methodologies due to the continuous flow advantages, herein we present a new methodology for the cyanation of lupanine (**Figure 1**) under batch and flow conditions [5]. The approach employs commercially available equipment under both conditions for the direct electrolysis of lupanine, affording namely access to iminium salts. A particularly very stable iminium was isolated and subsequently utilized as a key precursor for the synthesis of a diverse series of novel lupanine-quinolizidine alkaloid derivatives.

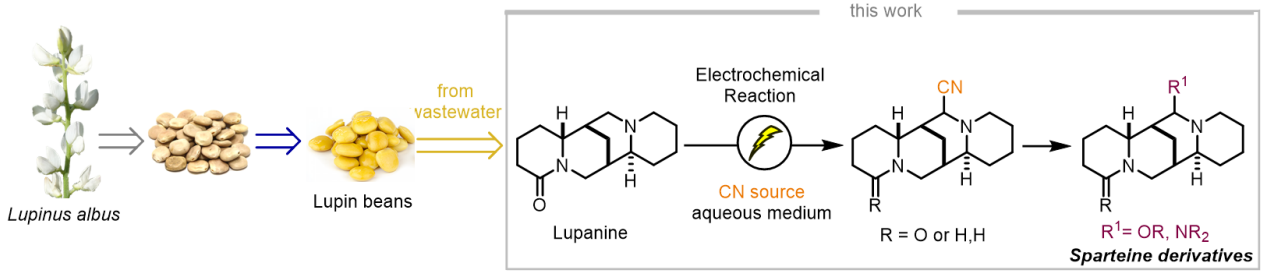


Figure 1. Electrochemical functionalization of quinolizidine alkaloids.

Acknowledgements: We thank the Fundação para a Ciência e a Tecnologia for financial support (2020/06352/BD, PTDC/QUI-QOR/1786/2021, UID/00100/2025, UID/PRR/100/2025, UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025), LA/P/0056/2020).

References

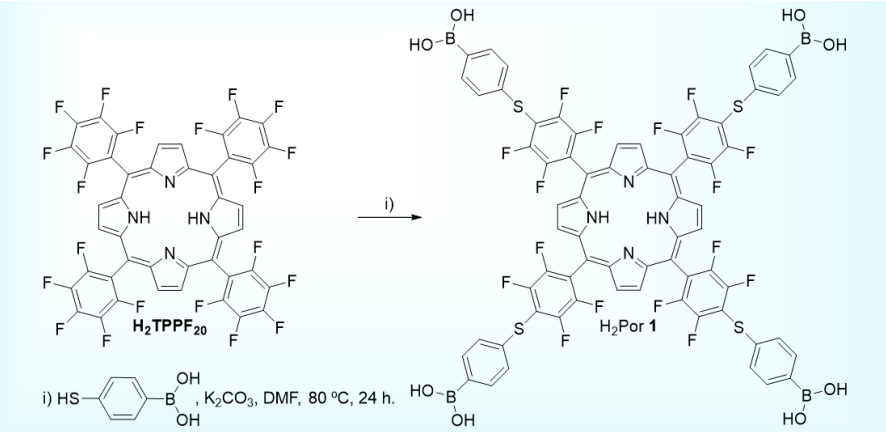
[1] S. Bunsupa, M. Yamazaki, K. Saito, Front. Plant Sci, **2012**, 3, 1.
[2] R. F. M. Frade, N. Maulide, B. Peng, C. A. M. Afonso, EP2808326A1; WO2014191261A1; 3-12-2013.
[3] F. V. Romeo, S. Fabroni, G. Ballistreri, S. Muccilli, A. Spina, P. Rapisarda. Sustain, **2018**, 10, 6.
[4] L. Capaldo, Z. Wen, T. Noël, Chem. Sci, **2023**, 14, 4230.
[5] R. M. Durão, D. B. Clemente, A. A. Muiz, S. Lima, D. F. Carvalho, S. De Vos, R. Jesus, A. Fortuna, C. A. M. Afonso, J. A. S. Coelho, ChemSusChem, **2024**, e202401305.

A light-activated porphyrin for the photodynamic inactivation of *S. aureus* and *E. coli*

Daiane N. Maronde[1,2*], Cátia Vieira[3], José E. R. Borges[2], Adelaide Almeida[3], Leandro Lourenço[1]

[1] *LAQV–REQUIMTE, Department of Chemistry, University of Aveiro, 3810–193 Aveiro, Portugal.*
[2] *LAQV–REQUIMTE, Department of Chemistry and Biochemistry, Faculty of Science, University of Porto, 4169–007 Porto, Portugal.*
[3] *CESAM, Department of Biology, University of Aveiro, 3810–193 Aveiro, Portugal.*
** E-mail: up202010482@edu.fc.up.pt*

Photodynamic inactivation (PDI) is a promising approach against resistant bacterial pathogens [1]. Porphyrin (Por) generate reactive oxygen species, while incorporated boronic groups increase efficacy by binding to bacterial surface glycans [2]. We report the synthesis and evaluation of a novel boronic acid-substituted free-base Por (H_2Por **1**), Scheme 1 [3]. Its antimicrobial efficacy was tested against *S. aureus* and *E. coli* bacteria. Assays were performed at concentrations of 5 and 10 μM under white light (0–360 J cm^{-2}), without and with potassium iodide (KI) coadjuvant. H_2Por **1** proved to be a potent antimicrobial photosensitizer against both strains. Significantly, the KI addition increased the PDI efficiency, allowing substantial bacterial inactivation even at lowest tested concentrations and light doses. These results highlight the great potential of this boronic derivative for efficient clinical applications.



Scheme 1. Synthesis of H_2Por **1**.

Acknowledgements: Thanks to the University of Aveiro, University of Porto, and FCT/MCTES (Fundação para a Ciência e a Tecnologia and Ministério da Ciência, Tecnologia e Ensino Superior) for the financial support LAQV-REQUIMTE (LA/P/0008/2020, DOI: 10.54499/LA/P/0008/2020; UIDP/50006/2020, DOI: 10.54499/UIDP/50006/2020; and UIDB/50006/2020, DOI: 10.54499/UIDB/50006/2020), CESAM (UID/50006 + LA/P/0094/2020, DOI: 10.54499/LA/P/0094/2020), and COMPETE2030-FEDER-00799000, funded by FCT/MCTES through national funds. Daiane Maronde and Cátia Vieira thank FCT for their PhD scholarships (DOI: 10.54499/UI/BD/153613/2022 and SFRH/BD/150358/2019, respectively).

References

[1] A. Lalezadeh; M. Fadaee; S. Saedi; J. Nezhadi; M.A. Ozma; S. Ahmadi; M. Mobaseri; H. S. Kafil, Curr. Microbiol. 2025, 82, 295.
[2] A. Galstyan; R. Schiller; U. Dobrindt, Angew. Chem. Int. Ed. 2017, 56, 10362.
[3] D. Maronde; C. Vieira; J. E. R. Borges; A. Almeida; L. M.O. Lourenço, Dyes Pigm. 2026, 246, 113429.

Monoterpenoid selenophenes derived from (-)-carvone with GPx-like activity

João P. Telo[1,*], Luís F. Veiros[1], Vânia André[1], João Ferreira da Silva[1], Gonçalo C. Justino[1], Alexandra M. M. Antunes[1]

[1]*Centro de Química Estrutural, Institute of Molecular Sciences, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1049-001 Lisboa, Portugal*

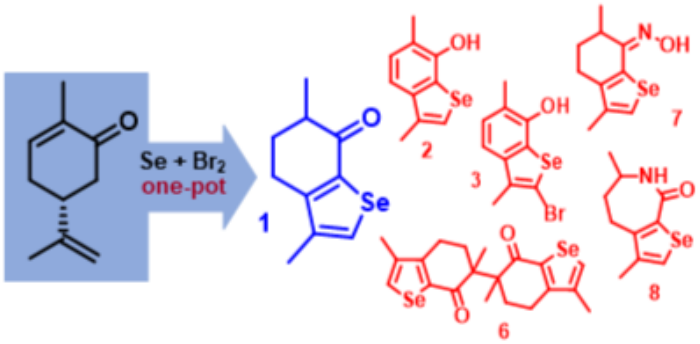
** E-mail: jptelo@tecnico.ulisboa.pt*

Organoselenium compounds have been recognized as potential therapeutic agents against several diseases. A significate number of selenium compounds show antitumor, antimicrobial, and antiviral properties, and have been suggested to be successful compounds in cancer chemoprevention and in cancer treatment.

Considerable efforts have been made into the synthesis of selenoderivatives of natural products, since this has been shown to generate enhanced or synergistic pharmacological activities. We report herein the one-pot reaction of the natural monoterpenoid (-)-carvone with selenium bromide which yields Mentoselenophenone **1**, together with minor amounts of phenols **2** and **3**.[1]

A number of derivatives of **1** have also been prepared: the α,α dimer **6**, the oxime **7** and its Beckmann rearrangement lactam **8**. Single crystal X-ray diffraction analysis confirmed the structure of compounds **1**, **4** and **6** without ambiguity. All except the lactam **8** show antioxidant GPx-like activity, with dimer **6** being the most active compound, followed by phenol **2** and oxime **7**. Studies on the potential biological effects of these compounds are in progress.

The synthesis of **1** proceeds through the reaction of the exocyclic carbon-carbon double bond and the endocyclic enol of (-)-carvone with the selenium bromide. The reactivity of enols towards selenium electrophiles have not been much used in the synthesis of selenophenes or other selenium compounds, and we think this might be an area to explore.



References

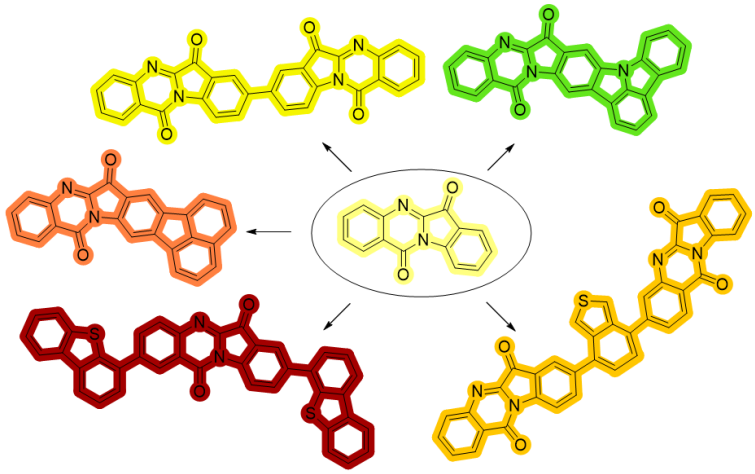
[1] Telo, J.P.; Veiros, L.F.; André, V.; Ferreira da Silva, J.; Justino, G.C.; Antunes, A.M.M.; Org. Biomol. Chem. 2025, 23, 2153–2162.

Cross-coupling approaches towards novel tryptanthrin derivatives

Cláudia Alves[1,2], Vítor Almodovar[1,2], João P. Prates Ramalho[3,4], Paulo D. Nunes Barradas[2], J. Sérgio Seixas e Melo[2], Anthony J. Burke[1,2]

*[1]Faculty of Pharmacy, University of Coimbra, Pólo das Ciências da Saúde, Azinhaga de Santa [2]Coimbra, 3000-548 Coimbra, Portugal. [2]University of Coimbra, Coimbra Chemistry Centre-Institute of Molecular Sciences (CQC-IMS), Departamento de Química, 3004-535 Coimbra, Portugal; [3]LAQV-REQUIMTE - University of Évora, Rua Romão Ramalho, 59, 7000-671 Évora, Portugal; [4]Departamento de Química, School of Science and Technology, University of Évora, Institute for Research and Advanced Studies, Rua Romão Ramalho, 59, 7000-671 Évora, Portugal; * E-mail: claudia.alves@ff.uc.pt*

Tryptanthrin is an indoloquinazoline alkaloid distinguished by its notable photophysical, photochemical, and redox behaviour.[1] Its structural adaptability—stemming from the ease with which functional groups can be modified—makes it a valuable platform in organic synthesis. Numerous natural and synthetic tryptanthrin derivatives have been described in the literature, largely examined for their diverse biological activities.[1,2] In this work, we employed several synthetic approaches—including Friedel–Crafts and Scholl reactions, as well as Suzuki–Miyaura, Kumada, and Buchwald–Hartwig cross-coupling protocols—to obtain new tryptanthrin-based molecules. We further evaluated their photophysical properties with the aim of assessing their potential as organic semiconductor materials (Scheme 1).



Scheme 1. Tryptanthrin-derived molecules envisioned based on the synthetic potential of the tryptanthrin core

Acknowledgements: We thank the Portuguese Foundation for Science and Technology (FCT) for funding the project ConChiMOL- New Structurally Contorted and Chiral Molecules for Optoelectronic Applications, (2022.01391.PTDC) and for scholarships (CDCA and VASA). The FCT is acknowledged for funding to CQC through projects UID/PRR/00313/2025 (https://doi.org/10.54499/UID/PRR/00313/2025) and UID/00313/2025 (https://doi.org/10.54499/UID/00313/2025) and the IMS (project LA/P/0056/2020 https://doi.org/10.54499/LA/P/0056/2020).

References

[1] Brandão, P., Marques, C., Pinto, E., Pineiro, M. & Burke, A. J. *New J. Chem.* **2021**, 45, 14633. Kaur, R.; Manjal, S. K.; Rawal, R. K.; Kumar, K. Bioorg Med Chem, 2017, 25, 4533–4552.

[2] a) Zou, Y.; Zhang, G.; Li, C.; Long, H.; Chen, D.; Li, Z.; Ouyang, G.; Zhang, W.; Zhang, Y.; Wang, Z. *Int J Mol Sci* **2023**, 24, 1450 b) Zhou, X., *RSC Med. Chem.*, **2024,**15, 1127.

Selective synthesis of purple *versus* green-coloured azo-dyes with halochromic and antimicrobial properties

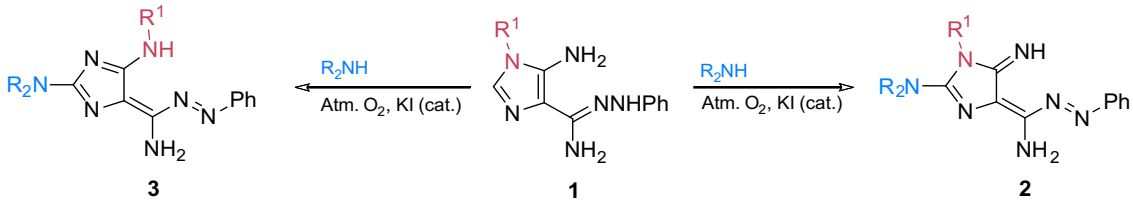
Mariana P. Silva[1] , Alice M. Dias[1,*]

[1]*Chemistry Research Centre, Department of Chemistry, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal*

** E-mail: ad@quimica.uminho.pt*

The use of dyes in industry is currently led by azo dyes, which are simple to manufacture and possess advantageous properties such as a wide range of colours, luminosity and good dyeing performance, allowing applications in numerous fields, namely photopharmacology and chemosensing [1]. The photophysical and biological attributes of these dyes can be improved through the addition of heterocyclic moieties, expanding the scope of their applications [2]. In particular, the addition of an imidazole scaffold enhances antimicrobial activity [3].

Previous work by the group led to the synthesis of a new class of purple-coloured azo dyes (**2**) with halochromic properties and potent antimicrobial activity against pathogenic yeast, mainly against *C. krusei* and *C. neoformans* [4]. The method to obtain these dyes has since been updated and the use of a more sustainable O_2/KI oxidant system allowed regeneration of the oxidant. Using this method, green-coloured azo dyes (**3**) were obtained, showing an even more significant red-shift in their absorption spectrum, while maintaining potent antimicrobial activity against *C. neoformans* [5]. The synthesis of both classes of dyes relies on the reaction between reported amidrazones **1** and secondary amines (**Scheme 1**). As they share key intermediates, deeper understanding of these synthetic pathways was essential to achieve selective synthesis of azo dyes **2** and **3**. The mechanisms and optimal conditions to obtain the selective synthesis of each class of 2-aminoimidale azo dyes, as well as a comparison of their photophysical, halochromic and antimicrobial properties, will be presented.



Scheme 1. Selective synthesis of 2-aminoimidazole azo dyes **2** and **3**.

Funding: The author Mariana P. Silva received a PhD fellowship (2025.01993.BDANA) by the Portuguese Foundation for Science and Technology (FCT).

Acknowledgements: This work was supported by the Portuguese Foundation for Science and Technology (FCT) in the framework of the Strategic Funding UID/00686/2025 (Chemistry Centre of University of Minho).

References

[1] Jerca, F.; Jerca, V.; Hoogenboom, R.; Nat. Rev. Chem. 2021, 6, 51-69.
[2] Mezgebe, K.; Mulugeta, E.; RSC Adv. 2022,12, 25932–25946.
[3] Siwach, A.; Verma, P. K.; BMC Chem. 2021, 15, 1–69.
[4] Dantas, D. et al.; Chem. Commun. 2023, 59, 2791-2794.
[5] Silva, M. P. et al.; Org Biomol Chem. 2025, 23, 4983-4996.

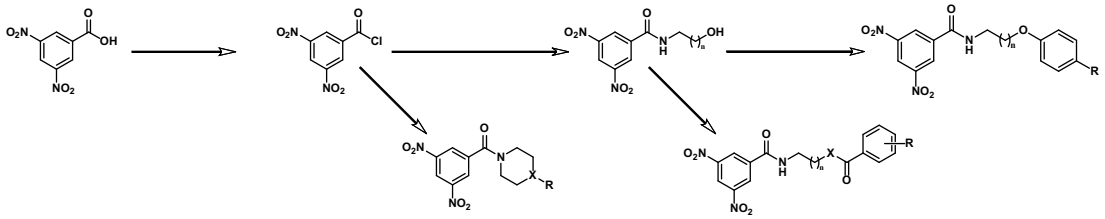
Design, synthesis and activity of flexible nitrobenzamides as antitubercular agents targeting DprE1

Tiago Delgado[1], J. P. Pais[2], A. Fortuna[1,3], P. J. Costa[3], D. Pires[1,4], E. Anes[1], L. Constantino[1*]

[1]Research Institute for Medicines (iMed.UL), Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal; [2]Selvita, Poland; [3]Instituto de Biosistemas e Ciências Integrativas (BioISI) and Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal.; [4]Global Health and Tropical Medicine, GHTM, Universidade Nova de Lisboa, 1349-008 Lisboa, Portugal.

** E-mail: lconstantino@ff.ulisboa.pt*

Tuberculosis has once again become the leading cause of death from a single infectious agent and remains one of the world's deadliest infectious diseases. Antimicrobial resistant strains are also a worrying concern among the scientific community, highlighting the urgent need for new therapeutic strategies [1]. One of the most promising drug targets is decaprenylphosphoryl-β-D-ribose 2'-epimerase (DprE1), an essential enzyme in the biosynthesis of the mycobacterial cell wall [2]. Nitrobenzamides are a class of inhibitors of this target that have shown potent antitubercular activities. These compounds are believed to act as suicide inhibitors, forming a covalent bond with Cys387 of DprE1 after a FAD-dependent activation of the nitro group, blocking in this way substrate access to the active site of the enzyme[2]." Our group has been exploring nitrobenzamide-based scaffolds, with a particular focus on introducing structural flexibility—an underexplored but potentially crucial factor for the inhibition efficacy [3,4]. The synthesis began with 3,5-dinitrobenzoic acid as the nitroaromatic core, which was coupled with linear or cyclic amines to generate the corresponding amides [3,4], followed by the introduction of terminal aromatic groups through ether, ester, or amide bonds [4]. Several compounds displayed promising activity (MIC 35–150 nM), supporting the importance of flexibility. Parallel computational studies were conducted to explore the structure–activity relationships, compare our molecules with known DprE1 inhibitors, and confirm the proposed mechanism of action. Together, these synthetic and computational results highlight the structural factors crucial for potency and provide a basis for the rational design of the next-generation of inhibitors.



Scheme 1. Overview of the synthesis of substituted amide derivatives starting from 3,5-dinitrobenzoic acid.

Funding: This research was funded by Fundação para a Ciência e Tecnologia (FCT), PhD Grant 2024.02626. It also received financial support from FCT (via iMed.ULisboa) from projects UIDB/04138/2020 and UIDP/04138/2020.

References

[1] Global Tuberculosis Report 2023. Geneva: World Health Organization; 2023; ISBN 978-92-4-008385-1.

[2] J. Piton et al. Structural studies of Mycobacterium tuberculosis DprE1 interacting with its inhibitors. Drug Discovery Today. 2017, pp. 526-533

[3] J. P. Pais et al. "Synthesis, Activity, Toxicity, and In Silico Studies of New Antimycobacterial N-Alkyl Nitrobenzamides." Pharmaceuticals 17,5 (2024) 608

[4] Delgado, Tiago et al. "Development of New Drugs to Treat Tuberculosis Based on the Dinitrobenzamide Scaffold." Pharmaceuticals 17,5 (2024) 559

Breaking cancer resistance through the combinatorial use of Ru- and Se-based compounds

Catarina Henriques[1,2]*; C. Riganti[3]; A. Valente[2]; A. M. M. Antunes[1]

[1]Centro de Química Estrutural, Institute of Molecular Sciences, Department of Chemical Engineering, Instituto Superior Técnico, University of Lisbon, Lisbon, Portugal; [2]Centro de Química Estrutural, Institute of Molecular Sciences and Department of Chemistry and Biochemistry, Faculty of Sciences, University of Lisbon, Lisbon, Portugal; [3]Department of Oncology, University of Torino, Torino, Italy.

** E-mail: catarina.a.henriques@tecnico.ulisboa.pt*

Cancer continues to be one of the top causes of death worldwide, with multidrug resistance (MDR) posing a significant obstacle to effective treatment [1,2]. Building on our previous work with ruthenium complexes and organoselenium compounds [3–6], we investigated a combined strategy to combat MDR in cancer by using selenium-based compounds alongside the ABC efflux pump inhibitor RT151 (a Ru(II)-cyclopentadienyl compound) in chemoresistant non-small cell lung cancer (NSCLC) cell lines. While structurally diverse families of selenium compound exhibited no individual cytotoxic effects, their combination with RT151 resulted in robust synergistic responses. Of the 10 combinatorial therapies tested, two demonstrated the greatest potential. Mechanistic studies have indicated that RT151 exerts its inhibitory effect on efflux pumps, thereby rendering cells more susceptible to the biological effects of selenium-based compounds. This has been demonstrated to be associated with mitochondrial dysfunction and mitochondrial protein sulfhydration. Importantly, these combinations exhibited notable selectivity towards cancer cells. Overall, our results highlight ruthenium–selenium combinations as promising dual-action therapies that can both kill NSCLC cells and enhance chemosensitivity in resistant cells. This study introduces a new hybrid approach that targets two different mechanisms to overcome MDR in cancer.

Acknowledgements: Fundação para a Ciência e a Tecnologia (FCT) is acknowledged for funding Centro de Química Estrutural (UIDB/00100/2020 and UIDP/00100/2020) and Institute of Molecular Sciences is an Associate Laboratory (LA/P/0056/2020). Joint funding from FCT and the COMPETE Program through grant RNEM-LISBOA-01-0145-FEDER-022125 funding are also gratefully acknowledged. Catarina Henriques acknowledge FCT for her PhD fellowship (UI/BD/154408/2023).

References

[1] Chen, T.; Xiao, Z.; Liu, X.; Wang, T.; Wang, Y.; Ye, F.; Su, J.; Yao, X.; Xiong, L.; Yang, D. H.; Pharmacol. Res. 2024, 202, 107099.
[2] Bhatia, K.; Asmita Das, B.; Life Sci. 2020, 258, 118134.
[3] Teixeira, R. G.; Belisario, D. C.; Fontrodona, X.; Romero, I.; Tomaz, A. I.; Garcia, M. H.; Riganti, C.; Valente, A.; Inorg. Chem. Front., 2021, 8, 1983–1996.
[4] Teixeira, R. G.; Salaroglio, I. C.; Oliveira, N. F. B.; Sequeira, J. G. N.; Fontrodona, X.; Romero, I.; Machuqueiro, M.; Tomaz, A. I.; M. Garcia, M. H.; Riganti, C.; Valente, A.; J. Med. Chem., 2023, 60, 14080-14094
[5] Martins, I. L.; Charneira, C.; Gandin, V.; Silva, J. L. F.; Justino, G. C.; Telo, J. P.; Vieira, A. J. S. C.; Marzano, C.; Antunes, A. M. M.; J. Med. Chem. 2015, 58, 4250−4265.
[6] Santos, I.; Ramos, C.; Mendes, C.; Sequeira, C.O.; Tomé, C.S.; Fernandes, D.G.H.; Mota, P.; Pires, R.F.; Urso, D.; Hipólito, A.; *et al.*; Nutrients. 2019, 11, 2523.

Developing an asymmetric catalytic version of the Barbier reaction: seeking new BACE-1 inhibitors

Maria G. Rodrigues[1]*, Mariana Pinto[1,2], Catarina A. Montargil[1,2], Anthony J. Burke[1,2]

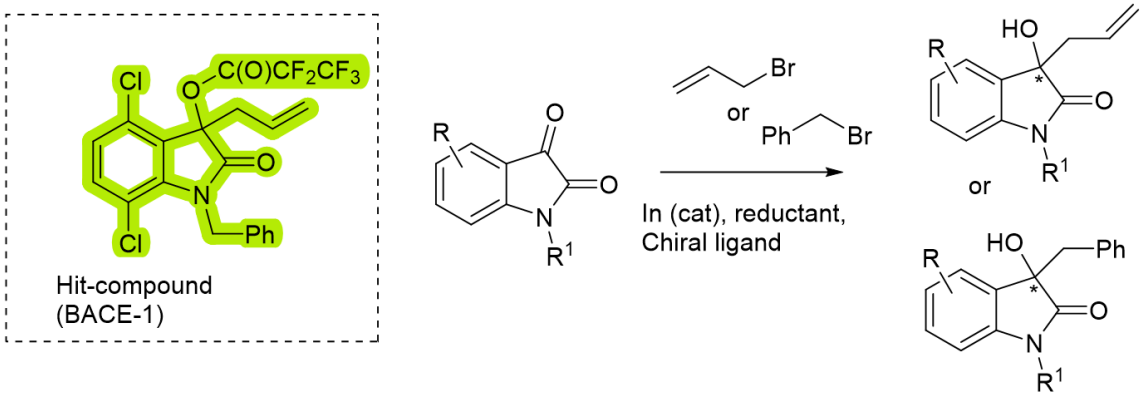
[1] *Laboratory of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Coimbra, 3000-548 Coimbra, Portugal.;* [2] *Coimbra Chemistry Centre – Institute of Molecular Sciences (CQC-IMS), Chemistry Department, University of Coimbra, 3004-535 Coimbra, Portugal.;*

** E-mail: mariadagracarodrigues0405@gmail.com*

Alzheimer's disease is a progressive and irreversible neurodegenerative disease and is characterized by the presence of amyloid plaques (Aβ), hyperphosphorylated tau protein, and neuronal damage [1]. It is necessary to develop and continue to search for alternative and effective methodologies.

Recently we have developed allylated oxindoles that were shown to inhibit the enzyme BACE-1 which is critical for Aβ formation. We have obtained interesting examples with good potential (Scheme 1 shows our Hit-compound) [2]. However, molecular docking has shown that one of the enantiomers is always more active than the other, and for this reason we became interested in the selective synthesis of the active enantiomers.

In this communication we discuss the development of an Indium catalysed asymmetric Barbier reaction to achieve this objective (Scheme 1).



Scheme 1. The asymmetric catalytic Barbier reaction for accessing chiral non-racemic BACE-1 inhibitors.

Acknowledgements: We thank the Fundação para a Ciência e a Tecnologia for funding through the strategic project UIDB/00313/2020 | UIDP/00313/2020 to Coimbra Chemistry Centre – Institute of Molecular Sciences (CQC IMS) and to LAQV-REQUIMTE through the project UIDB/500026/2020 | UIDP/50006/2020. COMPETE 2020 - Operational Programme for Competitiveness and Internationalization and Portuguese national funds via FCT – Fundação para a Ciência e a Tecnologia, under projects UIDB/04539/2020, UIDP/04539/2020 and LA/P/0058/2020.

References

[1] M, Y., & Shetty, N. S. (2025). Advances in the Synthetic Approaches to β-Secretase (BACE-1) Inhibitors in Countering Alzheimer's: A Comprehensive Review. *ACS Omega*, *10*(32), 35367–35433.

[2] Montargil, C. A., Pinto, M., Resende, R., Carreiro, E. P., García-Sosa, A. T., Santos, A. E., & Burke, A. J. (2025). Exploring the potential of new acetylated unsaturated Oxindole derivatives as multi-target inhibitors for BACE1 and BuChE. *Bioorganic & Medicinal Chemistry*, *131*, 118419–118419.

Light-triggered modulation of VEGFR2: photoresponsive sorafenib derivatives as antiangiogenic agents

Sara Hummeid [1*], Marta P. Carrasco[1], Patricia Remón[1,2], Uwe Pischel[1,2], Rui Moreira[3]

[1] *Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal;* [2] *CIQSO – Center for Research in Sustainable Chemistry, University of Huelva, Huelva, Spain.*

* *E-mail: s.hummeid@ff.ulisboa.pt*

Angiogenesis is tightly regulated in healthy adults but is essential for tumor growth [1,2]. VEGFR2, a key tyrosine kinase receptor, plays a central role in this process, making it an attractive target for anticancer therapy and for probing angiogenic signalling. Photopharmacology offers a strategy to reduce off-target effects by designing ligands that become active only upon light exposure [3,4].

Here, we present novel photoactivatable inhibitors derived from known VEGFR2 inhibitors and engineered to be switched on **in situ** using biocompatible wavelengths. Light-induced structural changes generate isomers with distinct geometries and differential activity toward VEGFR2. We synthesized and fully characterized new photoresponsive sorafenib derivatives and evaluated their biological activity before and after irradiation **Figure 1**. One compound showed particularly promising light-dependent inhibition, highlighting its potential as a tool for controlled drug delivery and the development of new antiangiogenic therapies. Further biological studies are ongoing.

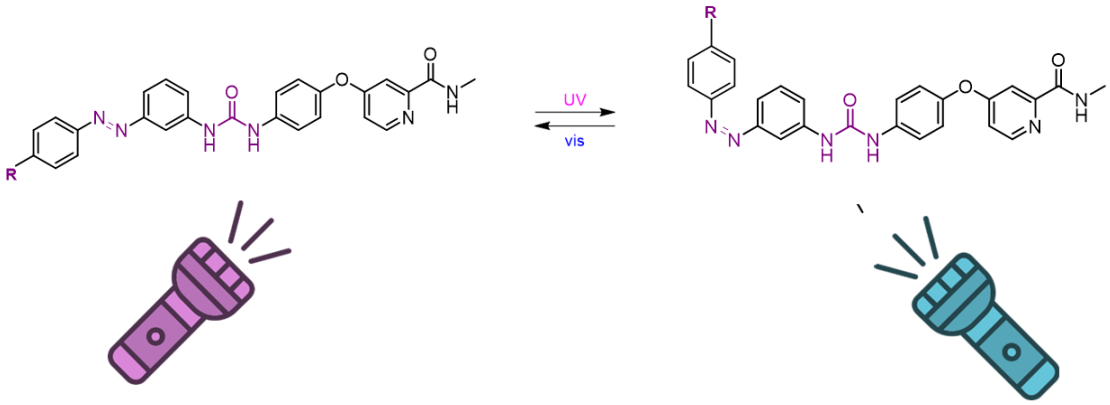


Figure 1. Photocotrollable sorafenib derivative.

Funding: The work was financially supported by Fundação para a Ciência e Tecnologia, Portugal (grant 2021.05453.BD) and by the Spanish Ministerio de Ciencia e Innovación (PID2020-119992GB-I00 for U.P.).

References

[1] González, S.D.; Marion, N.; Nolan, S.P.; *Chem. Rev.* **2009**, *109*, 3621.
[2] Hahn, F.E.; *Angew. Chem. Int. Ed.* **2006**, *45*, 1348.
[3] Kobauri, P.; Dekker, F.J.; Szymanski, W.; Feringa, B.L.; *Angew. Chem. Int. Ed.* **2023**, *62*, e202300681.
[4] Laczi, D.; Johnstone, M.D.; Fleming, C.L.; *Chem. Asian J.* **2022**, *17*, e202200200.

Length-dependent antimicrobial properties of peptide–ionic liquid conjugates

Inês Costa[1,*], Ana Gomes[1], Mariana Ferreira[1], Patrícia Correia[1], Iva Fernandes[1], Paula Gameiro[1], Paula Gomes[1]

[1] *LAQV/REQUIMTE - Department of Chemistry and Biochemistry, Faculty of Sciences, University of Porto, Portugal*
** E-mail: up202106843@fc.up.pt*

Antimicrobial resistance has become a major global health issue, risking the effectiveness of current treatments for several infections, including infected wounds, such as diabetic foot ulcers. Developing new compounds and improving existing therapeutics is therefore crucial [1]. Peptides are appealing drug candidates due to their biocompatibility, cell permeability, and non-immunogenic properties [2], however, their therapeutic application is constrained by size, structural stability, and production costs.

Previous work described by Gomes *et al.*, has shown a peptide-ionic liquid conjugate that combines wound-healing ability, provided by a cosmeceutical peptide, with antimicrobial activity due to the ionic liquid building block, making such conjugates suitable for treating diabetic foot ulcers [3,4]. To investigate the impact of peptide length on the antimicrobial efficacy and cytotoxic profile of the final conjugates, a series of shorter cosmeceutical peptides and peptidomimetic analogues was synthesized and tested *in vitro*. By changing both peptide length and other structural factors, we could establish a structure-activity relationship for antimicrobial efficacy and cytotoxic response. Overall, this work underscores the potential of peptide-ionic liquid conjugates as therapeutically promising solutions.

Funding:
This work received financial support from the PT national funds (FCT/MECI, Fundação para a Ciência e Tecnologia and Ministério da Educação, Ciência e Inovação) through the project UID/50006/2025 -Laboratório Associado para a Química Verde - Tecnologias e Processos Limpos.

Acknowledgements:
AG thanks PT national funds (FCT/MECI, Fundação para a Ciência e Tecnologia and Ministério da Educação, Ciência e Inovação) for AGs contract 2022.08044.CEECIND/CP1724/CT0004 (DOI: https://doi.org/10.54499/2022.08044.CEECIND/CP1724/CT0004) and for the exploratory project reference 2023.12331.PEX, (DOI https://doi.org/10.54499/2023.12331.PEX). IF acknowledges her assistant professor contract CEECINST/00064/2021.

References:

[1] Tang, K.W.K., B.C. Millar, and J.E. Moore, Antimicrobial Resistance (AMR). Br J Biomed Sci, 2023. 80: p. 11387.
[2] Wang, L., et al., Therapeutic peptides: current applications and future directions. Signal Transduct Target Ther, 2022. 7(1): p. 48.
[3] Gomes, A., et al., Boosting Cosmeceutical Peptides: Coupling Imidazolium-Based Ionic Liquids to Pentapeptide-4 Originates New Leads with Antimicrobial and Collagenesis-Inducing Activities. Microbiol Spectr, 2022. 10(4): p. e0229121.
[4] Gomes, A., et al., Enhancement of wound healing in diabetic mice by topical use of a peptide-ionic liquid conjugate. Int J Biochem Cell Biol, 2025. 180: p. 106753.

Luminol-based chemiluminescent cyanines as new internal light sources in photodynamic therapy

Joana Agostinho[1,*], Simão Gonçalves[1], Mariana Matias[2], Samuel Silvestre[1], Paulo Almeida[1]

[1]RISE-Health, Departament of Chemistry, Faculty of Sciences, University of Beira Interior, Rua Marquês de Ávila e Bolama, 6201-001 Covilhã, Portugal; [2]RISE-Health, Departament of Medical Sciences, Faculty of Health Sciences, University of Beira Interior, Avenida Infante D. Henrique, 6200-506 Covilhã, Portugal
** E-mail: joana.agostinho@ubi.pt*

Photodynamic Therapy (PDT) is an emerging therapeutic approach that uses light-activated photosensitizing compounds to produce reactive oxygen species with cytotoxic action, thus having antimicrobial and antitumor potential. Despite its numerous advantages, such as high selectivity and low toxicity, its clinical efficacy is limited by the poor penetration of laser light into tissues [1].

To overcome this limitation, this work focuses on the development of chemiluminescent cyanines based on the luminol system, capable of generating light *in situ*, which makes them effective in deeper tissues. Luminol and its analogues are compounds that typically, when oxidized by species such as hydrogen peroxide, abundant in cancer cells, decompose emitting light in different regions of the electromagnetic spectrum [2]. In cyanine luminescence case the exact emission is expected to depend on their structure and to be intense and not very dispersed.

Thus, this work presents the preparation of the key precursors benzimidazole and benzothiazole conveniently substituted with a methyl group in position 2, functionalized with the luminol system, capable of producing an extended structural set of chemiluminescent cyanines. The synthetic route chosen to precursor's preparation consists of 12 steps, of which 6 have been completed, with individual step yields ranging from 45% to 95%. The characterization of the compounds is performed using 1D and 2D ^{1}H- and ^{13}C-Nuclear Magnetic Resonance spectroscopy. In this way, the synthesis of different chemiluminescent cyanines from the precursors obtained is expected. The optical and luminescent properties of the synthesized cyanines will be evaluated, with a view to their applicability as light sources in PDT, namely spectral characterization, including stability and emission time, followed by the in vitro study of their cytotoxic effects in different cell lines.

Funding: Portuguese Foundation for Science and Technology (FCT) and European Regional Development Fund (FEDER) - financial support of the research center CICS-UBI (UIDB/0079/2020 and UIDP/00709/2020). UBI + Skills (Programa Impulso Jovens STEAM), University of Beira Interior. The NMR spectrometers are part of the National NMR Facility supported by FCT-Portugal (ROTEIRO/0031/2013-PINFRA/22161/2016, cofinanced by FEDER through COMPETE 2020, POCI and PORL and FCT through PIDDAC).

References

[1] Zhang, Y.; Hao, Y.; Chen, S.; Xu, M. Photodynamic therapy of cancers with internal light sources: Chemiluminescence, Bioluminescence, and Cerenkov Radiation. Front Chem. 2020, 8:770.

[2] Lu, Z.; Wang, Y.; Zhang, P.; Sheng, Y.; Sun, Y.; Bradley, M.; Zhang, R. Design and in vitro photodynamic evaluation of self-illuminating nanospheres loaded with polyurethane containing protoporphyrin IX for anticancer and antibacterial applications. J Mater Sci. 2025, 60, 16351–16363.

Photoactive glycodendritic conjugates for cancer imaging and therapy

Gustavo Caldeira*, Cláudia P. S. Ribeiro, Sara R. D. Gamelas, João P. C. Tomé

Centro de Química Estrutural & Institute of Molecular Sciences, Departamento de Engenharia Química, Instituto Superior Técnico – Universidade de Lisboa, 1049-001, Lisbon, Portugal

** E-mail: gustavo.caldeira@tecnico.ulisboa.pt*

Although substantial progress has been made in cancer diagnosis and therapy, the disease remains a major health challenge in developed countries, underscoring the continued need for improved targeting and treatment strategies [1,2]. Among current approaches, fluorescence imaging (FI) provides a powerful tool for real-time visualization of cancer and treatment progression, while photodynamic therapy (PDT) enables spatially controlled therapy [3]. Nevertheless, many photosensitizers (PS) and fluorophores (Fl) (e.g. BODIPYs and porphyrins), suffer from hydrophobicity, which limits aqueous solubility and selective accumulation in tumors [4]. A promising strategy to overcome these issues involves conjugation with carbohydrates, which can enhance water solubility and exploit the overexpression of carbohydrate-binding proteins on cancer cell surfaces to improve targeting [5]. In this context, glycodendritic systems offer a versatile approach for optimizing the functional features of such bioconjugates [5].

Here, we report the design and synthesis of new bioconjugates modified with dendritic scaffolds functionalized with distinct carbohydrates (Figure 1).

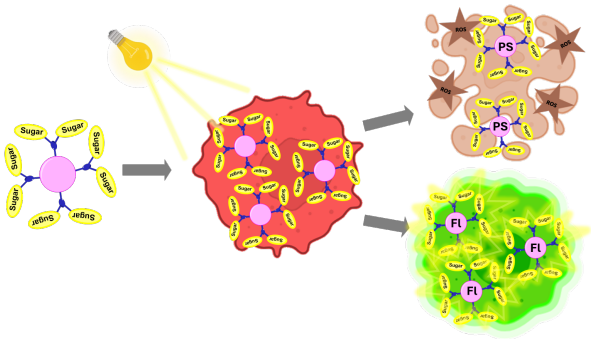


Figure 1. Photoactive Glycoconjugates and their applications in PDT and FI.

Acknowledgements: Thanks are due to Centro de Química Estrutural (UIDB/00100/2020, https://doi.org/10.54499/UIDB/00100/2020, and UIDP/00100/2020, https://doi.org/10.54499/UIDP/00100/2020), and to Institute of Molecular Sciences (LA/P/0056/2020, https://doi.org/10.54499/LA/P/0056/2020), both funded by Fundação para a Ciência e a Tecnologia.

References

[1] World Health Organization (WHO). Cancer; Geneva, Switzerland, 2019. Available online: https://www.who.int/health-topics/cancer (accessed in 2025).
[2] Ethirajan, M.; Chen, Y.; Joshi, P.; Pandey, R. K.; Chem. Soc. Rev., 2011, 40, 340–362.
[3] Mao, Z.; Kim, J. H.; Lee, J.; Xiong, H.; Zhang, F.; Kim, J. S.; Coord. Chem. Rev., 2022, 476, 214908.
[4] Cheng, H.; Cao, X.; Zhang, S.; Zhang, K.; Cheng, Y.; Wang, J.; Zhao, J.; Zhou, L.; Liang, X.; Yoon, J.; Adv. Mater., 2023, 35, 2207546.
[5] Pereira, J. C.; Pereira, P. M. R.; Beirão, S.; Girão, H.; Tomé, J. P. C.; Fernandes, R.; JPP, 2023, 27, 471–478.

Optimizing SIRT1 activators for selectivity: a structure-based strategy to reduce off-target effects

Bernardo Fragoso[1], Anthony Burke[1,2], Maria Manuel C. Silva[1,3]

[1] *Faculty of Pharmacy, University of Coimbra, 3000-548, Coimbra, Portugal.*
[2] *University of Coimbra, Coimbra Chemistry Centre-Institute of Molecular Sciences (CQC-IMS), Departamento de Química, 3004-535 Coimbra, Portugal.*
[3] *Centre for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal.*
Email: bernardo.filipe2001@hotmail.com

Sirtuins (SIRTs) are NAD^+-dependent deacetylases that regulate key metabolic pathways and multiple cellular processes, including inflammation, oxidative stress, apoptosis, proliferation, senescence, and DNA repair.[1-2] Among the seven mammalian sirtuins, SIRT1 is the most extensively studied and has been associated with lifespan extension and neuroprotection, as well as with cardiovascular and oncogenic processes when dysregulated.[3-6] Sirtuin Activating Compounds (STACs), such as the natural compound resveratrol and synthetic Sirtris molecules, enhance SIRT1 activity but frequently show limited selectivity, leading to off-target effects.[7]

This work aimed to identify more selective SIRT1 activators using computational approaches. Molecular docking studies were performed in SeeSAR, both against SIRT1 and against a panel of predicted off-targets. From an initial compound library, the highest-affinity SIRT1 binders were identified, and structural analogues were designed to improve affinity while reducing interactions with off-targets. The most selective candidates were prioritized.

References

[1] Haigis, M. C.; Sinclair, D. A. *Annu. Rev. Pathol.* **2010**, *5*, 253–295.
[2] Chang, H.-C.; Guarente, L. *Trends Endocrinol. Metab.* **2014**, *25*, 138–145.
[3] Guarente, L. *Cold Spring Harb. Symp. Quant. Biol.* **2011**, *76*, 81–90.
[4] Donmez, G.; Outeiro, T. F. *EMBO Mol. Med.* **2013**, *5*, 344–352.
[5] Houtkooper, R. H.; Cantó, C.; Wanders, R. J.; Auwerx, J. *Endocr. Rev.* **2010**, *31*(2), 194–223.
[6] Lin, Z.; Fang, D. Genes Cancer. **2013**, 4, 97–104.
[7] Hubbard, B. P.; Sinclair, D. A. *Trends Pharmacol. Sci.* **2014**, *35*, 146–154.

Synthesis of magenta-coloured imidazole-based azo dyes

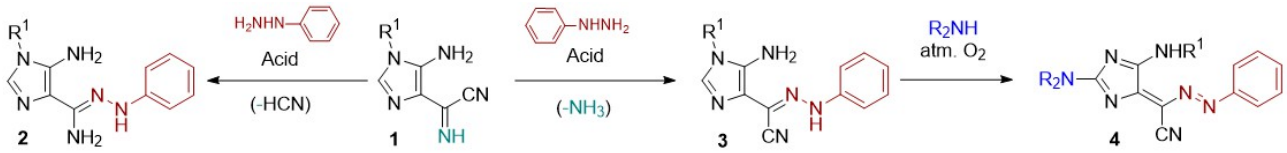
Margarida Fernandes[1], Alice M. Dias[1,*]

[1] CQ-UM – Chemistry Centre, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal

** E-mail: ad@quimica.uminho.pt*

Imidazoles are heterocyclic compounds that occupy a noticeable place in medicinal chemistry, due to their wide structural diversity and recognised bioactivity [1]. Azo dyes are highly versatile chromophores with significant tuneable electronic structures, strong halochromic responses, and broad therapeutic potential [2]. Heteroaryl azo dyes frequently exhibit enhanced photophysical properties and biological activities. Aminoazobenzenes constitute a prominent subclass of azo dyes in which electron-donating amino groups strongly modulate the π–π* and n–π* transitions of the azobenzene chromophore, enhancing intramolecular charge-transfer characteristics [3].

In our research group, studies on the condensation of 4-cyanoformimidoyl 5-aminoimidazole precursors (**1**) with aromatic hydrazines in acidic medium showed that 5-aminoimidazole 4-carboxamidrazones (**2**) or imidazole-based hydrazonoyl cyanides (**3**) may be obtained, depending on the reaction conditions. The amidrazones **2** underwent rapid oxidation in the presence of atmospheric air followed by the addition of secondary amines, leading to novel purple or green-coloured azoimidazole dyes [4,5]. As the structures of 4-hydrazonoyl cyanides **3** and 4-carboxamidrazones **2** both share the 5-aminoimidazole and phenyl hydrazone moieties, previous formation of azoimidazoles from amidrazones **2** prompted us to evaluate the reactivity of compounds **3** with secondary amines in contact with atmospheric air. A fast reaction occurred with the formation of dark-magenta solids, which were identified as the azo dye structures **4** based on the NMR, IR and MS spectroscopic data (**Scheme 1**). Synthesis and characterisation results will be presented and discussed.



Scheme 1. Synthesis of azo dyes **4** from imidazoles **1**, phenyl hydrazine and secondary amines.

Acknowledgements: This work was supported by the Portuguese Foundation for Science and Technology (FCT) in the framework of the Strategic Funding UID/00686/2025 (Chemistry Centre of University of Minho)

References

[1] Ribeiro, A. I.; *et al.*; Bioorg Med Chem Lett 2014, Volume 24, pp. 4699–4702
[2] Alsantali, R. I.; *et al.*; Elsevier 2022, Volume 199, 110050
[3] Jerca, F. A.; Jerca, V. V.; Hoogenboom, R.; Nat Rev Chem 2022, Volume 6, pp. 51-59
[4] Dantas, D. *et al.*; Chem Com 2023, Volume 59, 2791–2794.
[5] Silva, M. P.; *et al.*; Org Biomol Chem 2025, Volume 23, 4983-4996.

Design and synthesis of tryptophanol-derived PROTACs for selective degradation of DNA-contact p53 mutants

Tomás G. Monteiro[1,*], Ricardo J. Ferreira[1], Maria M. M. Santos[1,*]
[1]*Research Institute for Medicines (iMed. ULisboa), Faculdade de Farmácia Universidade de Lisboa, Lisboa, Portugal.*
** E-mail: mariasantos@ff.ulisboa.pt / tomasmonteiro1@edu.ulisboa .pt*

Proteolysis-targeting chimeras (PROTACs) have emerged as a novel modality in drug discovery, offering a catalytic mechanism of action and the ability to degrade, rather than inhibit, disease-driving proteins. Several PROTACs have already advanced into clinical trials, demonstrating encouraging efficacy and safety profiles and validating targeted protein degradation as a viable therapeutic strategy (for example: ARV-471 to degrade the estrogen receptor). [1]
The tumour suppressor protein p53 remains a central focus in cancer biology. Mutations in the *TP53* gene occur in nearly half of human cancers, with most clustering in the protein's DNA-binding domain. [2] Among these, DNA-contact mutants (for example: R273H, R280K) constitute a clinically challenging subgroup linked to therapeutic resistance and increased metastatic behavior. [3]
To address these challenges, we pursued the development of PROTACs capable of degrading DNA-contact p53 mutants. Building on our group's earlier discovery of enantiopure tryptophanol-derived isoindolinones as ligands that reactivate mutant p53, [4] we designed and synthesized new PROTACs incorporating these scaffolds (Figure 1).

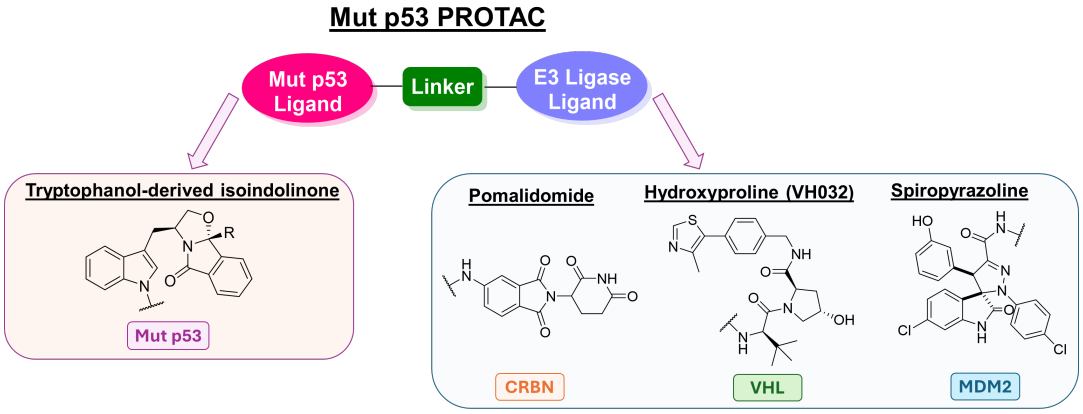


Figure 1. Design and Synthesis of novel PROTACs to degrade DNA-contact p53 mutants with different E3 ligase-ligands.

Funding: This work was supported by National Funds (Fundação para a Ciência e a Tecnologia) through iMed.ULisboa (UID/04138/2025), LISBOA2030-FEDER-00735600 (Project nº 16199) and PhD fellowship 2022.11539.BD (R. Ferreira).

References

[1] Vetma, V.; O'Connor, S.; Ciulli, A. *Annual Rev of Cancer Bio*. **2025**; 9: 119-140
[2] Hassin, O.; Oren, M. *Nat Rev Drug Discov*. **2023**;22: 127-144.
[3] Huang, Y.; Jiao, Z.; et al., *Eur J Med Chem*. **2024**; 265: 116-121.
[4] a) Lopes, F.; et al., *ChemMedChem*. **2025**;20: e202500600. b) Barcherini, V. ; et al., *ChemMedChem*. **2021**;16: 250-258. c) Ferreira, R.J. ; et al., *ACS Pharmacol Transl Sci*. **2025**;14: 655-674. d) Espadinha, M. ; et al., *Eur. J. Med. Chem*. **2022** ;241 : 114637.

Amphiphilic D-A-π-A benzothiadiazoles: photophysical insights for sensing and bioimaging applications

Mathilde L. Boland[1], Sónia C. S. Pinto[1,2], Lígia C. Gomes-da-Silva[2], João Pina[2], Susana P. G. Costa[1], M. Manuela M. Raposo[1,*]

[1]*Chemistry Centre of the University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal;*
[2]*University of Coimbra, CQC-IMS, Department of Chemistry, Rua Larga, 3004-535 Coimbra, Portugal*
** E-mail: mfox@quimica.uminho.pt*

Recently, donor-π-acceptor (D-π-A) benzothiadiazole derivatives have drawn significant attention due to their tunable optical and electronic properties, along with effortless functionalization, high photostability, and biocompatibility [1-3], supporting applications in optoelectronics, optical chemosensing, and bioimaging [4-6]. In this communication, we report the design, synthesis and photophysical studies of the aldehyde precursor (**1**) and two positively charged amphiphilic benzothiadiazoles (**2**-**3**) with a D-A-π-A structure (**Figure 1A**). The compounds showed a promising detection for cyanide in dimethylsulfoxide, as well as a cellular uptake with cytoplasmatic accumulation in structures likely in lysosomes and/or endosomes of 4T1 cells (**Figure 1B**). Overall, the experimental and theoretical results elucidate how structure and solvent polarity influence photophysics, guiding the design of charge-transfer chromophores for bioimaging, photoacoustic tomography, and optical chemosensing.

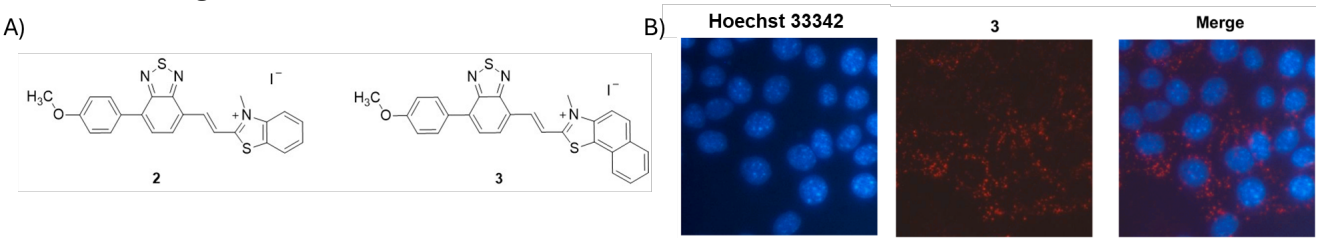


Figure 1. A) Structures of D-A-π-A benzothiadiazole derivatives **2**-**3**. B) Representative images of 4T1 cells incubated with benzothiadiazole **3** for 3 h (red), and cell nucleus stained with Hoechst 33342 (blue).

Funding: The authors acknowledge the Portuguese Foundation for Science and Technology (FCT), for the Strategic Funding to Centro de Química da Universidade do Minho (CQ-UM, UID/00686/2025), a PhD grant to S.C.S. Pinto (2022.12455.BD) and for funding Coimbra Chemistry Centre projects UIDB/00313/2025 and UIDP/00313/2025. Thanks are also due to the Portuguese NMR Network.

References

[1] Neto, B. A. D.; Correa, J. R.; Spencer, J.; Chem. Eur. J., 2022, 28, e202103262.
[2] Tu, Y.; Zhou, Y.; Zhang, D.; Yang, J.; Li, X.; Ji, K.; Wu, X.; Liu, R.; Zhang, Q.; ACS Appl. Bio Mater., 2021, 4, 5222-5230.
[3] Freidus, L.G.; Pradeep, P.; Kumar, P.; Choonara, Y.E.; Pillay, V. Drug Discov. Today 2018, 23, 115–133.
[4] Fernandes, S. S. M.; Pereira, A.; Ivanou, D.; Mendes A.; Raposo, M. M. M.; Dyes Pigm., 2018, 151, 89-94.
[5] Sun, Y. T.; Zhang, C.; Gao, L. X.; Liu, M. M.; Yang, Y.; Shao, A.; Zhou, Y. B.; Zhu, Y. L.; Li, J.; Wang, W. L.; ChemPhysChem, 2023, 24, 17.
[6] Boland, M.; Pinto, S.; Gomes-da-Silva, L. C.; Pina, J.; Costa, S. P. G.; Raposo, M. M. M.; Dyes Pigm., 2025, 240, 112825.

Synthesis of 2-aminopurines and pyrrolo[2,3-*d*]imidazoles from common imidazole precursors: mechanistic studies

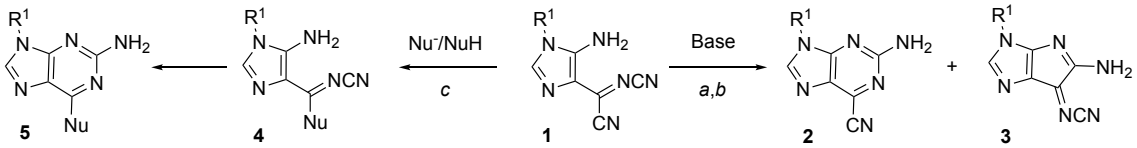
Paulo Pereira[1], João Ribeiro[1], Nádia Senhorães, Paulo J. G. Coutinho[2], Alice M. Dias[1,*]

[1] *CQ-UM – Chemistry Centre of University of Minho, Campus de Gualtar, 4710-057 Braga*
[2] *CF-UM-UP – Centre of Physics of Minho and Porto Universities; and LaPMET – Laboratory of Physics for Materials and Emergent Technologies, University of Minho, Campus de Gualtar, 4710-057 Braga*

** E-mail: ad@quimica.uminho.pt*

The development of the imidazole-based compounds is rapidly expanding, not only because this heterocycle is found in several natural compounds, but also because it is part of multiple classes of approved drugs [1]. Playing several important roles in the cell, purine nucleobases have been a valuable source of inspiration in the drug design of purine-based compounds with a wide range of biological activities [2]. Pyrrole is another important scaffold present in co-factors and other important natural products, and therapeutic applications of synthetic pyrroles include a diversity of biological activities [3].

As part of a research program aiming to develop new 2-aminopurine derivatives from imidazole precursors and cyanamide, a series of key intermediates **1** were obtained in very good yield [4,5]. A comprehensive study on the reactivity of these intermediates led us to find that they undergo three competitive reactions in the presence of bases: (a) intramolecular cyclization to obtain highly fluorescent 2-amino-6-cyanopurines **2**; (b) intramolecular cyclization to obtain 5-aminopyrrolo[2,3-*d*]imidazoles **3**; and (c) nucleophilic addition to generate imidazoles **4**, the key precursors in the synthesis of important 6-substituted 2-aminopurines **5**. (**Scheme 1**). Synthetic studies, theoretical calculations and mechanisms will be presented and discussed.



Scheme 1: The synthesis of 2-aminopurines **2** and **4**, and 5-aminopyrrolo[2,3-*d*]imidazoles **3** from imidazoles **1**.

Acknowledgements: The authors thank the Foundation for Science and Technology (FCT) for financial support through the Chemistry Center of the University of Minho (UID/00686/2025) and the Centre of Physics of the Universities of Minho and Porto (UID/04650/2025).

References

[1] Alghamdi, S. S.; *et al.*; Drug Des. Devel. Ther., 2021, Volume15, 3289–3312.
[2] Legraverend, M.; *et al.*; Bioorg. Med. Chem., 2006, Volume 14, 3987.
[3] Basha, N.J.; *et al.*; Mol Divers, 2022, Volume 26, 2915–2937.
[4] Gonçalves, J.M.; *et al.*; Eur. J. Org. Chem 2023, Volume 26, e202300176.
[5] Senhorães, N. R..; *et al.*; Org. Biomol. Chem. 2024, Volume 22, 1500 – 1513.

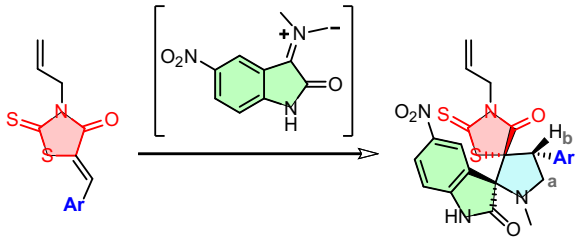
1,3-Dipolar cycloaddition of *N*-allyl rhodanines: synthesis and anticancer evaluation of spiro derivatives

Redouane Er-raqioui[1,2,3], José A. S. Cavaleiro[2], M. Amparo F. Faustino[2], Maurizio Viale[4], El Mostapha Rakib[1,3], Maria da Graça P. M. S. Neves[2], Florbela Pereira[5], Nuno M. M. Moura[2]

[1] *Laboratory of Molecular Chemistry, Materials and Catalysis, Faculty of Sciences and Technics, Sultan Moulay Slimane University, Beni-Mellal, BP 523, Morocco.*
[2] *LAQV-REQUIMTE, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal.*
[3] *Higher School of Technology, Sultan Moulay Slimane University, BP 336, Fkih Ben Salah, Morocco.*
[4] *U.O. Bioterapie, IRCCS Ospedale Policlinico San Martino, L.go R. Benzi, 10, 16132 Genova, Italy.*
[5] *LAQV-REQUIMTE, Department of Chemistry, NOVA School of Science and Technology, Universidade Nova de Lisboa, 2829-516 Caparica, Portugal.*
** E-mail: gneves@ua.pt*

Rhodanine is a versatile heterocyclic scaffold widely explored in the development of biologically active molecules, including compounds with notable anticancer potential [1]. Among synthetic strategies, 1,3-dipolar cycloaddition with azomethine ylides provides a powerful route to access spiro-oxindole and pyrrolidine-based frameworks, which are often associated with enhanced biological activity [2].

This communication discusses the reactivity of *N*-allyl 5-arylidene rhodanine derivatives with azomethine ylides generated from 5-nitroisatin and sarcosine, leading to new spiro-oxindole cycloadducts (**Scheme 1**). Their structural characterization, anticancer activity against A2780 (ovarian), A549 (lung), and MDA-MB-231 (breast) cell lines, and molecular docking studies will be presented. The docking results indicate favourable interactions with *h*15-LOX-2, supporting a possible anticancer mechanism and reinforcing the potential of these rhodanine-based cycloadducts.



Scheme 1. General structure of adducts from *N*-allyl 5-arylidene rhodanines and azomethine ylides.

Funding and Acknowledgements:
The authors acknowledge financial support from the University of Aveiro and FCT/MCTES (UID/50006/2023, LAQV) and thank the Erasmus+ program for supporting student mobility. N. M. M. Moura and Florbela Pereira thank FCT for their Assistant Research Positions (2023.06495.CEECIND/CP2840/CT0031 and CEECIND/01649/2021, respectively). Support from the Italian Ministry of Health through the "Ricerca Corrente 2024" grant is also gratefully.

References

[1] Mousavi, S. M.; Zarei, M.; Hashemi, S. A.; Babapoor, A.; Amani, A. M. *Nanomedicine & Biotechnology* **2019**, *7*, pp. 1132–1148.
[2] Pookkandam, S.; Parambil, S.; Veettil, P.; Dehaen, W. *Synthesis* **2022**, *54*, pp. 910–924.

First identification and characterization of a novel psychoactive substance: *N*-isopropylbutylone in a Portuguese seized sample

Diogo Videira-Quintela[1,*], Helena Gaspar[2], Maria João Caldeira[1]

[1]Laboratório de Polícia Científica da Polícia Judiciária (LPC/PJ), Novo edifício Sede da Polícia Judiciária, Rua Gomes Freire, 1169-007 Lisboa, Portugal; [2]BioISI – Biosystems and Integrative Sciences, Universidade de Lisboa, Lisboa, Portugal

** E-mail: diogo.quintela@pj.pt*

Synthetic cathinones is a group of Novel Psychoactive Substances (NPS) that continue to emerge rapidly in illicit drug markets, posing significant risks due to their higher potency and unpredictable pharmacology [1]. The structural diversity is a challenge for routine analytical workflows, especially in the presence of positional isomers. This study reports the first detection of a novel synthetic cathinone in Portugal, seized by the Portuguese Criminal Police. The compound was detected and identified by the Portuguese Forensic Science Laboratory and then confirmed with the collaboration of the Faculty of Sciences from the University of Lisbon. Firstly, the seized powder was analysed by colorimetric assays and GC-MS, which allowed the identification of the seized powder as a synthetic cathinone (as the major component), more specifically *N*-propylbutylone or *N*-isopropylbutylone. After that, ATR-FTIR was used as a second technique, thereby enabling the identification of the compound as *N*-isopropylbutylone. Finally, the structural confirmation was made by NMR spectroscopy, marking its first recorded identification in Portugal.

Acknowledgements: This work was done within the scope of the protocol established between the Forensic Science Laboratory from Portuguese Criminal Police and Faculty of Sciences from the University of Lisbon. The authors wish to thank experts and staff from the Drugs and Toxicology Sector of Forensic Science Laboratory from Portuguese Criminal Police for technical and forensic support.

References

[1] UNODC, The challenge of New Psychoactive Substances – A technical update (United Nations publication, 2024).

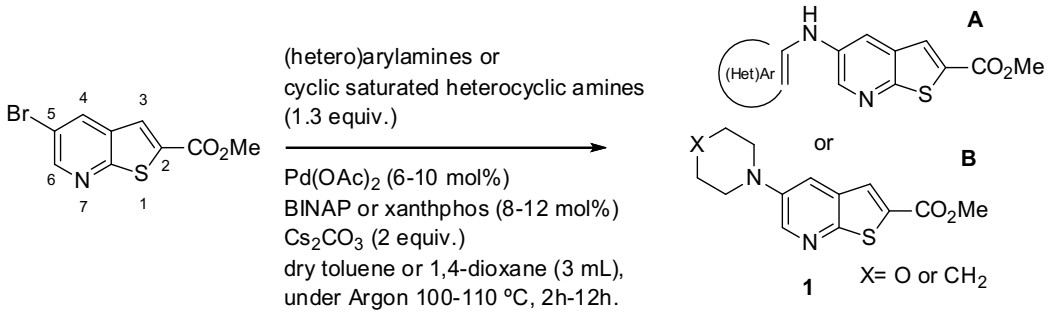
Synthesis, antiparasitic activity and SARs of methyl 5-(hetero)aryl or alkylaminothieno[2,3-*b*]pyridine-2-carboxylates

Juliana P. Sousa[1], Francisco Ribeiro[1], Nuno Santarém[2], Anabela Cordeiro-da-Silva[2,3], Maria-João R.P. Queiroz[1*]

[1]*Centre of Chemistry (CQ-UM), University of Minho, Gualtar, 4710-057 Braga, Portugal*
[2] *Host-Parasite Interactions, IBMC/I3S, Rua Alfredo Allen, 208, 4200-135 Porto, Portugal*
[3] *Laboratório de Microbiologia, Departamento de Ciências Biológicas, Faculdade de Farmácia, Universidade do Porto, Portugal*
** E-mail: mjrpq@quimica.uminho.pt*

The palladium-catalyzed C-N cross-coupling, Buchwald-Hartwig amination, has become a widely used method for synthesizing diarylamines from arylhalides and anilines [1]. Thieno[2,3-*b*]pyridine derivatives are of particular interest owing to their wide-ranging biological properties, including anti-inflammatory, antiparasitic, antiviral, antifungal, and antidiabetic activities [2].

In this work, we describe the synthesis of new twenty methyl-5-[(hetero)aryl- or alkylamino]thieno[2,3-*b*]pyridine-2-carboxylates **1** in good to high yields using a Buchwald–Hartwig coupling of methyl 5-bromothieno[2,3-*b*]pyridine-2-carboxylate with aniline derivatives, heteroarylamines (**Scheme 1A**), and saturated heterocyclic amines (**Scheme 1B**). Compounds **1** were fully characterized by m.p.,^{1}H and ^{13}C NMR and HRMS.



Scheme 1A and B. Synthesis of methyl 5-(hetero)aryl or alkylaminothieno[2,3-*b*]pyridine-2-carboxylates **1**.

The antiparasitic activity of amines **1** was evaluated against *Trypanosoma brucei* and *Leishmania infantum* promastigotes, as well as intracellular amastigotes. Cytotoxicity was assessed in PMA-differentiated THP-1 cells using the MTT assay. Structure-activity relationships (SARs) were identified and will be discussed. The most promising compounds presented IC_{50} values below 10 μM and no significant cytotoxicity (CC_{50} > 100 μM), highlighting them as promising lead candidates.

Acknowledgements: Thanks are due to FCT-Portugal for financial support to CQ-UM (UID/0686) and COST Action 21111 OneHealthDrugs.

References

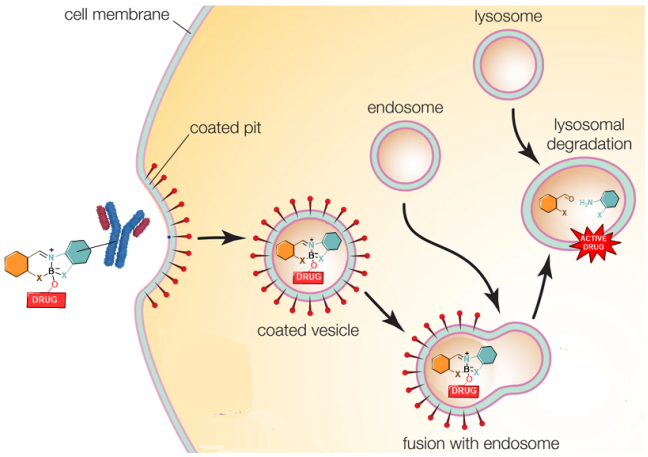
[1] Dorel, R.; Grugel, C.P.; Haydl, A.M. *Angew. Chem. Int. Ed.* **2019**, *58*, 17118-17129
[2] Abuelhassan, S.; Bakhite, E.A.; Abdel-Rahman, A.E.; El-Mahdy, A.F.M.; Saddik, A.A.; Marae, I.S.; Abdel-Hafez, S.H.; Tolba, M. *J Heterocycl. Chem.* **2023**, *60*, 458-470.

AZABY as a novel pH-sensitive linker for targeted drug conjugates

Eduardo F.F. Reis[1*], Pedro M.P. Góis[1], Uwe Pischel[2], David Ng[3], Fábio M.F. Santos[1]

[1] Research Institute for Medicines (iMed.ULisboa) Faculdade de Farmácia, Universidade de Lisboa, Portugal [2] CIQSO-Centre for Research in Sustainable Chemistry and Department of Chemistry University of Huelva, Spain [3] Max Plank Institute for Polymer Research, Germany
** E-mail: eduardofreis@edu.ulisboa.pt*

The UN Sustainable Development Agenda highlights the need to reduce premature mortality from non-communicable diseases, including cancer, by 2030. We present the AZABY platform, based on B-complexes engineered as pH-responsive linkers for use in antibody–drug conjugates (ADCs). ADCs improve on the limited selectivity of conventional therapies, and their performance relies on the linker chemistry that modulates drug release [1]. B-complexes offer new opportunities, B–O bonds have tunable electronic properties that enable precise pKa adjustment and promote faster cleavage under acidic lysosomal conditions [2]. This platform stands out for its modularity, multifunctionality and hydrolytic stability tuning [3]. Recent studies show a 7-fold faster release at pH 4.5 versus pH 7.4, underscoring the potential of this platform for safer and more effective cancer therapeutics.



Scheme 1: Mechanism of action of an antibody–drug conjugate (ADC) containing a AZABY as a pH-sensitive linker

Acknowledgements: Agradecemos à Fundação para a Ciência e Tecnologia pelo apoio financeiro. (2021.04125.CEECIND; 2023.14170.PEX https://doi.org/10.54499/2023.14170.PEX. ; PTDC/QUI-OUT/3989/2021 and *UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025)*).

References

[1] Yang, X., Pan, Z., Choudhury, M. R., Yuan, Z., Anifowose, A., Yu, B., Wang, W., & Wang, B. (2020). *Medicinal Research Reviews*, *40*(6), 2682–2713.
[2] António, J. P. M., Russo, R., Carvalho, C. P., Cal, P. M. S. D., & Gois, P. M. P. (2019). *Chemical Society Reviews*, *48*(13), 3513–3536.
[3] Taniguchi, T. (2022). *Chemistry – A European Journal*, *28*(19), e202104333.

pH-Responsive ruthenium-peptide conjugates for metastatic breast cancer targeting

Marco Sá[1,*], Filipa Mendes[2], Fernanda Marques[2], María A. Jiménez[3], Tânia S. Morais[4,5]

[1] Centro de Química Estrutural, Institute of Molecular Sciences, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal; [2] Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico, Universidade de Lisboa, Estrada Nacional 10 (km 139, 7), 2695-066 Bobadela LRS, Portugal; [3]Institute of Physical Chemistry Blas Cabreras (IQF-CSIC), Serrano 119, E-28006 Madrid, Spain; [4]Centro de Química Estrutural, Institute of Molecular Sciences, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1, 1049-001 Lisboa, Portugal; [5]Associação do Instituto Superior Técnico para a Investigação e Desenvolvimento (IST-ID), Avenida António José de Almeida, 12, Lisboa, 1000-043, Portugal
** E-mail: marcosa@alunos.fc.ul.pt*

Metastatic breast cancer (MBC) remains a major clinical challenge, representing a significant fraction of breast cancer diagnoses. Despite advances in treatments, there is still no cure for MBC, and current therapies exhibit limited efficacy and often cause severe side effects due to the lack of selectivity [1]. In this context, we are advancing a platform of smart metallodrug delivery systems based on ruthenium complexes that are designed to recognize both BC primary tumor and metastases [2]. Our approach takes advantage of the overexpression of fibroblast growth factor receptor (FGFR) in cancer cells by using an FGFR-specific peptide to achieve selective delivery to cancer cells. This peptide is covalently linked to a cytotoxic Ru(II)(η^5-C_5H_5) complex through a linker cleavable at the mildly acidic conditions characteristic of the tumor microenvironment. Such design enables selective accumulation of the conjugates in cancer tissues while ensuring controlled activation of the therapeutic metal complex only at the tumor site. One of these systems, containing a hydrazone as a pH-responsive linker, showed high and selective antiproliferative activity against FGFR(+) BC cells, allied to the controlled release of the cytotoxic ruthenium complex in its active form [2]. In this work, we explore different pH-responsive linkers to conjugate Ru complexes to FGFR selective peptides, using either the cyclopentadienyl ligand or a bipyridine ligands as conjugating locations. Herein, we report the synthesis and characterization of these Ru-peptide conjugates, along with their drug release profile under pH conditions that mimic both bloodstream and tumor microenvironment. The 3D-conformational structure of the free peptide and conjugate was elucidated by NMR spectroscopy. The cytotoxic activity of these systems was evaluated in four breast cancer cell lines with different FGFR expression, at pH values that mimic the tumor microenvironment and bloodstream.

Acknowledgements: We thank the Fundação para a Ciência e Tecnologia (FCT), I.P./MCTES for the financial support through the projects UID/100/2025, UIDB/00100/2020 (CQE, DOI 10.54499/UIDB/00100/2020), LA/P/0056/2020 (IMS, DOI 10.54499/LA/P/0056/2020) and UID/04349/2025 (C²TN). Marco Sá and T. S. Morais thank FCT for the doctoral grant UI/BD/154814/2023 (DOI: 10.54499/UI/BD/154814/2023) and for support through the FCT Tenure program, respectively.

References

[1] Yin L.; Jiang-Jie D.; Xiu-Wu B.; Shi-Chag Y.; Breast Cancer Res. 2020, 22, 1-13.
[2] Machado J. F.; Sá M.; Pires I.; Tarita M. S.; Marques F.; Coelho J. A. S.; Mendes F.; Piedade M. F. M.; Machuqueiro M.; Jiménez M. A.; Garcia M. H.; Correia J. D. G.; Morais T. S.; Dalton Trans 2024, 53, 7682-7693

Evaluating toxicity and anti-osteogenic activity of artemisinin-inspired endoperoxides in zebrafish larvae

Yaryna S. Buzan[1,2,*], Gil Martins[1], Bruno M. S. Ferreira[1,3], Inês C.C. Costa[1,2], Paulo J. Gavaia[1,3], Maria L. S. Cristiano[1,2]

[1]Centro de Ciências do Mar do Algarve (CCMAR/CIMAR-LA), Campus de Gambelas, University of Algarve, 8005-139 Faro, Portugal; [2]Department of Chemistry and Pharmacy, Faculty of Sciences and Technology, FCT, Campus de Gambelas, University of Algarve, 8005-139 Faro, Portugal; [3]Faculty of Medicine and Biomedical Sciences, Campus de Gambelas, University of Algarve, 8005-139, Faro, Portugal

** E-mail: buzanyaryna@gmail.com*

Artemisinin inspired endoperoxides, such as 1,2,4,5-tetraoxanes, show important antiparasitic activities [1,2], including antimalarial efficacy. Their pharmacological action is ascribed to multitarget mechanisms that include the inhibition of *Plasmodium falciparum* ATPase 6 (a SERCA Ca^{2+}-ATPase) [3,4]. Due to potential impacts on calcium balance [5-7], we evaluated the toxicity and osteogenic activity of five 1,2,4,5-tetraoxanes and three non-peroxidic controls in zebrafish (*Danio rerio*) larvae. The LC_{50} values were established, and non-lethal concentrations were tested. Operculum mineralization, behavioural responses, morphology, and expression of genes for calcium regulation (*atp2a1*), osteogenesis (*sp7, oc2*), and oxidative stress (*sod1, cat*) were assessed.

All compounds reduced zebrafish larvae operculum mineralization, indicating anti-osteogenic activity. The ether controls required higher concentrations, suggesting that the peroxide bond enhances osteogenesis inhibition. Some derivatives caused larval deformities and impaired locomotion ability, whereas others produced selective anti-osteogenic effects without systemic toxicity. *atp2a1* downregulation likely contributes to reduced mineralization.

One 1,2,4,5-tetraoxane exerted anti-osteogenic activity at nanomolar concentrations, without behavioral or gene-expression changes, representing the most promising analogue for therapeutic contexts requiring suppression of bone formation. Our findings suggest that the presence of a peroxide bond is not, by itself, a good predictor of anti-osteogenic activity or systemic toxicity, although it is likely to be involved in the inhibitory activity over osteogenesis.

Funding: We acknowledge the financial support from FCT - Foundation for Science and Technology, Portugal, through contracts UID/04326/2025, UID/PRR/04326/2025 and LA/P/0101/2020 (DOI:10.54499/LA/P/0101/2020), and the doctoral grant 2023.04904.BDANA (Y.S.B.), and from the operational programmes CRESC Algarve 2020 and COMPETE 2020, through contract EMBRC.PT ALG-01-0145-FEDER-022121.

References

[1] Terent'ev, A. O.; Borisov, D. A.; Vil', V. A.; Dembitsky, V. M.; Beilstein J. Org. Chem. 2014, 10, 34–114.
[2] Woodley, C. M.; Amado, P. S. M.; Cristiano, M. L. S.; O'Neill, P. M.; Med. Res. Rev. 2021, 41, 3062–3095.
[3] Meunier, B.; Robert, A.; Acc. Chem. Res. 2010, 43, 1444–1451.
[4] O'Neill, P. M.; Rawe, S. L.; Borstnik, K.; Miller, A.; Ward, S. A.; Bray, P. G. et al.; ChemBioChem 2005, 6, 2048–2054.
[5] Eckstein-Ludwig, U.; Webb, R. J.; Van Goethem, I. D. A.; East, J. M.; Lee, A. G.; Kimura, M.; et al.; Nature 2003, 424, 957–961.
[6] Naik, P. K.; Srivastava, M.; Bajaj, P.; Jain, S.; Dubey, A.; Ranjan, P.; et al.; J. Mol. Model. 2011, 17, 333–357.
[7] Xu, T.; Feng, Q.; Jacob, M. R.; Avula, B.; Mask, M. M.; Baerson, S. R. et al.; Antimicrob. Agents Chemother. 2011, 55, 1611–1621.

Detection of microRNA biomarkers using an optical nanosensor

Sara R, D. Gamelas [1,*], Carolina Canilho,[1] João P. C. Tomé[1], Pedro M. R. Paulo[1]

[1]*Centro de Química Estrutural - Institute of Molecular Sciences, Universidade de Lisboa;*

** E-mail: sara.gamelas@tecnico.ulisboa*

Several diseases can be detected by analyzing circulating nucleic acids in blood, particularly microRNAs, which have become key biomarkers for minimally invasive diagnostics [1]. MicroRNAs are short, non-coding RNA sequences (21–23 nucleotides) whose expression is often altered in pathological conditions. Because they remain stable in biofluids and can be correlated with disease state, their detection through blood analysis—liquid biopsy—offers a promising route for early diagnostics[1,2]. To achieve highly sensitive detection, we aim to develop an optical nanosensor integrated into an optofluidic platform. The sensor couples a DNA-recognition unit to a gold nanorod, which serves as a plasmonic nanoantenna that amplifies fluorescence signals at the single-molecule level. In the final architecture, this recognition unit will be positioned using DNA origami to ensure nanoscale spatial control; however, at this initial stage, we implement a simplified system in which a short oligo-DNA sequence serves as the capture element complementary to the target microRNA. The detection strategy relies on a two-step mechanism. First, the target microRNA binds to the capture sequence. Second, its presence is reported through a fluorescent "dye imager," a complementary DNA strand labeled with a free-base porphyrin fluorophore. Transient hybridization of the dye imager produces short fluorescence bursts that can be monitored using single-molecule fluorescence microscopy on a confocal microscope. By recording fluorescence intensity time traces in the presence of a single gold nanorod, we characterize the plasmonic antenna's enhancement and assess its influence on imager brightness and binding dynamics. This proof-of-concept study lays the foundation for a future optofluidic nanosensor capable of sensitive, specific microRNA detection for liquid biopsy applications.

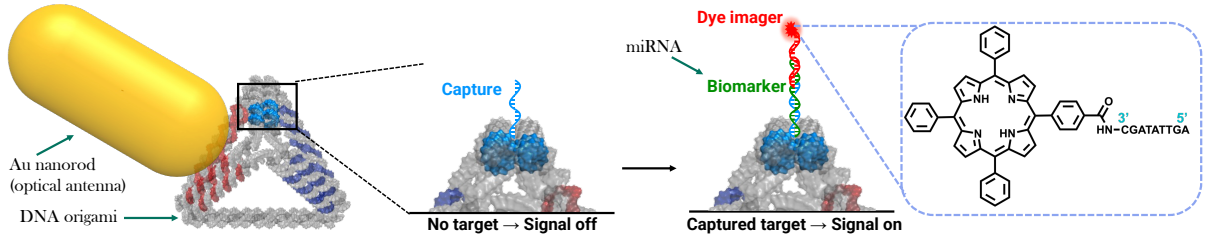


Figure 1. Single molecule biomarker detection using DNA origami and gold nanorod.

Acknowledgements: Centro de Química Estrutural is a Research Unit funded by Fundação para a Ciência e a Tecnologia (FCT) through projects UIDB/00100/2020 (https://doi.org/10.54499/UIDB/00100/2020), UIDP/00100/2020 (https://doi.org/10.54499/UIDP/00100/2020). Institute of Molecular Sciences is an Associate Laboratory funded by FCT through project LA/P/0056/2020 (https://doi.org/10.54499/LA/P/0056/2020). Also, to the FCT Project 2022.04076.PTDC. S.R.D.G acknowledges FCT for a fellowship through project NanoSens-RNA (https://doi.org/10.54499/2022.04076.PTDC).

References

[1] Pantel, K., Alix-Panabières, C. Nat Rev Clin Oncol 2019 16, 409–424.
[2] Peng, Y., Croce, C. Sig Transduct Target Ther 2016, 1, 15004.

Metabolite profile and neurotoxic effects of synthetic cannabinoids mixtures seized in Portugal

Rita P. Lopes[1,2,3], Cláudia C. Miranda[3,4], Cláudio Leal[5], Maria J. Caldeira[5], Alexandra M. M. Antunes[2], Helena Gaspar[1]

[1]BioISI – BioSystems and Integrative Sciences, Universidade de Lisboa, Lisboa, Portugal; [2]Centro de Química Estrutural – Institute of Molecular Sciences, Universidade de Lisboa, Lisboa, Portugal; [3]Department of Bioengineering and iBB – Institute for Bioengineering and Biosciences, Universidade de Lisboa, Lisboa, Portugal; [4]AccelBio – Collaborative Laboratory to Foster Translation and Drug Discover, Catanhede, Portugal; [5]Laboratório de Polícia Científica da Polícia Judiciária – Setor de Drogas e Toxicologia, Rua Gomes Freire, 1169-007 Lisboa.

** E-mail: rita.padinha.lopes@tecnico.ulisboa.pt*

Synthetic cannabinoids are the main group of New Psychoactive Substances (NPS) monitored by the European Union Drugs Agency (EUDA) [1]. These compounds are designed to mimic the effects of THC and often show higher toxicity due to their strong affinity for cannabinoid receptors. They are frequently sold as mixtures or combined with other substances, which can result in synergistic interactions and harmful effects [2].

To evaluate the effects of combining two cannabinoids on neurotoxicity and metabolic profiles, two seized samples: Mixture 1 (ADB-5'Br-Inaca and ADB-5'Br-Pinaca) and Mixture 2 (ADB-5'Br-Inaca and ADB-5'Br-Butinaca), as well as their respective purified individual cannabinoids, were tested in differentiated SH-SY5Y cells and pooled human S9 liver fraction. Both mixtures showed higher neurotoxicity than the individual cannabinoids, with lower LC_{50} and steeper dose-response curves. They also induced alterations in metabolic pathways. Some metabolites were detected in cannabinoid mixture incubations that were not identified in incubations with individual cannabinoids. Overall, these results suggest that co-exposure of multiple synthetic cannabinoids can enhance neurotoxicity and modify metabolism through potential synergistic interactions.

Acknowledgements: Centro de Química Estrutural (UID/00100/2025) is a Research Unit funded by Fundação para a Ciência e Tecnologia (FCT, Portugal) through projects UIDB/00100/2020 (https://doi.org/10.54499/UIDB/00100/2020) and UIDP/00100/2020 (https://doi.org/10.54499/UIDP/00100/2020) Institute of Molecular Sciences is an Associate Laboratory funded by FCT through project LA/P/0056/2020. Work supported by UID/04046/2025 – Instituto de Biosistemas & Ciências Integrativas Centre grant from FCT, Portugal. Joint funding from FCT and the COMPETE Program through grant RNEM-LISBOA-01-0145-FEDER-022125 funding are also gratefully acknowledged. We also acknowledge funding received from FCT, through Institute for Bioengineering and Biosciences through projects UIDB/04565/2020 and UIDP/04565/2020 (https://doi.org/10.54499/UIDP/04565/2020), and through Investimento RE-C05-i02–Missão Interface N.o01/C05-i02/22. FCT is also acknowledged for the PhD grant 2022.11339.BD to RPL.

References

[1] European Monitoring Centre for Drugs and Drug Addiction. European Drug Report 2025: Trends and Developments. Available from https://www.euda.europa.eu/publications/european-drug-report/2025/new-psychoactive-substances_en. Accessed: 26 November 2025;

[2] Brents, L.K. et al. Differential Drug-Drug Interactions of the Synthetic Cannabinoids JWH-018 and JWH-073: Implications for Drug Abuse Liability and Pain Therapy. *J. Pharmacol. Exp. Ther.* 2013, 346, 350-361.

New psychoactive substance *N*-propyl ephenidine detected and identified in a Portuguese police seizure: the first notification in Europe

Carla Filipa Ferreira[1], Christopher D. Maycock[2], M. Rita Ventura[2], Maria João Caldeira[1*]

[1]*Laboratório de Polícia Científica da Polícia Judiciária (LPC/PJ), Novo edifício Sede da Polícia Judiciária, Rua Gomes Freire, 1169-007 Lisboa, Portugal*

[2]*Instituto de Tecnologia Química e Biológica António Xavier, Universidade Nova de Lisboa, Av. da República 2780-157 Oeiras, Portugal.*

** E-mail: joao.caldeira@pj.pt*

Since the late 2000s, a new trend of synthetic molecules with similar effects to traditional illicit drugs have appeared. New Psychoactive Substances have been emerging in the street market and on the Internet on a regular basis. Their properties change regularly, due to structural modification to circumvent legislation. A suspected purplish powder was seized by the Portuguese Criminal Police in July 2025. To address the challenges in identifying new emerging drugs, such as the lack of standards, the seized material was analysed by colorimetric tests, GC-MS, FTIR and NMR. Firstly, colorimetric tests for classic drugs were used, where a negative result was obtained. Therefore, a representative sample was analysed by GC-MS. The mass spectrum of the major chromatographic peak was compared with international databases and identified as *N*-propyl Ephenidine **1** (α-phenyl-*N*-propyl-benzeneethanamine). However, since mass spectrum cannot differentiate *N*-propyl Ephenidine **1** from its structural isomer *N*-isopropyl Ephenidine **2** (N-(1-methylethyl)-α-phenyl-benzeneethanamine), FTIR was used as a second technique allowing the N-propyl Ephenidine **1** identification after manual comparison with literature data [1]. Since the NMR characterization of this new compound was not available, NMR experiments were performed and confirmed the structure of **1**. This communication represented the first recorded occurrence in Europe, notified to the EU Early Warning System on New Psychoactive Substances.

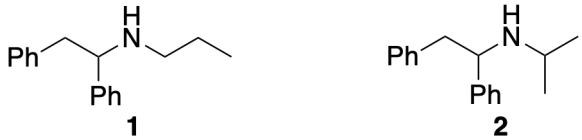


Figure 1. Chemical Structure of (1) *N*-propyl Ephenidine (α-phenyl-N-propyl-benzeneethanamine) and (2) *N*-isopropyl Ephenidine (N-(1-methylethyl)-α-phenyl-benzeneethanamine)

Funding: MOSTMICRO-ITQB R&D Unit (UIDB/04612/2020, UIDP/04612/2020) and LS4FUTURE Associated Laboratory (LA/P/0087/2020). The NMR data was acquired at CERMAX, ITQB NOVA, Oeiras, Portugal with equipment funded by FCT, project AAC 01/SAICT/2016.

Acknowledgements: This work was done within the scope of the protocol established between the Forensic Science Laboratory from Portuguese Criminal Police and the Bioorganic Chemistry Laboratory at ITQB NOVA. The authors wish to thank experts and staff from the Drugs and Toxicology Sector of Forensic Science Laboratory from Portuguese Criminal Police for technical and forensic support.

References

[1] Algar, J.; Lawes, D.; Carroll, A.; Caldicott, D.; McLeod, M. Drug Test Anal 2025, 16, 1144-1154.

Optimized tryptophanol-derived ligands targeting R273H and R280K mutant p53

Ricardo J. F. Ferreira[1,*], Tomás Monteiro[1], Lídia Gonçalves[1], Ana P. Leandro[1], Maria M. M. Santos[1,*]

[1]*Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa. Lisboa, Portugal*

** E-mail: ricardojferreira@edu.ulisboa.pt / mariasantos@ff.ulisboa.pt*

R273H and R280K mutants p53 are two DNA-contact mutations frequently found in colorectal and breast cancers [1]. Cancers carrying these mutations remain particularly difficult to treat, as they promote tumor development, often leading to increased cell proliferation and metastasis. In addition to these factors, there is currently no approved drug capable of reactivating mutant (mut-) p53 to its wild-type (wt-) status. Consequently, there is growing interest in employing small molecules to revert mut- p53 back to its functional form, offering a hopeful therapeutic strategy for combating cancers bearing these p53 variants [2].

Previously, our group developed enantiopure tryptophanol-derived oxazoloisoindolinones with *in vitro* and *in vivo* activity capable of reactivating the R273H and R280K mutants p53 [3]. In this communication, we will disclose our most recent results on the optimization of the developed tryptophanol-derived isoindolinone scaffold. Novel isoindolinones were synthesized based on the most active derivatives identified to stabilize R273H and R280K mut p53. The new compounds were tested against wt-, mut-R273H and mut-R280K p53 DNA-binding domain (BDB) using a differential scanning fluorimetry (DSF) assay. DSF assay showed that 18 compounds stabilize the R273H mut p53DBD, and 24 compounds stabilize the R280K mut p53DBD. The anti-proliferative activity of the most promising hits was evaluated in different cancer cells with distinct status of p53.

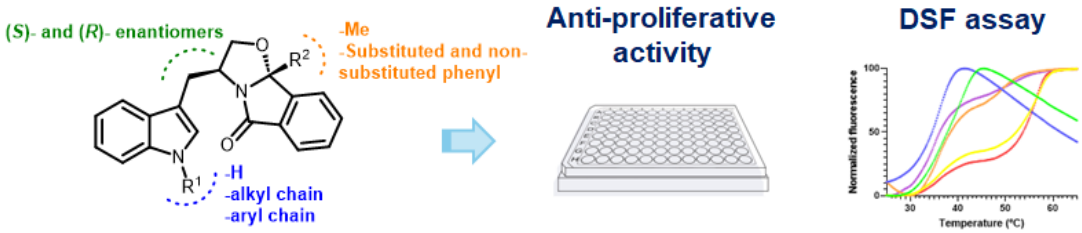


Figure 1. Hit-to-lead optimization on the tryptophanol-derived scaffold to target R273H and R280K mutants p53.

Funding: Fundação para a Ciência e a Tecnologia through iMed.ULisboa (UID/04138/2025, https://doi.org/10.54499/UID/04138/2025), project 16199 – LISBOA2030-FEDER-00735600, project PTDC/QUI-QOR/1304/2020 and PhD fellowship 2022.11539.BD (Ricardo Ferreira).

References

[1] Nishikawa, S.; Iwakuma, T.; Cancers (Basel), 2023, 15, 429.

[2] Lim, D.V.; Woo, W.H.; Lim, J.X.; Loh, X.Y.; Soh, H.T.; Lim, S.Y.A.; Lee, Z.Y.; Yow, H.Y.; Hamzah, S.B.; Sellappans, R.; Foo, J.B.; Curr Mol Pharmacol. 2024, 17, e140923221042.

[3] a) Barcherini, V.; Loureiro, J.B.; Sena, A.; Madeira, C.; Leandro, A.P.; Saraiva, L.; Antunes, A.M.M.; Santos, M.M.M.; Pharmaceuticals, 2023, 16, 146. b) Ferreira, R.J.F.; Barcherini, V.; Roma-Rodrigues, C.; Sikorová, M.; Saraiva, L.; Leandro, A.P.; Baptista, P.V.; Fernandes, A.R.; Antunes, A.M.M.; Santos, M.M.M.; ACS Pharmacol. Transl. Sci. 2025, 8, 1726.

Reductive heterocyclization of 2-nitrobenzylidenes for selective quinoline *N*-oxide synthesis

Vera Alves[1,2], Gustavo Maia[1,2], João L. Serrano[1,2], Paulo Almeida[1,2], Samuel Silvestre[1,2,*]

[1] Chemistry Department, Faculty of Sciences, University of Beira Interior, Rua Marquês D'Ávila e Bolama, 6201-001 Covilhã, Portugal; [2] RISE-Health – Faculty of Sciences, University of Beira Interior, Rua Marquês D'Ávila e Bolama, 6201-001 Covilhã, Portugal.

** E-mail: sms@ubi.pt*

Quinoline *N*-oxides are aromatic azaheterocycles bearing an oxygen bound to nitrogen often described as zwitterion species [1] These derivatives are of distinct interest due to their amphiphilic nature and wide scope of bioactivities, which may include antimicrobial, anti-inflammatory, anticonvulsant, antimalarial, and analgesic effects [2,3]. Quinoline *N*-oxides can be synthesized through either the direct oxidation of the heteroatom in quinolines or via reductive heterocyclization reactions, the latter providing a valuable option for creating functionalized frameworks from nitro-precursors [1]. In this approach, the reductive heterocyclization of unsaturated α,β-ketone systems containing an *ortho*-nitroaryl motif involves the partial reduction of the nitro group to hydroxylamine, enabling intramolecular Michael addition and promoting the cyclization to the *N*-oxide heterocycle. However, mostly existing metal-mediated reductions performed in acidic media consistently yield non-selective mixtures of quinoline and quinoline *N*-oxide products, which limit their synthetic efficiency and downstream applications. Given our interest in developing bioactive azaheterocycles, our research group decided to develop a tin-based process to perform the referred reductive heterocyclization aiming to improve chemoselectivity towards quinoline *N*-oxide formation and interesting results were achieved. With this process, several new quinoline *N*-oxide derivatives could be prepared for further *in vitro* biological evaluation as potential antitumor agents.

Funding: Portuguese Foundation for Science and Technology (FCT) and European Regional Development Fund (FEDER) - financial support of the research center CICS-UBI (UIDB/0079/2020 and UIDP/00709/2020). The NMR spectrometers are part of the National NMR Facility supported by FCT-Portugal (ROTEIRO/0031/2013-PINFRA/22161/2016, cofinanced by FEDER through COMPETE 2020, POCI and PORL and FCT through PIDDAC).

References

[1] Y. Wang, L. Zhang, Recent Developments in the Chemistry of Heteroaromatic *N*-Oxides, Synthesis, 47 (2015) 289-305.

[2] Y.B. Rajesh, Quinoline heterocycles: synthesis and bioactivity, Heterocycles-Synthesis and Biological Activities, IntechOpen 2018.

[3] S. Bawa, S. Kumar, S. Drabu, R. Kumar, Structural modifications of quinoline-based antimalarial agents: Recent developments, J Pharm Bioallied Sci, 2 (2010) 64-71.

Biofilm dynamics and extracellular vesicle profiles of mosquito-derived *Pseudomonas* spp.

Maria Carvalho[1,2]*, Margarida Marques[1,2], Carmen Fernandez Becerra[3], Sandra N. Pinto[2], Henrique Silveira[1]

[1]Global Health and Tropical Medicine (GHTM), Instituto de Higiene e Medicina Tropical (IHMT), Universidade Nova de Lisboa, Lisbon, Portugal; [2]Institute for Bioengineering and Biosciences (iBB), Instituto Superior Técnico, Universidade de Lisboa, Lisbon, Portugal; [3]Barcelona Institute for Global Health (ISGlobal), Barcelona, Spain

** E-mail: mariadcarvalho@ihmt.unl.pt*

Malaria, caused by *Plasmodium* and transmitted by *Anopheles* mosquitoes, remains a major global health challenge. Rising insecticide resistance increased the interest in strategies targeting vector competence [1–3]. The mosquito midgut microbiota shapes immunity and parasite development, and bacterial biofilms - structured extracellular polymeric matrices - can alter midgut ecology and interfere with parasite invasion [2], while vesicle-mediated microbial communication has been linked to colonisation resistance to *Plasmodium* [3].

We examined two mosquito-derived isolates with contrasting phenotypes. *Pseudomonas mendocina* forms thick, mucoid, structured biofilms under midgut-like conditions, whereas *Serratia marcescens* forms more modest ones [4]. Given its markedly stronger biofilm-forming phenotype, *P. mendocina* was selected as the primary model for downstream analyses.

We optimised an enrichment workflow for bacterial extracellular vesicles (EVs) combining centrifugation, filtration and ultrafiltration. EVs carry lipids, proteins and signalling molecules involved in biofilm maturation and cell–cell communication [5]. EVs isolated from 24 h *P. mendocina* biofilms showed higher yields than those from 6 h cultures. Dot-blot assays detected a stronger lipopolysaccharide (LPS) signal, a key component of Gram-negative membranes, in 24 h EVs, which also had ~6-fold higher protein content, consistent with stage-dependent EV composition [6]. Nanoparticle tracking analysis revealed that 24 h EVs displayed narrower and more stable size distributions than 6h samples, which showed greater heterogeneity. Across conditions, *S. marcescens* produced larger EVs, consistent with known differences in outer-membrane structure and OMV biogenesis [7]. Preliminary in vivo assays in *Anopheles stephensi* suggest that colonisation by *P. mendocina* may influence parasite development, evidenced by a reduction in oocyst burden.

Funding: This work is funded by national funds through FCT – Fundação para a Ciência e a Tecnologia, I.P., under the R&D unit GHTM (UID/04413/2025), the Associated Laboratory REAL (LA/P/0117/2020), and iBB – Institute for Bioengineering and Biosciences (UIDB/04565/2020). ***Acknowledgements:*** We thank the IHMT-NOVA animal facility staff for assistance with mosquito and animal husbandry, and the IGTP/ISGlobal team for support with EV analyses.

References

[1] Dong, Y. et al. *Cell Host Microbe* 2009, 5, 273–283.
[2] Chattopadhyay, A. et al. *Biocatal. Agric. Biotechnol.* 2022, 40, 102305.
[3] Jiang, Y. et al. *Cell Host Microbe* 2023, 31, 1655–1667.
[4] Marques, M. et al. *ACS Omega* 2025, 10, 49426–49438.
[5] Schwechheimer, C.; Kuehn, M.J. *Nat. Rev. Microbiol.* 2015, 13, 605–619.
[6] Schooling, S.; Beveridge, T. *Nat. Rev. Microbiol.* 2006, 4, 538–550.
[7] Gao, X. et al. *Trends Microbiol.* 2021, 29, 662–675.

Synthesis and photophysical characterization of axially functionalized silicon(IV) naphthalocyanines with phototheranostic potential

Pedro M. R. Santos[1,4,5]*, Benjamin Proto[2,4], Debalina Mondal[3], Alicia Voge[2,4,5], Kevin Stamplecoskie[2], João P. C. Tomé[1], Juan Chen[4], Nahyun Kwon[4], Gang Zheng[4,5]

[1] Department of Chemical Engineering, Instituto Superior Técnico, Lisboa, Portugal; [2] Department of Chemistry and Chemical Engineering, École supérieure de Chimie, Physique, Électronique de Lyon, Lyon, France; [3] Department of Chemistry, Queen's University, Kingston, Canada; [4] Princess Margaret Cancer Centre University Health Network Toronto, ON M5G 1L7, Canada; [5] Department of Medical Biophysics, University of Toronto, Toronto, Canada.

** E-mail: pedro.m.r.santos@tecnico.ulisboa.pt*

Photo-based therapies such as photodynamic (PDT) and photothermal therapy (PTT) offer minimally invasive cancer treatment with high spatial selectivity, however most photosensitizers are (photo)activated within the 600-650 nm range, where tissue penetration remains suboptimal for the deep-seated tumors [1]. Naphthalocyanines (Ncs) have attracted significant attention due to their strong > 800 nm absorption [2]. Despite this advantage, clinical translation has been limited by their extreme hydrophobicity and poor compatibility with biological environment. To overcome these challenges, we synthesized axially modified silicon naphthalocyanines (SiNcs) bearing ligands with diverse structural and electronic properties. This strategy enabled: (1) efficient encapsulation into biocompatible PEG-PCL micelles while preserving the photophysical properties of SiNc, yielding stable nanoformulations for PTT; and (2) the introduction of click-reactive groups for the synthesis of folate-targeted SiNc bioconjugates for selective delivery. Both approaches improved solubility, reduced aggregation and expanded functional versatility, demonstrating robust *in vivo* phototheranostic performance, reinforcing axial ligand engineering as a powerful route for next-generation SiNc-based therapeutic platforms.

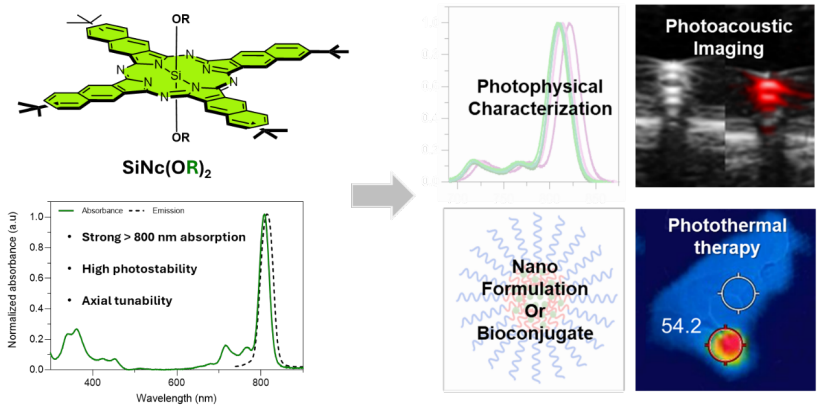


Figure 1. Schematic overview of the design and development of axially modified silicon naphthalocyanines (SiNcs).

Funding: This work is supported by the Canadian Institute for Health Research (CIHR PJT 190047), the Canada Research Chairs Program (950-232468), and the Princess Margaret Cancer Foundation. P.M.R.S. Ph.D. scholarship (ref. 2023.02393.BD) supported by Fundação para a Ciência e Tecnologia (FCT).

References

[1] A. Sordillo, Y. Pu, S. Pratavieira, Y. Budansky, R. R. Alfano, J. Biomed. Opt. **2014**, 19, 056004.

[2] P.Santos, B.Proto, D. Mondal, A. Voge, C. Hoskin, K. Stamplecoskie, J. Tomé, J.Chen, N. Kwon, G. Zheng *ChemistryEurope*, **2025**, e202500249.

Targeting PI3K overexpression in cancer cells: molecular docking-guided design of novel 2,6,9-trisubstituted purine derivatives

Nuno Ferreira[1,*], Maria Alice Carvalho[1], Filipe Teixeira[1]

[1]*Centre of Chemistry of University of Minho, Campus de Gualtar, Universidade do Minho, 4710-057 Braga, Portugal*

** E-mail: pg57349@alunos.uminho.pt*

Hyperactivation of PI3K signalling cascades is one of the most common events in cancer cells, making selective PI3K inhibition an interesting route for designing novel anti-cancer drugs [1]. Despite recent advances in the clinical development of selective PI3K inhibitors several limitations such as relatively narrow therapeutic window, dose-limiting toxicities and mechanisms of resistance represent serious drawbacks to their therapeutic application emphasising the need to discover new chemical entities to target specific PI3K isoforms [2].
In this work, we report a systematic survey of the binding ability of 34 2,6,9-trisubstituted purine derivatives to the human PI3Kα lipid kinase. For this purpose, a new model of the PI3Kα was prepared using existing structural data[3], and Molecular Modelling methods. A systematic docking scan of the enzyme's volume was carried out for each purine derivative, using partially overlapping search grids. Although high-affinity scores (DG_{bind} <-9.5 kcal/mol) were observed across all compounds, the lowest DG_{bind} were associated with one preferred binding location, whereas lower-affinity compounds were found elsewhere (Figure 1). The results suggest some correlation between a compound's affinity and its preferred attachment region, unveiling some preliminary information on how different substitution patterns may help direct the compounds affinity towards a given region of the enzyme, hinting at a possible path for the rational design of isoform-specific PI3K inhibitors.

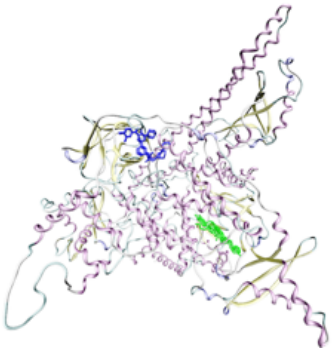


Figure 1: Structure of PI3Kalpha, and selected lowest-energy poses for the three most affine compounds (depicted in green), and three low-affinity compounds (depicted in blue).

Funding: This work received financial support from Fundação para a Ciência e Tecnologia and Ministério da Educação, Ciência e Inovação) through the projects UID/00686 –Centre of Chemistry of University of Minho (CQ-UM)

References

[1] Yang, J.; Nie, J.; Ma, X.; Wei, Y.; Peng, Y.; Wei, X.; Mol. Cancer, 2019, 18.
[2] Caste, P.; Toska, E.; Engelman, J.A.; Scaltriti, M.; Nat Cancer, 2021, 2 (6), 587–597
[3] Yang, H.; *et al.* ACS Med. Chem. Lett. 2015, 6 (5), 531-536.

Design of pH-dependent fluorescent complexes between a boronic acid-pyranoflavylium dye and diol-rich bioactives

Beatriz Senra, Mariana Cunha, Ana Pires, Ricardo Dias, Victor Freitas, Luís Cruz

REQUIMTE/LAQV, Department of Chemistry and Biochemistry, Faculty of Sciences, University of Porto, Porto, Portugal.
** E-mail: luis.cruz@fc.up.pt*

Smart materials composed by bioactive compounds and stimuli-responsive dyes are currently of great interest in different disciplines, from the food industry to biomedical applications in sensing, theranostics, imaging, and drug/gene delivery [1,2]. This work provides the synthesis and structural characterization of a new symmetrical pyranoflavylium-boronic acid derivative, and its potential for complexation of diol-rich analytes such as (+)-catechin, L-lactic acid, and D-glucose was evaluated. The model systems were studied by fluorescence technique in the presence and absence of those ligands and were able to recognize those analytes with different association constants and in a pH-controlled fashion. Overall, (+)-catechin revealed the greatest affinity with the dye, with an association binding constant (K_a) of 48895 ± 1 M^{-1} rather than with L-lactic acid (K_a 595 ± 2 M^{-1}) or D-glucose (K_a 7 ± 2 M^{-1}). The interaction between (+)-catechin and the pyranoflavylium receptor was demonstrated to be pH-dependent, occurring near of the dye pK_a (pH~8), while for acidic pH values the (+)-catechin is released from the dye recovering the initial fluorescence of its free flavylium cation species. The formation of the diol-boronate ester complex was confirmed by ^{11}B NMR spectroscopy in the presence of (+)-catechin only at a neutral pH value

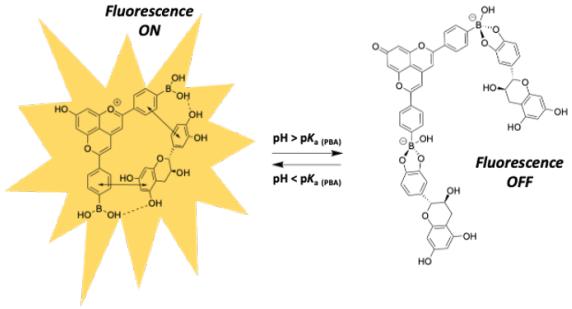


Figure 1. pH-dependent fluorescence interaction modes between boronic acid-pyranoflavylium receptor and a catechol-rich polyphenol.

Funding: This work received financial support from the PT national funds (FCT/MECI, Fundação para a Ciência e Tecnologia and Ministério da Educação, Ciência e Inovação) through the project UID/50006/2025 DOI 10.54499/UID/50006/2025 -Laboratório Associado para a Química Verde - Tecnologias e Processos Limpos.
Acknowledgements: Mariana Cunha and Ana Sofia Pires acknowledge the PhD grants from FCT (2024.01342.BD and 2021.08670.BD, respectively). Luís Cruz gratefully acknowledges FCT for the research contract funded through the Individual Call to Scientific Employment Stimulus with reference DOI:10.54499/2023.07923.CEECIND/CP2842/CT0001.

References

[1] Mrinalini, M.; Prasanthkumar, S. ChemPlusChem 2019, 84, 1103
[2] Whyte, G. F.; Vilar, R.; Woscholski, R. J. Chem. Biol. 2013, 6, 161.

Synthesis of nucleos(t)ide analogs based on sugar-fused 1,4-diox-2-ene scaffolds

Mpanzu Nelo[1,2]*, Radek Jorda,[3] Nuno M. Xavier[1]

[1]*Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal*

[2]*Centro de Química Estrutural - Institute of Molecular Sciences, Faculdade de Ciências,Universidade de Lisboa Ed. C8, 5° Piso, Campo Grande, 1749-016 Lisboa, Portugal*

[3]*Departament of Experimental Biology, Faculty of Sience, Palacký University Olomouc, Šlechtitelů 27, 78371 Olomouc, Czech Republic*

** E-mail: nelompanzu@gmail.com*

The synthesis of nucleoside and nucleotide analogs (NAs) is a topic of notorious and continuous interest in organic and medicinal chemistry, due to their ability to mimic their physiological counterparts and interfere with/inhibit nucleic acid synthesis, nucleotide metabolism or cell signalling [1,2]. These groups of molecules have become important for treating diseases whose progress depends on nucleotide-dependent events, namely cancer and viral infections. Low selectivity to affected cells, poor oral bioavailability and drug resistance are commonly associated with NAs [1,2] and therefore the search for novel bioactive nucleos(t)ide-based molecules that may overcome these issues is of utmost importance.

In this communication we present the synthesis of constrained isonucleosides and isonucleotide analogs in which the nucleobase is linked to a sugar-fused 1,4-diox-2-ene moiety. The fused bicyclic system enables reducing conformational flexibility, which is an important aspect to consider in the development of more selective bioactive molecules.

Their synthesis was based on the access to butane 2,3-diacetal (BDA)-protected sugar precursors comprising different functionalities, such as azido or halo derivatives, and further N-glycosylation. Staudinger-phosphite or Arbuzov-type reactions were used for the installation of phosphate group mimetics in the structures, while azido-alkyne 1,3-dipolar cycloaddition enabled the synthesis of triazole-containing derivatives.

Preliminary results on the *in-vitro* anticancer potential of the newly synthesized compounds will also be disclosed.

Acknowledgements: The authors thank FCT for funding: projects UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025, iMed-Ulisboa), UIDB/00100/2020, UIDP/00100/2020 (CQE) and LA/P/0056/2020 (IMS). M. Nelo also thank Instituto Nacional de Gestão de Bolsas de Estudos do Governo de Angola.

References:

[1] Jordheim, L. P., Durantel, D., Zoulim, F., Dumontet, C..,Nat. Rev. Drug. Discov 2023, 12, 447-464

[2] Hruba, L. Das, V.; Hajduch, M.; Dzubak, P. *Biochem. Pharmacol.* 2023, *215*, 115741.

Valorization of *Iris pseudacorus* L.: metabolomic profiling by GC-MS

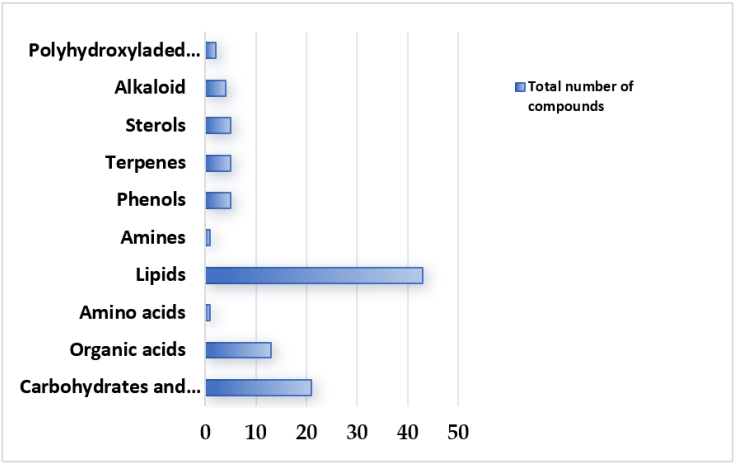
Helena L. M. Nangacovié*, Diana C. G. A. Pinto

LAQV & Chemical Department of the University of Aveiro, 3810-193 Aveiro, Portugal
**E-mail: hnangacovie@ua.pt*

Iris pseudacorus L., commonly found in Portuguese flora, has not been thoroughly investigated regarding its specialized metabolites and biological activities. This study aims to provide a comprehensive evaluation of *I. pseudacorus* by characterizing the specialized metabolite profile across different plant organs, including flowers, leaves, stems, and rhizomes, aiming to assess their biological activity in the future.

The methodological approach involves hexane extraction combined with GC-MS analysis for qualitative and quantitative metabolite profiling. Structural elucidation is supported by spectral libraries, injection of standards under the same conditions, and computational matching tools, enhancing the reliability of metabolite identification.

Preliminary results indicate a diverse metabolite profile, including terpenes, sterols, fatty acids, amino acids, eicosanoids, and carbohydrates. Patterns of organ-specific distribution were observed, suggesting functional differentiation among the plant parts. The findings of this research provide new insights into the chemical profile of *I. pseudacorus*, highlighting its potential as a promising source of bioactive natural products and laying the foundation for future applications.



Acknowledgment: This work was funded by the Foundation for Science and Technology (FCT) and the Ministry of Science, Technology, and Higher Education (MCTES) through the project UID/50006/2025 - The Associated Laboratory for Green Chemistry (LAQV) of the Network of Chemistry and Technology (REQUIMTE).

Synthesis and functionalization of diketopyrrolopyrrole derivatives for biological applications

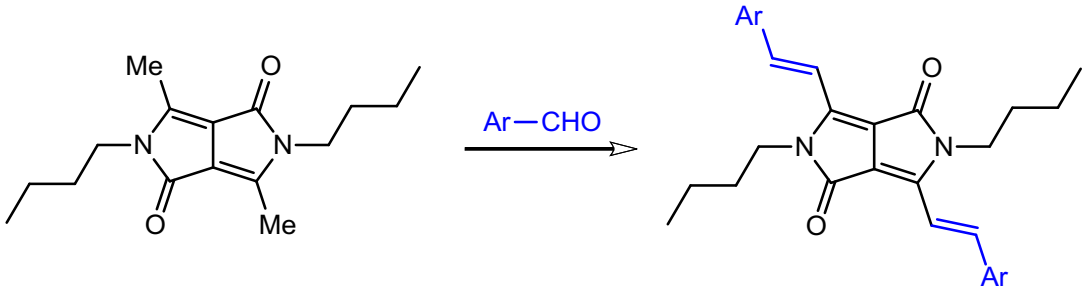
Nina Wang[1,*], Augusto C. Tomé[1]

[1] *LAQV-REQUIMTE, Department of Chemistry, University of Aveiro, 3010-193 Aveiro, Portugal*

** E-mail: ninawang@ua.pt*

Diketopyrrolopyrrole (DPP) derivatives have received increasing attention due to their numerous advantages, including long absorption and emission wavelengths, good photophysical properties, high fluorescence quantum yields, and large Stokes shifts. Their exceptional high photothermal and photochemical stabilities, low dark toxicity, efficient reactive oxygen species (ROS) generation and thermal effects make them highly promising for biological applications [1–4]. Therefore, the development of novel DPP derivatives is of great significance.

Here, we synthesized a series of DPP derivatives via Knoevenagel condensation (**Scheme 1**) based on a novel DPP scaffold reported by Feng et al. in 2019 [5]. Further functionalization was carried out to facilitate their biological application, particularly as fluorescent probes and as photosensitizers for the photodynamic therapy of cancer and photoinactivation of microorganisms.



Scheme 1. Synthetic route for diketopyrrolopyrrole derivatives.

Acknowledgements: Thanks are due to the University of Aveiro and Fundação para a Ciência e a Tecnologia (FCT) for the financial support to the UID/50006/2025 – Laboratório Associado para a Química Verde – Tecnologias e Processos Limpos. Thanks are also due to the Portuguese NMR and Mass Spectrometry Networks.

References

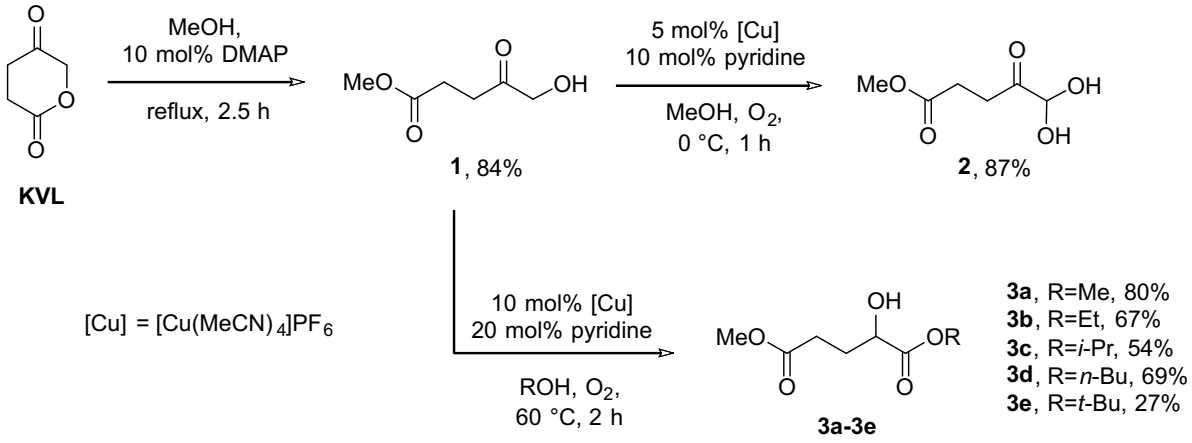
[1] J. Wang, Y. Hang and J. Hua, Sens. Actuators B. Chem., 2019, 282, 232–242.
[2] H. Xu, Y. Yang, L. Lu, Y. Yang, Z. Zhang, C.-X. Zhao, F. Zhang and Y. Fan, Anal. Chem., 2022, 94, 3661–3668.
[3] L. Yuan, Y. Su, B. Yu, Y. Shen and H. Cong, Biomater. Sci., 2023, 11, 985–997.
[4] W. Sun, X. Wang, Z. Cheng, X. Wang, N. Fan, P. Dong, M. Tong, Y. Liu and W. Sun, Biomed. Pharmacotherapy, 2023, 158, 114071.
[5] D. Feng, G. Barton and C. N. Scott, Org. Lett., 2019, 21, 1973–1978.

Copper-catalyzed synthetic transformations of biorenewable synthons to metabolites

Hristo Petkov, Svilen Simeonov*

Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Acad. G. Bonchev str., bl. 9, 1113 Sofia, Bulgaria
**E-mail: svilen.simeonov@orgchm.bas.bg*

4-Keto-δ-valerolactone (KVL) is an important biorenewable compound, readily available from furfuryl alcohol [1]. It is used for the preparation of a recyclable and biodegradable polymer poly(4-ketovalerolactone) [2]. In the present study we aimed to diversify its use as a platform molecule for the production of some valuable plant and human metabolites. We achieved the high-yielding synthesis of 5-hydroxylevulinic acid methyl ester **1**, a plant metabolite, via methanolysis of KVL (Scheme 1). Furthermore, by applying a modified and optimized procedure for a copper-catalyzed oxidation of α-hydroxyketones [3], we successfully obtained 5,5-dihydroxylevulinic acid methyl ester **2** and a series of 2-hydroxyglutaric acid diesters **3a-3e** (Scheme 1). The diacid of **3a-3e** is an important plant and human metabolite. Noteworthy, dimethyl 2-hydroxyglutarate **3a** was prepared on a gram scale in high yield by a one-pot copper-catalyzed tandem reaction directly from KVL. To our knowledge, this is the first example of such transformation and a practical synthetic route toward valuable metabolites.



Scheme 1. Methanolysis of KVL and subsequent Cu-catalyzed transformations

Acknowledgments: The authors acknowledge the National Scientific Program "VIHREN" (grant КП-06-ДВ-1) for the financial support. This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951996 Biomass4Synthons.

References:

[1] M. Dangalov, A. Fernández-Figueiras, M. A. Ravutsov, E. Vakarelska, M. K. Marinova, N. R. Candeias, S. P. Simeonov, *ACS Catalysis* **2023,** *13* (3), 1916-1925.
[2] S. Xu, Y. Wang, T. R. Hoye, *Macromolecules* **2020,** *53 (12)*, 4952-4959.
[3] S. Zheng, W. Smit, A. Spannenberg, S. Tin, J. G. de Vries, *Chemical Communications* **2022,** *58*, 4639-4642

Synthesis of novel potentially bioactive azido nucleosides and related hydroxymethyl triazole derivatives

Tânia Moreira[1,2*], Jennifer Szilagyi[1], Ana C. Fernandes[2], Nuno M. Xavier[3]

[1]*Centro de Química Estrutural - Institute of Molecular Sciences, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal*
[2]*Centro de Química Estrutural- Institute of Molecular Sciences, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1049-001 Lisboa, Portugal*
[3] *Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal*
** E-mail: tmmoreira@fc.ul.pt*

Nucleoside and nucleotide analogs constitute important groups of molecules in medicinal chemistry. Their physiological counterparts are fundamental building blocks of nucleic acids, while they play essential biological roles in cell division, cellular signalling, and metabolic regulation. Therefore, nucleos(t)ide analogs have become valuable therapeutic agents, namely for the treatment of viral infections and cancer [1,2]. Currently there are more than 30 nucleoside-based approved chemotherapeutic drugs [3]. However, despite their significant therapeutic potential, several limitations are associated with their use, namely low oral bioavailability and development of resistance of cancer and virus-infected cells [1,2]. Therefore, new bioactive nucleoside/tide-like compounds with improved and alternative mechanisms of action are required to overcome these issued.

In this context, in this communication we will present the synthesis of a variety of azido nucleosides and hydroxymethyl triazole derivatives built on xylofuranosyl templates for further evaluation of their bioactivity. The synthetic pathway included xylofuranose precursors and key steps such as azidation, *N*-glycosylation and azide-alkyne 1,3-dipolar cycloaddition. To enable the molecules to penetrate into cells, a hydrophobic moiety was introduced in their glycosyl moieties. Derivatization at the azido functionality was also performed for the installation of phosphate surrogate moieties, including α-aminophosphonate systems.

Acknowledgements:
The authors thank FCT for funding: projects UID/00100/2023 (CQE, https://doi.org/10.54499/UIDB/00100/2020 and https://doi.org/10.54499/UIDP/00100/2020), LA/P/0056/2020 (IMS, https://doi.org/10.54499/LA/P/0056/2020) and UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025, iMed-Ulisboa). FCT is also acknowledged for the PhD scholarship UI/BD/154822/2023.

References

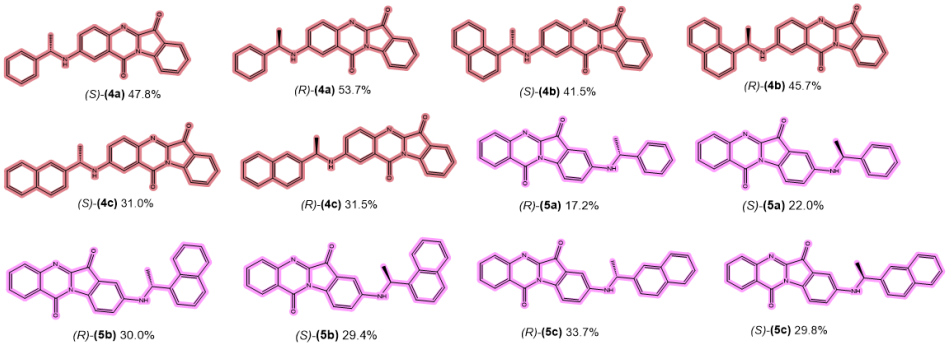
[1] Hruba, L. Das, V.; Hajduch, M.; Dzubak, P. *Biochem. Pharmacol.* 2023, *215*, 115741.
[2] Jordheim, L. P., Durantel, D., Zoulim, F., Dumontet, C..,Nat. Rev. Drug. Discov 2023, 12, 447-464
[3] Seley-Radtke, K. L, Yates, M. K., Antiviral Res. 2018, 154, 66

Novel chiral amino tryptantrins: new functional materials for chiroptical applications

Yasmine Fernine[1,2,3]*, Carolina Marques[4], Pedro Cruz[3], João P. Prates Ramalho[5],João Avô[6], Hugo Cruz[6], Sandra Gago[6], Luís Branco[6], Rui Brito[3], Henrique L. Gomes[7] Anthony J. Burke [1,2]

[1]Faculty Pharmacy, University of Coimbra, Pólo das Ciências da Saúde, Azinhaga de Santa Comba, 3000-548 Coimbra, Portugal; [2]University of Coimbra, Coimbra Chemistry Centre-Institute of Molecular Sciences (CQC-IMS), Departamento de Química, 3004-535 Coimbra, Portugal; [3]Centro de Química de Évora, University of Évora, Institute for Research and Advanced Studies, Rua Romão Ramalho, 59, 7000 Évora, Portugal; [4]LAQV-REQUIMTE, University of Évora, Institute for Research and Advanced Studies, Rua Romão Ramalho,59, 7000-641, Évora, Portugal; [5]HERCULES Laboratory, IN2PAST—Associate Laboratory for Research and Innovation in Heritage, Arts, Sustainability and Territory, University of Évora, 7000-809 Évora, Portugal; [6]LAQV-REQUIMTE, Department of Chemistry, NOVA School of Science and Technology, NOVA University of Lisbon, 2829-516 Caparica, Portugal; [7]Instituto de Telecomunicações, Departamento de Engenharia Electrotécnica e de Computadores, Universidade de Coimbra, 3030-290 Coimbra, Portugal.
** E-mail: fernineyassmine@gmail.com*

At the current time there is a need for new and easily accessible optoelectronic materials for innovative technologies ranging from smart screens to biomedical and diagnostic devices. Many of their components are chiral and thus it is essential to introduce chirality into these molecules in a sustainable and efficient manner. To address this challenge, we have developed novel chiral functional materials based on easily accessible aminotryptantrin cores which have very good chiroptical properties (Figure 1). In this communication, we will discuss their synthesis, physicochemical characterization, theoretical aspects and chiroptical characteristics [1].



Scheme 1. Synthesis of the tryptanthrin derivatives (**4a-c**), (**5a-c**).

***Acknowledgements*:** We thank the Portuguese Foundation for Science and Technology (FCT) for funding the project ConChiMOL- New Structurally Contorted and Chiral Molecules for Optoelectronic Applications, (2022. 01391.PTDC). Also, FCT is acknowledged for funding through the strategic project UIDB/00313/2020| UIDP/00313/2020 to Coimbra Chemistry Centre-Institute of Molecular Sciences (CQC-IMS). This work was financed by national funds from FCT - Fundação para aCiência e a Tecnologia, I.P., under the scope of the project UID/50006/2023 of the Associate Laboratory for Green Chemistry - LAQV REQUIMTE

References

[1] Pucci, Andrea, et al. "Association phenomena of a chiral perylene derivative in solution and in poly (ethylene) dispersion." *Reactive and Functional Polymers* 70.12 (2010): 951-960.

Exploring the potential of urea-based scaffolds for new therapeutic options in cystic fibrosis

Margarida Pereira[1,*], Alexandre Barros[1], Mark Leahy[2], Vasco Cachatra[1], Luka Clarke[2], Margarida Amaral[2], Cristina Moiteiro[1]

[1] Centro de Química Estrutural, Institute of Molecular Sciences, Faculty of Sciences, University of Lisboa, Campo Grande, 1749-016 Lisboa, Portugal; [2] BioISI– Biosystems & Integrative Sciences Institute, Faculty of Sciences, University of Lisboa, Campo Grande, 1749-016 Lisboa, Portugal

** E-mail: fc58466@alunos.ciencias.ulisboa.pt*

Cystic fibrosis (CF) is a rare, severe and life-shortening monogenetic disease resulting from pathogenic variants in the gene that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which is responsible for transporting chloride anions across epithelial tissues. The malfunction of this channel leads to thick mucus secretions, recurrent respiratory infections, and a progressive deterioration of lung function.[1] Even though innovative CFTR modulator therapies such as Kaftrio[2] exist, these options are not effective for all variants and thus not all patients are eligible to get them. Nonsense variants – those which introduce premature termination codons (PTCs) into CFTR mRNA (e.g. G542X, W1282X) – account for a substantial proportion of modulator-refractory variants. These produce unstable mRNA which is degraded through nonsense-mediated decay (NMD), and any resulting translated protein is truncated and thus, almost always, non-functional. With this challenge, it becomes urgent to study alternative strategies to improve CF treatment options.

In recent years, our group has been involved in developing a library of urea/thiourea-based synthetic receptors with the potential to act as chloride transporters.[3,4] Within the scope of the project "*Karen Menzies PTSuppress SRC026*", different structural series of bis-(thio)ureas with central aromatic platforms linked to functionalized benzo[*b*]thiophenes were tested for activity in both NMD inhibition and PTC read-through via a microscopy assay performed in HEK293T Flp-In cells stably expressing a CFTR mini-gene construct. Here, we present the synthesis of bis-ureas with central aromatic platforms, including structures linked to functionalized benzo[*b*]thiophenes and different sugar units, to evaluate the impact of different substituents on the PTC-rescuing activity in CF cellular models.

Funding: Work supported by the CF Trust (UK) for the Karen Menzies "PTSuppress" project (SRC026), centre grants UID/00100/2025, UID/PRR/100/2025 and LA/P/0056/2020 (to CQE and IMS), and UID/04046/2025 (to BioISI UID/00100) from FCT/MCTES, Portugal, and the ORGESTRA Doctoral Network (EC HORIZON-MSCA-2022-DN-01-01-101120108) from the EU.

References

[1] Mall, M. A.; Burgel, P. R.; Castellani, C.; Davies, J. C.; Salthe, M.; Taylor-Cousar, J. L.; Nat Rev Dis Primers 2024, 10, 53.
[2] Purkayastha, D.; Agtarap, K.; Kristy Wong, K.; Onella Pereira, O.; Jannie Co, J.; Smita Pakhale, S.; Salmaan Kanji, S.; J Cyst Fibros 2023, 22(3), 478-483.
[3] Moiteiro, C.; Marques, I.; Ryder, W. G.; Cachatra, V.; Carvalho, S.; Chen, L.; Goodfellow, B. J.; Gale, P. A.; Félix, V.; Eur J Org Chem, 2022, 2022 (3), e202101484.
[4] Vieira, P.; Miranda, M. Q.; Marques, I.; Carvalho, S.; Chen, L.; Howe, E. N. W.; Zhen, C.; Leung, C. Y.; Spooner, M. J.; Morgado, B.; da Cruz e Silva, O. A. B.; Moiteiro, C.; Gale, P. A.; Félix, V; Chem Eur J, 2019, 26, 888–899.

Synthesis and chiral resolution of biologically active terpene-based cannabidiol analogues

Gabriel V. L. Marques[1,2*], Maria Emília Sousa[2], Carla Fernandes[2], Renata B. de Oliveira[1]

[1]*Laboratório de Química Farmacêutica, Faculdade de Farmácia - UFMG, Belo Horizonte, Brazil;*
[2]*Laboratório de Química Orgânica e Farmacêutica, Departamento de Ciências Químicas, Faculdade de Farmácia, Universidade do Porto, Centro Interdisciplinar de Investigação Marinha e Ambiental (CIIMAR), Universidade do Porto, Portugal.*
** E-mail: leirbaglm@gmail.com*

Cannabinoids, such as CBD, Δ^9-THC and nabilone, are important therapeutic tools for clinically challenging conditions and have shown promising pre-clinical results in various pathology models [1]. New terpene-based CBD analogues were synthesized (**Figure 1**) and their activities evaluated against SARS-CoV-2 and ACE2 [2], paclitaxel-induced neuropathic pain [3], and acute pain and inflammation (data not yet published). Nevertheless, their synthetic procedures are not enantioselective, yielding isomeric mixtures.

In this work, we propose the chiral resolution of these substances to evaluate them individually and better understand the pharmacological contribution of each isomer to their activities. The analytical method for chiral resolution was developed (amylose-based stationary phase; *n*-hexane/ethanol as mobile phase) and the amylose tris-3,5-dimethylphenylcarbamate chiral stationary phase was chosen to scale-up to the preparative scale under normal phase elution conditions.

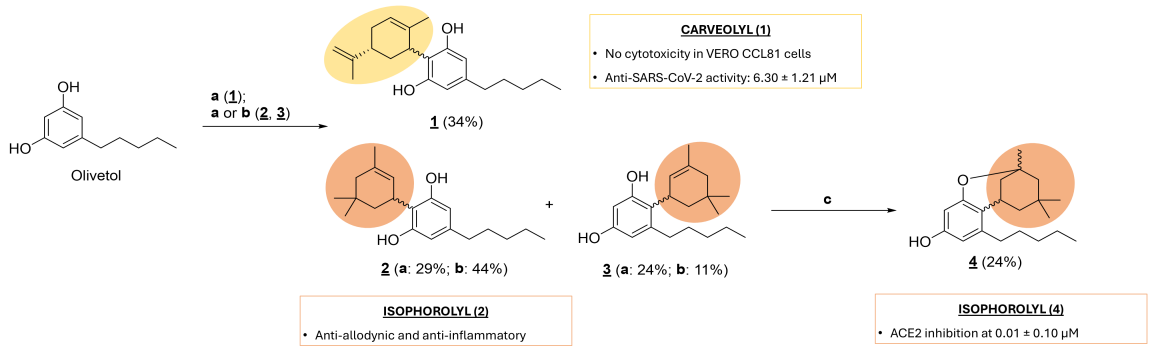


Figure 1. Synthetic routes and reported biological activities of terpene-based CBD analogues. Conditions: **a** Al_2O_3, DCM, $BF_3.Et_2O$, corresponding allylic alcohol, 40 °C, 10~30 s, then $NaHCO_3$(aq); **b** $MgSO_4$, $CHCl_3$, $BF_3.Et_2O$, corresponding allylic alcohol, 0 °C, 3 h, then $NaHCO_3$(aq); **c**: acid media (spontaneous on silica chromatography).

Funding: FAPEMIG, CAPES, CNPq. FCT - Fundação para a Ciência e a Tecnologia, I.P., and by the European Commission's Recovery and Resilience Facility, UID/04423/2025 (https://doi.org/10.54499/UID/04423/2025), UID/PRR/04423/2025 (https://doi.org/10.54499/UID/PRR/04423/2025), and LA/P/0101/2020 (https://doi.org/10.54499/LA/P/0101/2020).

References

[1] Pisanti, S. *et al.*; Pharmacol. Ther., 2017, 175, 133-150
[2] Marques, G. *et al*. Eur. J. Med. Chem., 2023, 260:115760, 1-10
[3] Marques, G. *et al*. Chem. Biodiversity, 2024, e202301935, 1-9

Electrochemical C7 functionalization of abietic and dehydroabietic acids: a greener oxidation strategy

Jéssica Macedo[1,2,3,*], João C.S. Simões[1], António Mendes Ferreira[2], Lucília Saraiva[3] and Teresa M.V.D. Pinho e Melo[1]

[1]Organic Chemistry Group, Coimbra Chemistry Centre – Institute of Molecular Sciences, Department of Chemistry, University of Coimbra, 3004-535 Coimbra, Portugal; [2] REQUIMTE-LAQV, Faculty of Pharmacy, University of Porto, 4050-313 Porto, Portugal; [3]United Resins, 3090-380 Figueira da Foz, Coimbra, Portugal

** E-mail: jemacedo1998@gmail.com*

Natural products continue to serve as valuable sources for medicinal chemistry and drug discovery. Colophony (rosin), a renewable resource obtained from coniferous trees, contains chiral diterpenic acids such as abietic (AA) and dehydroabietic acid (DHA) [1] with recognized biological potential. The valorization of this pine-resin feedstock has become a research topic of our research group, carried out in collaboration with the company United Resins. In a recent ground-breaking development, we have reported new biologically active scaffolds, spiro-β-lactam derived from 6-aminopenicillanic acid, exhibiting remarkable antiviral potency across multiple viral strains [2-4]. This successful strategy of exploring the specific three-dimensional molecular architecture of spirocyclic compounds to find new biologically active molecules is also being applied to abietane derivatives. Indeed, the spirocyclic motif, is a recurrent pharmacophore in active molecules [5]. A key intermediate in the synthesis of the target spiroabietanes is the oxidative C7 functionalization of AA and DHA to 7-oxoabietane. While previous AA and DHA oxidations relied on unsustainable, stoichiometric, and toxic reagents [6-8], the adoption of electrochemistry and flow chemistry provides greener alternatives that improve sustainability and support future industrial implementation. Further details of this study will be disclosed.

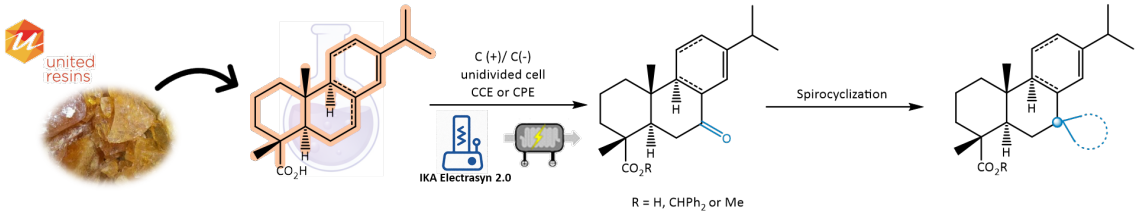


Figure 1. Sustainable electrochemical approach for the C7 oxidation of abietane derivatives, enabling access to key oxo intermediates for subsequent spirocyclization.

Acknowledgements: We acknowledge funding from the Coimbra Chemistry Centre – Institute of Molecular Sciences (CQC-IMS) which is supported by the Fundação para a Ciência e a Tecnologia (FCT), Portuguese Agency for Scientific Research. CQC is funded by FCT through projects UID/PRR/00313/2025 (https://doi.org/10.54499/UID/PRR/00313/2025) and UID/00313/2025 (https://doi.org/10.54499/UID/00313/2025) and IMS through special complementary funds provided by FCT (project LA/P/0056/2020 https://doi.org/10.54499/LA/P/0056/2020). Jéssica Macedo also thanks to the FCT for financial support (PhD fellowship: 2024.00332.BDANA).

References: [1] Ioannidis, K.; *et al.*; Molecules 2019, 24, 3603. [2] Alves, N. G.; *et al.*; Eur. J. Med. Chem. 2021, 215, 113263. [3] Alves, A.J.S.; *et al.*; Front. Chem. 2022, 10, 1017250. [4] Gonçalves, J.V.R.; *et al.*; J. Org. Chem. 2025, 90, 10225. [5] Bora, D.; *et al.*; Eur. J. Med. Chem. 2021, 215, 113263. [6] Alvarez-Manzaneda E.; *et al.* Tetrahedron. 63, 2007, 11204. [7] Monteiro S.M.C.S.; *et al.* New J. Chem. 25, 2001, 1091. [8] Rafferty, R.J.; *et al.* Angew. Chem. Int. Ed. 53, 2014, 220.

Fluorescent dihomooxacalix[4]arenes for the detection of nitroaromatic explosives in solution and in the vapour phase

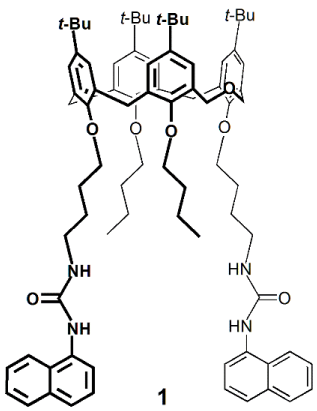
Paula M. Marcos[1,2*], Beatriz V. Gil[1], Alexandre S. Miranda[1], José R. Ascenso[3], Tiago Palmeira[1,4], Mário N. Berberan-Santos[4]

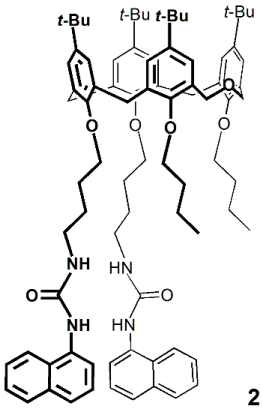
[1]CQE, FCUL, Edifício C8, 1749-016 Lisboa, Portugal; [2]FFUL, 1649-003 Lisboa, Portugal; [3]CQE, IST, 1049-001 Lisboa, Portugal; [4]IBB, IST, 1049-001 Lisboa, Portugal

** E-mail: pmmarcos @fc.ul.pt*

The detection of explosives is a major task in the fight against terrorism and in homeland security. Nitroaromatic compounds (NACs), such as trinitrotoluene (TNT), dinitrotoluene (DNT) and trinitrophenol (TNP), are common explosives used for military purposes and are the principal components of unexploded landmines. They are also considered environmental pollutants. Low-cost detection techniques, with high portability, high sensitivity and selectivity are needed for in-field analyte effective sensing. Luminescence-based methods fulfil these requirements [1]. Lately, a broad range of fluorescent sensors for explosive monitoring have been developed based on calixarenes [2]. Fluorophores like naphthalene, anthracene and pyrene are among the most incorporated in the calixarene framework, leading to potential fluorescent probes for NACs.

This work reports the affinity of dihomooxacalix[4]arene derivatives **1** and **2**, containing naphthylurea residues at the lower rim, towards selected NACs [3]. Their affinity in solution was determined by UV-Vis, fluorescence and NMR spectroscopy, and the sensing of NAC vapours was performed by dispersing the calixarenes in a PTFE matrix.





Funding: Authors thank FCT, Projects UID/00100/2025, UID/PRR/100/2025, LA/P/0056/2020 and UID/04565/2025.

References

[1] Li, L.; Lyu, X.; Liang, S.; Liu, Z. *Dyes and Pigments* **2023**, *220*, 111651.
[2] Kumar, R.; Sharma, A.; Singh, H.; Suating, P.; Kim, H. S.; Sunwoo, K.; Shim, I.; Gibb, B. C.; Kim, J. S. *Chem. Rev.* **2019**, *119*, 9657-9721.
[3] Gil, B. V.; Miranda, A. S.; Marcos, P. M.; Ascenso, J. R.; Palmeira, T.; M. N. Berberan-Santos, Schurhammer, R.; Hickey, N.; Joshi, S.; Geremia, S. *Molecules* **2025**, *30*, 3901.

Next-generation of organic upconverters: dithienopyrrole annihilators for TTA-UC-based bioimaging probes

Nuna Ramos[1,2], João Pina[2], Susana P.G. Costa[1], M. Manuela M. Raposo[1*]

[1]*Chemistry Centre of the University of Minho, Campus de Gualtar, 4710-057 Braga;*
[2]*University of Coimbra, CQC-IMS, Department of Chemistry, Rua Larga, 3004-535 Coimbra*
** E-mail: mfox@quimica.uminho.pt*

Triplet-Triplet Annihilation Upconversion (TTA-UC) is a photochemical process that converts low-energy photons into higher-energy emission, through sequential triplet sensitization and biomolecular annihilation. This particular approach uses two molecular components: a sensitizer, which absorbs the excitation light and an annihilator, which accepts the triplet energy to generate an emissive singlet state [1]. Owing to features such as large anti-Stokes shift, long luminescence lifetimes and high photostability, TTA-UC systems have emerged as an excellent platform for in vitro and in vivo bioimaging [2].

Motivated by these advantages, this work is based on the synthesis of new annihilator molecules bearing a dithienopyrrole core and on the comprehensive study of their photophysical properties. Steady-state and time-resolved measurements, together with TTA-UC experiments in deoxygenated toluene solutions using PtOEP as the sensitizer, were performed. The resulting TTA-UC systems exhibited efficient upconversion emission under the applied excitation conditions, highlighting dithienopyrrole based annihilators as promising candidates for next-generation of organic upconverters (**Figure 1**). These experiments were caried out with the aim of encapsulating these TTA-UC pairs into biocompatible PLGA nanoparticles, enabling their use as probes in bioimaging applications [3].

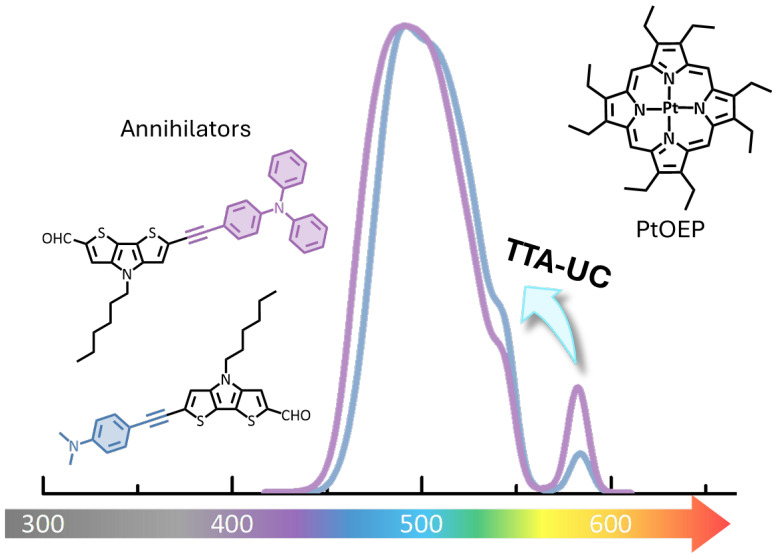


Figure 1. Upconversion emission of the TTA-UC systems, using dithienopyrrole as annihilators.

Funding: The authors acknowledge the Portuguese Foundation for Science and Technology (FCT), for the Strategic Funding to Centro de Química da Universidade do Minho (CQ-UM, UID/00686/2025), a PhD grant to N. Ramos (2022.09970.BD) and for funding Coimbra Chemistry Centre projects UIDB/00313/2025 and UIDP/00313/2025. Thanks are also due to the Portuguese NMR Network.

References

[1] Edhborg, F.; Olesund, A.; Albinsson, B.; Photochem. Photobiol. Sci. 2022, 21, 1143–1158.
[2] Huang, L; Kakadiaris, E.; Vaneckova, T.; Huang, K.; Vaculovicova, M.; Han, G.; Biomaterials 2019, 201, 77–86.
[3] Vepris, O.; Eich, C.; Feng, Y.; Zhang, H.; Kaijzel, E.L.; Cruz, L.J.; bioRxiv 2020, 9.

Synthesis of carbohydrate-based antibacterial agents with potential against multidrug-resistant Gram-negative bacteria

Catarina Maria[1*], N. M. Xavier[2], R. F. M. de Almeida[1], A. P. Rauter[1]

[1]Centro de Química Estrutural, Institute of Molecular Sciences (CQE-IMS), Faculdade de Ciências, Universidade de Lisboa, Campo Grande 016, 1749-016 Lisboa, Portugal; [2]Research Institute for Medicines (iMed.ULisboa), Faculdade de Farmácia, Universidade de Lisboa, Avenida Prof. Gama Pinto, 1649-003 Lisboa, Portugal;
[*]E-mail: cbmaria@fc.ul.pt

Gram-negative bacteria (GNB) are considered as top priority for research and development by the World Health Organization [1]. Over the past two decades, our group has been dedicated to address antimicrobial resistance by developing novel dodecyl deoxyglycosides as antibacterial agents with potential to target Gram-positive bacteria (GPB) [2-5]. The mechanism of action of these compounds is related to their interaction with phosphatidylethanolamine (PE) lipids present in the cytoplasmic membrane of GPB. In GNB, although these compounds presented promising results when interacting with their inner membrane (IM), they could not cross their outer membrane (OM), which presents distinct properties [5]. GNB also present a peptidoglycan cell wall between the OM and the IM that is composed of *N*-acetyl muramic acid-β-1,4-*N*-acetylglucosamine (MurNAc-β-1,4-GlcNAc) repeat units. Our objective is to synthesize carrier-linked prodrugs that mimic MurNAc-β-1,4-GlcNAc units, while bearing a dodecyl deoxyglycoside in the place of the GlcNAc moiety. For this approach, two classes of precursors should be synthesized: (i) the protected dodecyl glycosides and (ii) the protected carrier sugars, syntheses that will be followed by coupling of these precursors and deprotection. Computational studies will also be performed to select deoxygenation patterns and molecular structure.

With this approach, we aim at contributing with new antibiotic modes of action to overcome AMR.

Funding: Fundação para a Ciência e a Tecnologia (FCT) is gratefully acknowledged for the granting of the PhD Studentship 2023. 01083. UIDB. Also, FCT is acknowledged for funding of CQE (UID/100/2025) and IMS (LA/P/0056/2020) and iMed.ULisboa (UID/04138/2025; https://doi.org/10.54499/UID/04138/2025).

References

[1] World Health Organization; 2023 Antibacterial Agents in clinical Development and Preclinical Development: An Overview and Analysis; World Health Organization: Geneva, 2024.
[2] Silva, F.; et al.; Bioorg. Med. Chem. 2008, 16, 4083.
[3] Martins, A.; et al.; Eur. J. Org. Chem 2013, 2013, 1448.
[4] Dias, C.; et al.; Que. J. Org. Chem. 2019, 2019, 2224.
[5] Dias, C.; et al; Nat. Commun. 2018, 9, 4857.

Targeted unnatural amino acid substitutions in the polymyxin B scaffold drive broad antibacterial activity

Mariana E. Linhares[1,2*], Susana P. Lopes[2,3], Susana P. G. Costa[1]

[1]*Chemistry Centre of the University of Minho, Campus de Gualtar, 4710 -057, Braga, Portugal;*

[2]*Centre of Biological Engineering, University of Minho, Campus de Gualtar, 4710 –057, Braga, Portugal;*

[3]*LABBELS – Associate Laboratory, Braga/Guimarães, Portugal*

** E-mail: marianalinhares71@gmail.com*

Antimicrobial resistance is one of the most pressing global health challenges [1]. The World Health Organization highlighted several Gram-negative pathogens, including *Pseudomonas aeruginosa, Klebsiella pneumoniae*, and *Acinetobacter baumannii*, as well as Gram-positive bacteria (e.g. *Staphylococcus aureus*) as critical priorities, due to their high levels of multidrug resistance and the limited efficacy of current therapeutic options [2]. Polymyxins (PM) have re-emerged as last-resort antibiotics for treating infections caused by multidrug-resistant Gram-negative bacteria, despite concerns regarding nephrotoxicity and neurotoxicity. This renewed relevance has stimulated the development of new PM analogues with improved pharmacological profiles [3].

A common strategy is to replace selected amino acids in the native structure aiming to improve antimicrobial activity and toxicity. In this work, new polymyxin B (PMB) analogues were prepared by MW-SPPS, by incorporating structurally related unnatural amino acids in the native sequence. The new polymyxin analogues were evaluated against clinically relevant Gram-negative and Gram-positive bacterial pathogens, namely *Pseudomonas aeruginosa* and *Staphylococcus aureus*, by determining the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC). Structural differences in the analogues, especially at the cyclic heptapeptide part, resulted in promising activity against *P. aeruginosa* and effective anti-staphylococcal action against *S. aureus*.

Acknowledgements: The authors acknowledge funding by Fundação para a Ciência e Tecnologia (FCT) to the POLYmix-POLYmic project (2022.06595.PTDC), and in the framework of the Strategic Funding to the Chemistry Centre of the University of Minho (CQ-UM, UID/00686/2025, https://doi.org/10.54499/UID/00686/2025), and Centre of Biological Engineering (CEB, , UID/04469/2025, https://doi.org/10.54499/UID/04469/2025), and LABBELS (Associate Laboratory in Biotechnology, Bioengineering and Microelectromechanical Systems, LA/P/0029/2020, https://doi.org/10.54499/LA/P/0029/2020).

References

[1] Akram F.; Imtiaz M.; ul Haq I.; Emergent crisis of antibiotic resistance: A silent pandemic threat to 21st century. Microb Pathog, 2023, Volume 174, 105923. https://doi.org/10.1016/j.micpath.2022.105923

[2] World Health Organization. WHO Bacterial Priority Pathogens List, 2024: Bacterial Pathogens of Public Health Importance to Guide Research, Development and Strategies to Prevent and Control Antimicrobial Resistance. Geneva: World Health Organization, 2024. https://iris.who.int/bitstream/handle/10665/376776/9789240093461-eng.pdf?sequence=1

[3] Nang, S. C.; Azad, M. A. K.; Velkov, T.; Zhou, Q.; Li, J; Rescuing the last-line Polymyxins: achievements and challenges. Pharmacol. Rev., 2021, Volume 73, pp. 679-728. https://doi.org/10.1124/pharmrev.120.000020

Exploring iridium apigenin complexes: synthesis and cytotoxic studies

Maria João Ferreira[1,*], Mariana Louzeiro[1], Pedro Pinheiro[1], Ljiljana E. Mihajlović[2], Tobias Doliner[3], Miljan Ćorović[3],Jörg A. Schachner[3]

[1]*Centro de Química Estrutural, Institute of Molecular Sciences, Department of Chemical Engineering Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais 1, 1000-049 Lisboa, Portugal;* [2]*Innovation Center of the Faculty of Chemistry, Belgrade, Studentski trg 12–16, 11158 Belgrade, Serbia;* [3]*Institute of Chemistry, University of Graz, Schuberstr. 1, 8010 Graz, Austria*

** E-mail: m.joao.ferreira@tecnico.ulisboa.pt*

Apigenin (Fig. 1) is a naturally occurring flavone found in many fruits, vegetables and medicinal plants, that is known for its diverse biological activities.[1] n addition to its bioactivity, apigenin has recently been explored as a supporting ligand in rhenium chemistry, affording complexes with catalytic activity in epoxidation reactions.[2]

In this work, we report the reaction of $[Cp^*Ir\ Cl_2]_2$ with apigenin (apg) in methanol to afford complexes of the type [Cp*Ir (apg)Cl] and $[Cp^*Ir\ (apg)_2]$ (Fig. 1), that were isolated and structurally characterized. Preliminary biological studies performed on Jurkat cell lines reveal cytotoxic activity, highlighting the potential of iridium–apigenin complexes as bioactive metal-based compounds. Further investigations into their structure–activity relationships are currently underway.

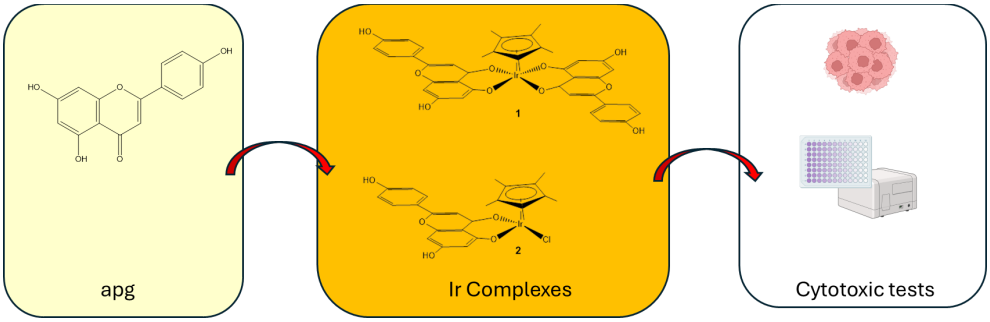


Figure 1. Ligand and Iridium complexes.

Funding: Project "Metal complexes of a naturally inspired framework functionalized for cytotoxic and catalytic efficiency", acronym MET-EFFECT, was funded by the European Research Executive Agency from the Marie Skłodowska-Curie Actions (call: HORIZON-MSCA-SE-2021), project number 101086373.

Acknowledgements: The authors acknowledge the European Research Executive Agency for funding MET-EFFECT, Centro de Química Estrutural is a Research Unit funded by Fundação para a Ciência e Tecnologia through projects UIDB/00100/2020 and UIDP/00100/2020. Institute of Molecular Sciences is an Associate Laboratory funded by FCT through project LA/P/0056/2020. We also acknowledge the Ministry of Science, Technological Development and Innovation of Republic of Serbia, grant number 451-03-66/2024-03/200288 and the Innovative Centre Faculty of Chemistry Belgrade Ltd, Studentski trg 12-16, Belgrade, Serbia. NAWI Graz is also acknowledged for financial support.

References

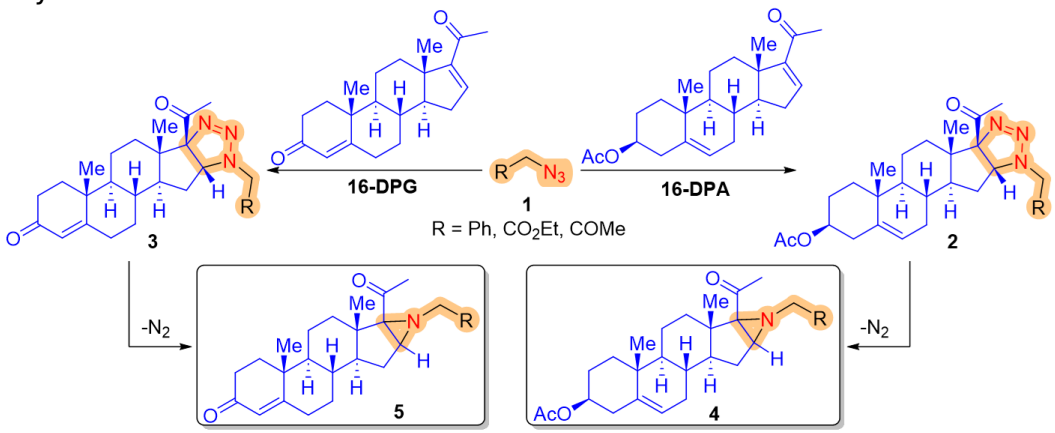
[1] Mihajlović, L.E.; Trif, M.; Živković, M.B.; Inorganics 2025, 13(8), 250-290.

[2] Milovanović, M.R.; Nikolić, S.R.; Dupé, A; Schachner, J.A. Mihajlović, L.E; Dalton Trans., 2025, 54, 11047-11055

A synthetic strategy towards novel aziridine-fused steroids

Terver J. Sase*, Susana M.M. Lopes, Ana L. Cardoso, Teresa M.V.D. Pinho e Melo
[1]*University of Coimbra, Coimbra Chemistry Centre-Institute of Molecular Science (CQC-IMS), Department of Chemistry,3000-535 Coimbra, Portugal.*
**E-mail: terversase@gmail.com*

Steroids are an important class of natural and synthetic bioactive compounds that exhibit a wide range of pharmacological activities. Structural modulation through introducing heteroatoms and/or heterocycles onto steroid backbone has emerged as the most fruitful strategy for the development of new therapeutics [1]. In our research group, 16-dehydropregnenolone acetate **(16-DPA)** and 16-dehydroprogesterone (**16-DPG**) have served as key building blocks for synthesizing ring-fused steroidal compounds with interesting biological properties [2]. These compounds have been obtained *via* [8π+2π] cycloaddition of diazafulvenium methides with steroids, as well as by pyrrolidine-induced annulation/cycloaddition reactions of steroidal 1-azadienes with carbonyl compounds [2]. This communication presents our efforts to expand this strategy for discovering new biologically active steroids. Hence, the 1,3-dipolar cycloaddition reactions of **16-DPA** and **16-DPG** towards organic azides were studied, leading to the corresponding chiral triazoline-fused steroids (Scheme 1). Subsequent N_2 extrusion, afforded novel aziridine-fused steroids. Details of this study will be discussed.



Scheme 1. Synthesis of Novel Heterocyclic-fused Steroids.

Funding: Coimbra Chemistry Centre-Institute of Molecular Sciences (CQC-IMS) is funded by Fundação para a Ciência e a Tecnologia (FCT), Portuguese Agency for Scientific Research, through projects UID/PRR/00313/2025 (https://doi.org/10.54499/UID/PRR/00313/2025) and UID/00313/2025 (https://doi.org/10.54499/UID/00313/2025) and IMS through special complementary funds provided by FCT (project LA/P/0056/2020, https://doi.org/10.54499/LA/P/0056/2020). PhD grant awarded to T. J. Sase from the Tertiary Education Trust Fund (TetFund), Nigeria.
Acknowledgements: The authors acknowledge the UC-NMR facility for the NMR data (www.nmrccc.uc.pt).

References:

[1] Sharma, K.; Kumar, H.; Priyanka; *Steroids* **2023**, *191*, 109171.
[2] a) Lopes S. M. M.; Pinho e Melo T. M. V. D., *et. al., Org. Biomol. Chem.* **2015**, *13*, 9127. b) Lopes S. M. M.; Pinho e Melo T. M. V. D., *et. al.*, *Steroids* **2017**, *122*, 16. c) Lopes S. M. M.; Pinho e Melo T. M. V. D., *et. al.*, *Eur. J. Med. Chem.* **2019**, *178*, 168. d) Lopes S. M. M.; Gomes C.S.B.; Pinho e Melo T. M. V. D. *Org. Lett.* **2018**, *20*, 4332. e) Lopes S. M. M.; Santos J. R. C.; Pinho e Melo T. M. V. D. *Org. Biomol. Chem.* **2021**, *19*, 1122. f) Lopes S. M. M.; Pinho e Melo T.M.V.D., *et. al. J. Steroid Biochem. Mol. Biol.* **2023**, *225*, 106194.

Stereoselective electrochemical 1,4-dicyanation of abietanes

Inês S. Martins[1,2],* Jaime A. S. Coelho[2], Carlos A. M. Afonso[1]

[1]*Instituto de Investigação do Medicamento (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal;* [2]*Centro de Química Estrutural, Institute of Molecular Sciences (CQE-IMS), Faculty of Sciences, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal.*

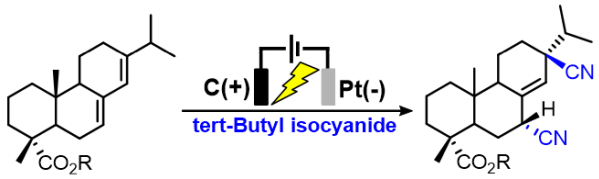
** E-mail: inesmartins5@edu.ulisboa.pt*

Colophony, a natural resin extracted from pine trees, has multiple industrial applications and is constituted by a group of diterpenes known as abietanes, which, along with their derivatives, have been found to have a wide variety of relevant biological activities [1,2].

The cyano moiety is a versatile group that is widely found in the structure of many valuable chemical products and can be converted into a variety of functional groups [3,4,5].

Electrochemistry has emerged as a powerful and sustainable tool, offering an alternative to traditional cyanation methods that often rely on hazardous reagents or harsh conditions [3,5,6]. Regarding the source of the cyano group, a variety of reagents have been used, including cyanide salts, metal- or metalloid-bound cyanides, cyano-group-containing reagents, and reagents that generate a cyano unit in situ during the reaction [5,6]. There has been great interest devoted to this latter class of cyanation reagents, particularly isocyanides, as they serve as versatile building blocks for the synthesis of a wide range of *N*-containing molecules [5,7].

Herein, we report the development of an electrochemical 1,4-dicyanation cyanation of abietanes, optimized through screening different conditions, such as electrode material, charge density, supporting electrolytes, cyano sources and solvents. Density functional theory (DFT) calculations were performed to gain mechanistic insights into the transformation. This work not only presents a novel electrochemical transformation of conjugated olefinic systems but also enables access to previously unexplored derivatives via functionalization at two underexplored olefinic positions of abietanes (Scheme 1).



R = H (AA) or Me (MAA) **up to 72% yield (79:21 d.r.)**

Scheme 1: Electrochemical double cyanation of abietic acid (AA) and methyl abietate (MAA).

***Acknowledgements*:** We thank the Fundação para a Ciência e a Tecnologia (FCT) through projects 2022.04623.PTDC, PTDC/QUI-QOR/1786/2021 (https://doi.org/10.54499/PTDC/QUI-QOR/1786/2021), UID/00100/2025, UID/PRR/100/2025, LA/P/0056/2020 (https://doi.org/10.54499/LA/P/0056/2020), UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025) for financial support. I.S.M. thanks FCT for a PhD scholarship (2022.11562.BD, https://doi.org/10.54499/2022.11562.BD).

References

[1] M.A. González, et al. *Eur. J. Med. Chem.* **2009**, 44, 2468–2472; [2] G. Eksi, et al. Analysis of diterpenes and diterpenoids. Recent Advances in Natural Products Analysis, S. M. Nabavi, M. Saeedi, S. F. Nabavi, A. T. S. Silva, Eds., Elsevier Inc., 2020, 313–345; [3] H. Hu, et al. *J. Energy Chem.* **2022**, 70, 542-575; [4] Y. Xia, et al. *Eur. J. Org. Chem.* **2021,** 48, 6658–6669; [5] Y. Shan, et al. *Chem. Commun.* **2024**, 60, 1546–1562; [6] M. Karkas, *Chem. Soc. Rev.* **2018**, 47, 5786–5865; [7] S. Thang, et al. *Org. Lett.* **2022**, 24, 2125–2130.

Phosphine-driven Umpolung γ-addition of iminochromanes to allenoates for the synthesis of functionalized 2*H*-chromenes

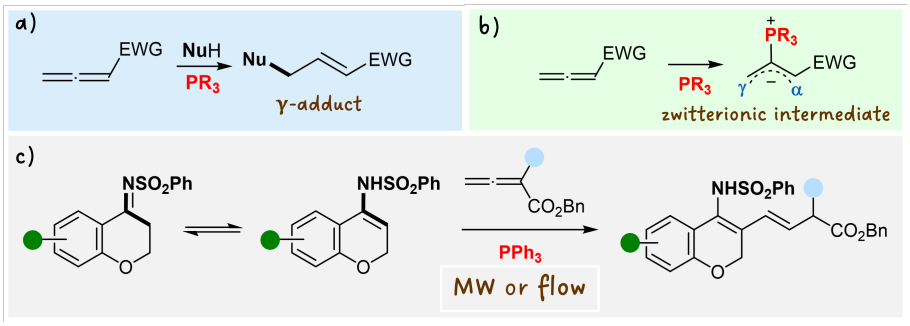
Maria I. L. Soares*, Gustavo F. M. Mourinho, Jéssica Macedo, Teresa M. V. D. Pinho e Melo

University of Coimbra, Coimbra Chemistry Centre - Institute of Molecular Sciences (CQC-IMS), Department of Chemistry, 3004-535 Coimbra, Portugal

** E-mail: misoares@qui.uc.pt*

Electron-deficient allenes, such as allenoates, are versatile building blocks due to their two orthogonal C=C bonds, which makes them highly reactive toward nucleophiles, electrophiles, and radicals, as well as in cycloaddition reactions [1]. Nucleophiles typically add to the α,β-C=C bond to give Michael-type adducts. However, in the presence of a catalytic amount of phosphine, the nucleophile adds to the β,γ-C=C bond of the allene. This occurs through the formation of a zwitterionic intermediate, resulting in the formation of γ-adducts (**Scheme 1a,b**).

Our group is interested in Lewis base-catalyzed reactions involving allenes and chromene substrates for constructing chromane scaffolds. While studying the reactivity of allenoates with 3-nitrochromenes, we described the synthesis of ring-fused chromanes via PPh_3- and DABCO-catalyzed annulation reactions [2]. More recently, we have explored the PPh_3-catalyzed umpolung nucleophilic addition of iminochromanes to allenoates, enabling the synthesis of substituted 2*H*-chromenes under both microwave irradiation (MW) and flow chemistry conditions (**Scheme 1c**). In this communication, further details of this study will be disclosed.



Scheme 1. Phosphine-catalyzed umpolung γ-addition of nucleophiles to electron-deficient allenes.

Funding: CQC-IMS is supported by the Fundação para a Ciência e a Tecnologia (FCT), Portuguese Agency for Scientific Research. CQC is funded by FCT through projects UID/PRR/00313/2025 (DOI: 10.54499/UID/PRR/00313/2025) and UID/00313/2025 (DOI: 10.54499/UID/00313/2025) and IMS through special complementary funds provided by FCT (project LA/P/0056/2020 DOI: 10.54499/LA/P/0056/2020). GFMM thanks *Programa Bolsas Novos Talentos Gulbenkian* and JM thanks FCT (2024.00332.BDANA) for financial support

Acknowledgements: The authors acknowledge the UC-NMR facility for obtaining the NMR data (www.nmrccc.uc.pt).

References

[1] a) Ma, S. *Aldrichim. Acta* **2007**, *40*, 91; b) Pinho e Melo, T. M. V. D. *Monatsh. Chem*. **2011**, *142*, 681.

[2] a) Soares, M. I. L.; Gomes, C. S. B.; Nunes, S. C. C.; Pais, A. A. C. C.; Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem*. **2019**, 5441. b) Soares, M. I. L.; Gomes, C. S. B.; Oliveira, M. C.; Marçalo, J.; Pinho e Melo, T. M. V. D. *Org. Biom. Chem*. **2021**, *19*, 9711.

Synthesis of analogues of marine-derived cyclopeptides and evaluation of antifungal synergistic effect with fluconazole

Ricardo Ribeiro,[1,2] Joana Cardoso,[1,2] Diana I.S.P. Resende,[1,2,3] Eugénia Pinto,[2,4] Emília Sousa,[1,2] and Carla Fernandes[1,2*]

[1] *LQOF, Laboratório de Química Orgânica e Farmacêutica, Departamento de Ciências Químicas, Faculdade de Farmácia, Universidade do Porto, Porto, Portugal.*
[2] *CIIMAR/CIMAR LA, Centro Interdisciplinar de Investigação Marinha e Ambiental, Universidade do Porto, Matosinhos, Portugal.*
[3] *ICBAS, Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal.*
[4] *Laboratory of Microbiology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal.*
** E-mail: cfernandes@ff.up.pt*

Fungal infections are a significant threat to human health. The emergence of multidrug-resistant strains of fungi and the growing prevalence of azole resistance in invasive fungal infections exacerbate the problem, with efflux pumps being a major cause of antifungal resistance and a prime target for several counteractive strategies. Marine cyclopeptides such as unnarmicins A and C are distinguished by their ability to overcome antifungal resistance, particularly through inhibition of efflux pumps such as fungal ABC transporters [1].

This work reports an initial *in silico* investigation of unnarmicin analogues interacting with the CaCdr1p efflux pump via molecular docking to identify the most promising candidates [2]. Subsequent total synthesis of unnarmicin-derived cyclopeptides was accomplished using solution-phase methods with orthogonal protecting/deprotecting groups and coupling reagents. Initial cyclization via amide-bond formation proved inefficient due to low yields and challenging purifications; consequently, the strategy was revised to employ a “CyClick” approach [3]. This methodology facilitated cyclization through imine formation and intramolecular trapping, yielding fused 4-imidazolidinone cyclopeptides.

The antifungal activity of the synthetized compounds was evaluated. Although they did not exhibit activity against a series of yeast strains, the combination of each compound with fluconazole (FLC) resulted in a reduced minimum inhibitory concentration relative to FLC alone. These results suggest a synergistic effect with FLC.

Funding and Acknowledgements: This research was supported by national funds through FCT within the scope of Base Funding UIDB/04423/2020 and UIDP/04423/2020 (Group of Marine Products and Medicinal Chemistry - CIIMAR). Ricardo Ribeiro thanks BYTPhD program by CIIMAR, grant provided by FCT UI/BD/150912/2021. Joana Cardoso acknowledges FCT for the individual PhD grant (2022.10043.BD) and Diana I.S.P. Resende for funding under the Scientific Employment Stimulus- Individual Call (Ref. 2022.00379.CEECIND/CP1728/CT0001, DOI: 10.54499/2022.00379.CEECIND/CP1728/CT0001).

References

[1] Tanabe, K., et al. Biochem. Biophys. Res. Commun., 2007, 364(4), 990-995.
[2] Ribeiro, R., et al. Drugs Drug Candidates, 2024, 3(3), 537-549.
[3] Adebomi, V., et al. Angew. Chem., 2019, 131, 19249-19256.

Synthesis, and structural and antimicrobial assessments of a modified CW49 peptide for enhanced wound repair

A. Francisca G. Silva[1,2], Sílvia M.M.A. Pereira-Lima[1], Helena P. Felgueiras[2], Jennifer Noro[1] and Susana P. G. Costa[1*]

[1]*Chemistry Centre of the University of Minho (CQ-UM), Campus of Gualtar, 4710-057 Braga, Portugal;*
[2]*Centre for Textile Science and Technology (2C2T), University of Minho, Campus of Azurém, 4800-058 Guimarães, Portugal;*
** E-mail: spc@quimica.uminho.pt*

Diabetes mellitus (DM) is a chronic metabolic disorder that ranks among the top ten leading causes of death worldwide, which led the World Health Organization to classify it as a global epidemic in 2021 [1]. Individuals with DM face an estimated 25% lifetime probability of developing diabetic foot ulcers chronic, hard-to-heal lesions that are highly prone to infection and may progress to systemic complications and even limb amputation [2]. The undecapeptide CW49 has shown encouraging biological activity by downregulating inflammatory mediators such as IL-6 and TNF-α while promoting the expression of angiogenesis-related proteins, all of which are advantageous for supporting wound repair in diabetic conditions [3]. Nevertheless, CW49 has not been associated with antimicrobial activity, an important feature for comprehensive wound management given that the presence of pathogenic microorganisms can further delay or impair tissue regeneration [4].

Here, we present the synthesis and characterization of a CW49 analogue designed to enhance the antibacterial performance while maintaining the anti-inflammatory properties of the original wound-healing peptide. Its antimicrobial efficacy was evaluated against both Gram-positive and Gram-negative bacteria, through minimum inhibitory and bactericidal concentration tests, which confirmed the enhanced antibacterial activity. The peptide was characterised by NMR spectroscopy, mass spectrometry and its secondary structure was evaluated by circular dichroism spectroscopy. Also, the cell wall disruption mechanism was evaluated through SEM analysis.

***Acknowledgements*:** The authors acknowledge the Portuguese Foundation for Science and Technology (FCT) for financial support to the Chemistry Centre of the University of Minho (CQ-UM, UID/00686/2025, https://doi.org/10.54499/UID/00686/2025) and a PhD grant (2022.11171.BD) to A.F.G. Silva. The authors acknowledge FCT, I.P. and Programa de Recuperação e Resiliência (PRR) through NextGenerationEU from the European Union, under the Strategic Projects UID/00264/2025 and UID/PRR/00264/2025 of Centre for Textile Science and Technology (2C2T) (https://doi.org/10.54499/UID/00264/2025 and https://doi.org/10.54499/UID/PRR/00264/2025). H.P.F. also acknowledges FCT for auxiliary researcher contract 2021.02720.CEEIND.

References

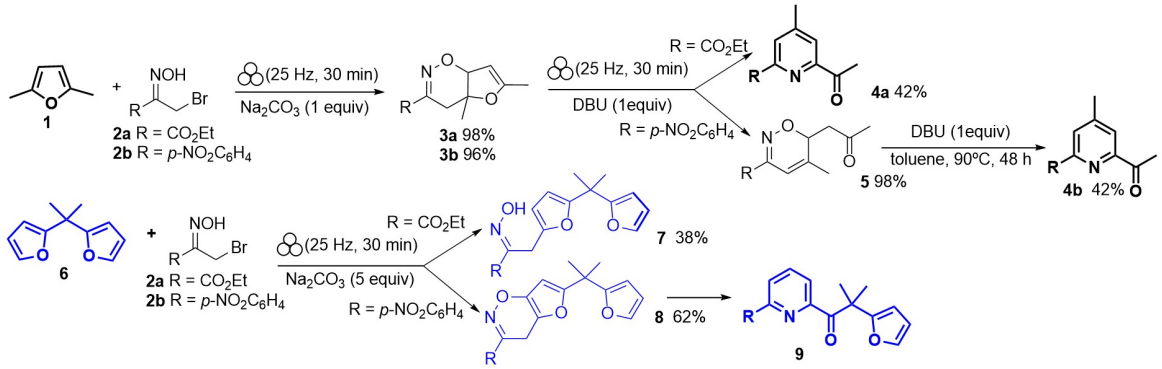
[1] Global Health Estimates 2021: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2021. World Health Organization: Geneva, 2024.
[2] Peter-Riesch, B.; The Diabetic Foot: The Never-Ending Challenge. In Novelties in Diabetes; Stettler, C., Christ, E., Diem, P., Eds.; Karger: Basel, 2016; Volume 31, pp. 108-134.
[3] Liu, H.; Duan, Z.; Tang, J.; Lv, Q.; Rong, M.; Lai, R.; FEBS Journal 2014, 281, 4633-4643.
[4] Silva, J.; Leal, E.C.; Carvalho, E.; Biomolecules 2021, 11, 1894-1915.

Mechanochemical synthesis of pyridines from furans

Daniel Almeida-Santos[1,*], Mariana Peixoto[1], Ana L. Cardoso, Teresa M. V. D. Pinho e Melo[1], Marta Pineiro[1]

[1]*CQC– IMS, Department of Chemistry, University of Coimbra, Portugal*
** E-mail: danielsantos1328@gmail.com*

Furans are key renewable feedstocks for sustainable chemical synthesis, offering a pathway to replace petroleum-derived products. [1] Among the high-value targets, N-heterocycles are particularly important due to their widespread applications. [2] The dienophilic behavior of furan derivatives towards nitrosoalkenes has been explored in solution, paving the way to a range of dihydro-furooxazines, which could be further transformed into other functionalized heterocycles by ring-opening reactions. [3] This study presents recent advances in mechanochemical strategies for the synthesis pyridines, derived from furans via hetero-Diels–Alder (HDA) reactions involving in situ generated nitrosoalkenes (Scheme 1).



Scheme 1. Synthesis of pyridines form furanes and bis-furanes under ball milling.

Pyridine could be obtained in two-step or via oxazine from furan **1** under ball milling. Bis-furans exhibited different reactivity: the reaction with oxime **2a** failed to form furoxazines, whereas oxime **2b** yielded furoxazines, opening the way for pyridine synthesis. This approach combined the atom economy and selectivity of HDA with solvent-free mechanochemistry, reducing energy input, time, and waste for sustainable synthesis. Alternative pathways were also identified, providing a basis for exploring new reactivities. Mechanistic insights and green metrics will be presented.

Funding: Project nº 15504, PT2030, Aviso MPr-2023-12: SACCCT – Projetos de Investigação Científica e Desenvolvimento Tecnológico (IC&DT) COMPETE2030-FEDER-00651000**.** CQC-IMS supported by the Fundação para a Ciência e a Tecnologia (FCT): UID/PRR/00313/2025 (https://doi.org/10.54499/UID/PRR/00313/2025) and UID/00313/2025 (https://doi.org/10.54499/UID/00313/2025) and IMS by FCT (project LA/P/0056/2020 https://doi.org/10.54499/LA/P/0056/2020). PhD Grant (M. Peixoto), 2022.12812.BD.
Acknowledgements: We acknowledge the UC-NMR facility for the NMR data (www.nmrccc.uc.pt).

References

[1] Werpy, et al, U.S. Department of Energy: 2004; p 76; Bielski, R et al, Green Chem., 2021,23, 7458-7487
[2] Yan, Q et al, Coord. Chem Rev. 2024, 502, 215622, Qi, H et al, Nature Commun. 2023, 14, 6329
[3] Pinho e Melo, T. M. V. D., et al. *Eur. J. Org. Chem*. 2015,6146-6151; (b) Pinho e Melo, T. M. V. D. et al *Eur. J. Org. Chem*. 2017,4011-4025.

Exploring the 2-benzylbenzimidazole scaffold: synthetic strategies for toxicological insights

Daniela R. Ferreira[1,2,3*], Nuno R. Neng[2,3], Alexandre Quintas[3], Helena Gaspar[1]

[1]BioISI-Biosystems & Integrative Sciences Institute, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, Lisboa, Portugal; [2]Centro de Química Estrutural, Institute of Molecular Sciences, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, Lisboa, Portugal; [3]Laboratório de Ciências Forenses e Psicológicas Egas Moniz, Egas Moniz Center for Interdisciplinary Research, Egas Moniz School of Health & Science, Quinta da Granja, Caparica, Portugal

** E-mail: fc64813@alunos.fc.ul.pt*

The 2-benzylbenzimidazole scaffold, the chemical core of the nitazene class of synthetic opioids, represents a privileged framework within benzimidazole chemistry, offering versatile positions for structural modification and access to diverse bioactive analogues. Interest in this structure emerged in the 1950s and 1960s, when a Swiss pharmaceutical company first reported 2-benzylbenzimidazole-derived analgesics with potency exceeding that of morphine, however, none reached the therapeutic market due to safety concerns. Over the past decade, several nitazene derivatives have emerged on the illicit drug market as new psychoactive substances, posing a major public health threat due to their association with high number of overdoses and fatal intoxications [1,2].

In this work, synthetic approaches were developed to generate a diverse library of 2-benzylbenzimidazole derivatives through systematic modifications at both the benzyl substituent and the benzimidazole core for future toxicological evaluation. The synthetic route was designed and optimised based on reported methodologies for 2-benzylbenzimidazole analogues described by Renton [3] and Vandeputte [4].

All synthetic precursors were characterised by NMR and HRMS to confirm their structures. These well-characterized nitazene analogues can serve as reliable standard in forensic and clinical contexts, aiding the identification and monitoring of these potent synthetic opioids, supporting harm reduction efforts and mitigation of associated public health risks.

Funding: BioISI—Biosystems & Integrative Sciences Institute Centre is funded by Fundação para a Ciência e a Tecnologia (FCT) through the project UID/04046/2025. Centro de Química Estrutural is a Research Unit funded by FCT through projects UID/00100/2025 and UID/PRR/00100/2025. Institute of Molecular Sciences is an Associate Laboratory funded by FCT through project LA/P/0056/2020 (https://doi.org/10.54499/LA/P/0056/2020). CiiEM has provided support through Project reference UID/4585/2025 (https://doi.org/10.54499/UID/04585/2025), funded by FCT. The authors acknowledge FCT for the provisional approval of the project SENTINEL (2024.2023.16046.ICDT), funded under the PT2030 program.

Acknowledgements: Daniela R. Ferreira would like to express her gratitude for the Ph.D. scholarship (No. 2024.03215.BDANA) awarded by FCT.

References

[1] Ujváry, I.; Christie, R.; Evans-Brown, M.; *et al*. ACS Chem. Neurosci. 2021, 12, 1072–1092.
[2] Hunger, A.; Kebrle, J.; Rossi, A.; *et al*. Arzneim.-Forsch. 1960, 10, 917–922.
[3] Renton, P.; Green, B.; Maddaford, S.; *et al*. ACS Med. Chem. Lett. 2012, 3, 227–231.
[4] Vandeputte, M. M.; Van Uytfanghe, K.; Layle, N. K.; *et al*. ACS Chem. Neurosci. 2021, 12, 1241–1251.

Novel pyrazole-based compounds as potent PARP-1 inhibitors in cancer cells

Inês M. Bastos[1,*], Mariana Vassal[2], Igor Marques[3], Vítor Félix,[3] Artur M. S. Silva[1], Sandra Rebelo[2], Vera L. M. Silva[1]

[1] *LAQV-REQUIMTE and Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal;* [2] *Institute of Biomedicine—iBiMED, Department of Medical Sciences, University of Aveiro, 3810-193 Aveiro, Portugal;* [3] *Department of Chemistry, CICECO – Aveiro Institute of Materials, University of Aveiro, 3810-193, Aveiro, Portugal.*

** E-mail: inesmbastos99@ua.pt*

Pyrazole and indazole scaffolds have attracted considerable interest due to their relevant medicinal properties, particularly their anticancer potential. Poly(ADP-ribose) polymerase-1 (PARP-1), a key enzyme involved in DNA repair, is often overactivated in cancer cells, making it an important therapeutic target. Notably, several reported PARP-1 inhibitors contain pyrazole or indazole cores, reinforcing the value of these scaffolds in anticancer drug design [1].

In this context, the synthesis of new pyrazole- and indazole-based compounds as potential PARP-1 inhibitors was performed via aza-Michael and Diels–Alder reaction strategies. The obtained compounds, collectively referred to as **PZ**, present key structural features associated with PARP-1 inhibition [2].

Then, PARP-1 inhibitory activity, antiproliferative effects in HeLa cells, and the ability to induce DNA damage were evaluated. Compound **PZ-5a** showed PARP-1 inhibitory activity comparable to that of benzamide, a known PARP-1 inhibitor, and exhibited a non-toxic profile, similar to that of the reference drug Olaparib. Compounds **PZ-5d** and **PZ-5e** were the most potent inhibitors, with IC_{50} values of 0.048 ± 0.019 μM and 0.046 ± 0.011 μM. Both induced significant DNA damage in HeLa cells, consistent with PARP-1 inhibition and accumulation of DNA strand breaks. They also markedly reduced cell viability, suggesting the potential to mimic HR deficiency in HR-proficient cells, potentially through dual-target activity, broadening their therapeutic potential in cancer treatment [2].

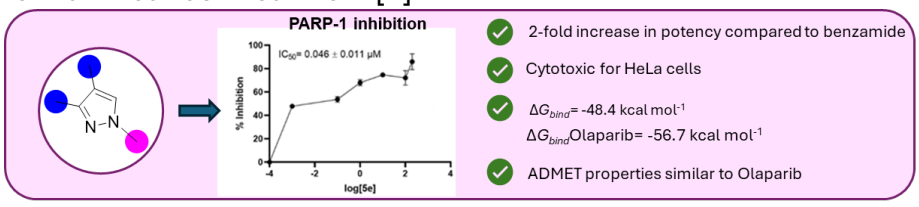


Figure 1. Pyrazole-based compounds as potent PARP-1 inhibitors.

Funding: This work received financial support from PT national funds (FCT/MCTES, Fundação para a Ciência e Tecnologia and Ministério da Ciência, Tecnologia e Ensino Superior) through the project units UIDB/50006/2020 and UIDP/50006/2020 (LAQV-REQUIMTE), and the Institute of Biomedicine (iBiMED)—UIDP/04501/2020 and UIDB/04501/2020, the COMPETE 2020 Program, the QREN and the European Union (Fundo Europeu de Desenvolvimento Regional), and from the project DNICAT-COMPETE2030-FEDER- 00792200 (nº 16740), funded by Compete 2030, Portugal 2030 and the European Union (https://doi.org/10.54499/2023.16414.ICDT).

Acknowledgements: Thanks are due to the University of Aveiro and FCT, the European Union, QREN, FEDER, and COMPETE for funding the LAQV-REQUIMTE (UIDB/50006/2020+ UIDP/50006/2020).

References

[1] Bastos IM, Rebelo S, Silva VLM. A review of poly(ADP-ribose)polymerase-1 (PARP1) role and its inhibitors bearing pyrazole or indazole core for cancer therapy. Biochem Pharmacol. 2024 Mar;221:116045.

[2] Bastos, Inês M.; "Pyrazoles and indazoles: potential PARP-1/PI3K dual inhibitors for cancer therapy." M.S. thesis, University of Aveiro, Portugal, 2023. http://hdl.handle.net/10773/44425

Aromatic aminopropyl lactams as potential anticancer agents for glioblastoma and hepatocellular carcinoma

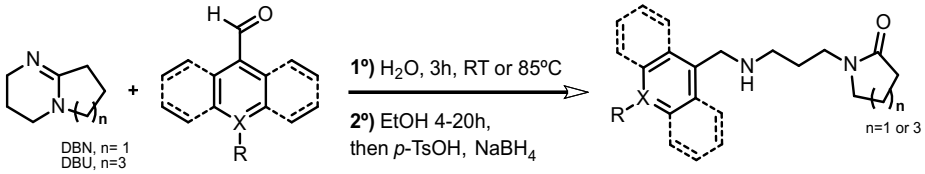
M. Margarida Martins[1,*], Bernardo Braga[1], Ruben Valente[2,3], Celine[2,3], Matilde Simão[2,3], Pedro V. Baptista[2,3], Alexandra R. Fernandes[2,3], Luísa M. Ferreira[1]

[1]Nova School of Science and Technology, Department of Chemistry, Campus da Caparica, 2825-149, Caparica (Portugal). [2]Associate Laboratory i4HB - Institute for Health and Bioeconomy, Faculdade de Ciências e Tecnologia, Universidade NOVA, 2819-516 Caparica, Portugal. [3]UCIBIO– Applied Molecular Biosciences Unit, Departamento de Ciências da Vida, Faculdade de Ciências e Tecnologia, Universidade NOVA, 2819-516 Caparica, Portuga

** E-mail: mmp.martins@campus.fct.unl.pt*

Glioblastoma (GB) and hepatocellular carcinoma (HCC) are aggressive cancers with limited treatments and high recurrence. Both exhibit overexpression of the histamine H3 receptor (H3R), a G protein-coupled receptor involved in tumor growth and metastasis [1–3]. This study explored Aromatic Aminopropyl Lactams (ArAPLs) as potential H3R antagonists. A library of ArAPLs was synthesised via a one-pot protocol involving hydrolysis of bicyclic amidines (DBN and DBU) to the corresponding *γ*- and *ε*-lactams, followed by reductive amination with aromatic aldehydes (Scheme 1).

Compounds **3.a**. and **4.a.** exhibited the most potential in 2D and 3D cell culture models of U87-MG (GB) and HepG2 (HCC) cells. While **4.a** displayed marked cytotoxicity (Scheme 1), **3.a** emerged as a promising candidate, demonstrating strong antiproliferative effects in HCC via cell cycle delay and transcriptional reprogramming. These findings offer valuable insights into the therapeutic modulation of H_3R-related pathways.



	2D cultures			3D spheroids	
	U87-MG	HepG2	Fibroblasts	U87-MG	HepG2
3.a. anthracene ring, X= C, R=H, n = 1	10.47 ± 0.07	13.34 ± 0.04	37.37 ± 0.01	71.35 ± 0.03	83.00 ± 0.03
4.a. anthracene ring, X= C, R=H, n = 3	19.17 ± 0.10	15.04 ± 0.04	28.83 ± 0.02	52.04 ± 0.01	110.00 ± 0.01

Scheme 1. Synthetic scheme to access the ArAPL library and relative IC50 values (μM) of the two best compounds in 2D monolayer cultures and in 3D tumor spheroids after 48 h of exposure.

Funding: This work was supported by the Associate Laboratory for Green Chemistry - LAQV and the Associate Laboratory Institute for Health and Bioeconomy - i4HB financed by national funds from FCT - Fundação para a Ciência e a Tecnologia, I.P., in the scope of the projects UIDP/50006/2020, UIDP/04378/2020 (10.54499/UIDP/04378/2020), UIDP/50006/2020 and UIDB/04378/2020 (10.54499/UIDB/04378/2020) and the project LA/P/0140/2020 of. MMM thanks the fellowship UI/BD/151278/2021.

Acknowledgements: FCT/MCTES is also acknowledged for the National NMR Facility Network (ROTEIRO/0031/2013-PINFRA/22161/2016, cofinanced by FEDER through COMPETE 2020, POCI, PORL, and FCT through PIDDAC).

References

[1] C. Zhang, Y. Yu, L. Ma and P. Fu, Onco Targets Ther 2020, 13, 3765-3776.
[2] D. Yu, J. Zhao, Y. Wang, J. Hu, Q. Zhao, J. Li and J. Zhu, Oncol Rep 2019, 41, 3347-3354
[3] P. Lauretta, R. Martinez Vivot, A. Velazco and V. A. Medina, Inflammation Research 2025, 74, 97.

Structure-based discovery of small-molecule inhibitors targeting a bacterial efflux pump through Fab-mimetic interactions

Festus O. Ogungbemiro [1,*], Vera M. S. Isca[1], Patricia Rijo[1,2,3], Daniel J. V. A. dos Santos[1,3*]

[1]CBIOS, Center for Research in Biosciences and Health Technologies, Universidade Lusófona, Lisboa, Portugal; [2]Center of Structural Chemistry, Institute of Molecular Sciences, University of Lisbon, Lisbon, Portugal; [3]Research Institute for Medicines (iMed.ULisboa), Faculty of Farmacy, Universidade de Lisboa, Lisboa, Portugal.
** E-mail: daniel.dos.santos@ulusofona.pt*

The NorA efflux pump of *Staphylococcus aureus* plays a central role in resistance to hydrophilic fluoroquinolones, making it an attractive target for efflux pump inhibitor (EPI) discovery. Recent cryo-EM structures of NorA complexed with Fab25 (PDB: 7LO7) and Fab36 (PDB: 7LO8) revealed conformationally distinct inhibitory states, with Fab36 exhibiting deeper binding and ~9-fold stronger affinity [1]. Leveraging these structural insights, this study employed a dual-strategy computational workflow to identify small molecules capable of replicating Fab-mediated inhibition. NorA–Fab25 and NorA–Fab36 complexes were prepared and superimposed to define a consensus inhibitory hotspot across TM4, TM5, TM7, TM8 and TM10. Both Fab-defined and full-pore docking grids were generated, enabling orthosteric and channel-blocking exploration. A curated set of 114 reference NorA inhibitors was docked using QVina to validate grid performance, followed by complex-based pharmacophore modeling derived directly from Fab36 interactions. Three pharmacophore hypotheses were constructed and screened against 2.54 million ChEMBL compounds [2], yielding filtered hit candidates predicted to reproduce key Fab contacts with Asn137, Phe140, Glu222, Phe303 and Asp307.

Top-ranked hits will be subjected to experimental validation using *S. aureus* 1199 (wild-type; basal NorA expression) and 1199B (quinolones resistante; NorA-overexpressing) strains. Planned assays include MIC determination, EtBr accumulation and efflux inhibition, SYTOX-Green membrane-permeability profiling, cytotoxicity and selectivity index evaluation, time-kill kinetics, synergy determination via checkerboard FIC, qRT-PCR/Western blot analysis of NorA expression, and resistance-induction studies. This integrated computational-experimental approach aims to identify potent, selective, novel, and non-cytotoxic NorA-Fab-mimetic inhibitors capable of restoring quinolone susceptibility and overcoming efflux-mediated resistance in *S. aureus*.

Funding: This work was funded by ILIND under projects COFAC/ILIND/CBIOS/2/2023 and FAZER+/ILIND/CBIOS/1/2025 and by FCT (Portugal), through the project with reference UID/04567/2025 and the PhD grant SFRH/BD/137671/2018.

References

[1] D. N. Brawley, D. B. Sauer, J. Li, X. Zheng, et al., Nat Chem Biol 2022, 18, 706–712.
[2] J. J. Irwin, K. G. Tang, J. Young, et al., J Chem Inf Model 2020, 60, 6065–6073.

Synthesis and modulation of human neutrophils' oxidative burst by floridoside phosphotriesters

Luís Pinheiro[1], Diogo Monteiro,[1] Marisa Freitas[2], Paula S. Branco[1*]

[1] *Department of Chemistry, NOVA School of Science and Technology, LAQV, REQUIMTE, Campus da Ca-parica, 2825-149 Caparica, Portugal*

[2]*LAQV, REQUIMTE, Laboratory of Applied Chemistry, Department of Chemical Sciences, Faculty of Pharmacy, University of Porto, 4050-313 Porto, Portugal*

** E-mail: paula.branco@fct.unl.pt*

Floridoside a natural product typically found in red algae [1] and it acylated derivatives have been associated with modulating redox homeostasis and inflammatory responses [2]. Therefore, we aimed to evaluate whether the newly synthesized floridoside phosphotriesters (**1b**-**1d**, **1f**-**1h**) and acylated floridoside derivative (**1e**) can modulate the oxidative burst in stimulated human neutrophils (**Figure 1**). The compounds were analysed for their cytotoxicity, with **1b** and **1h** being cytotoxic at 50 µM while the others showed no cytotoxicity in the tested concentrations. The detection of the neutrophils' oxidative burst was performed using multiple probes to evaluate the production of reactive species. Compound **1e** prevented the human neutrophils' oxidative burst (IC_{50} = 83 ± 7 µM) [3]. Taken together, these findings support further studies on floridoside derivatives in the context of neutrophil-driven inflammatory responses.

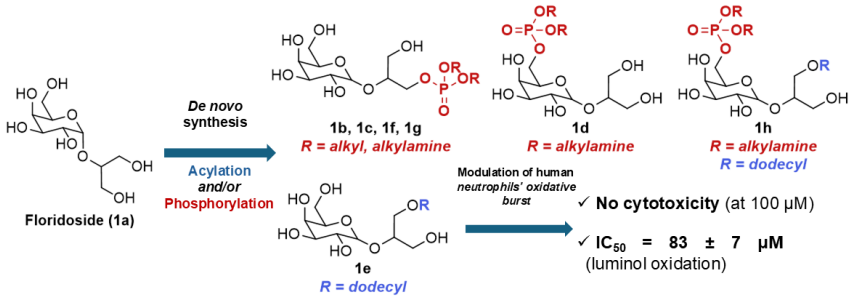


Figure 1. Structures of the synthesized compounds. The compounds were prepared via glycosylation of a thioglycoside donor with glycerol derivatives using NIS/TfOH as the promoter, followed by phosphorylation with $POCl_3$ in the presence of pyridine.

Acknowledgements: This work was financed by national funds from FCT - Fundação para a Ciência e a Tecnologia, I.P., under the scope of the project UID/50006/2023 of the Associate Laboratory for Green Chemistry-LAQV REQUIMTE. MF acknowledges her contract CEEC: 2020.04126.CEECIND/CP1596/CT0006 and LAQV/REQUIMTE: LA/P/0008/2020: DOI 10.54499/LA/P/0008/2020. LP acknowledges the Ph.D. grant UI/BD/151271/2021.

References

[1] Courtois, A.; Mar. Drugs, 2008, 6, 407–417.
[2] Pinheiro, P.; Freitas, M.M.; Branco, P.S.; ChemMedChem, 2024, 19, e202400315.
[3] Pinheiro, L.; Cipriano, C.; Santos, F.; Máximo, P.; Fernandes, E.; Freitas, M.; Branco, P.S.; Molecules, 2025, 30, 2850.

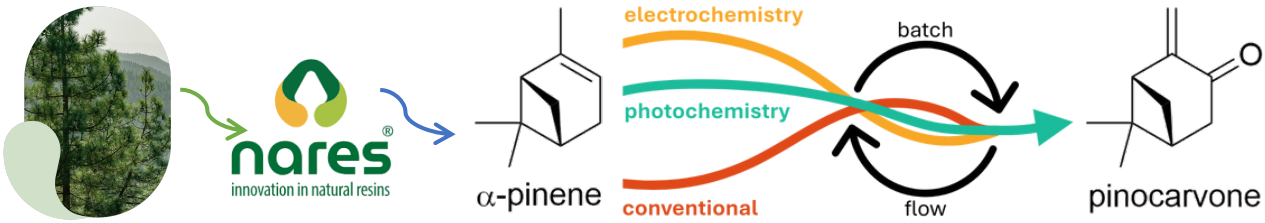
Photochemical and electrochemical oxidation pathways for the conversion of α-pinene to pinocarvone

Ricardo M. Gomes[1,*], João C. S. Simões[1], Teresa M. V. D. Pinho e Melo[1]

[1]*University of Coimbra, Coimbra Chemistry Centre-Institute of Molecular Sciences (CQC-IMS) and Department of Chemistry, 3004-535 Coimbra, Portugal*

** E-mail: ricardo4mgomes@gmail.com*

The selective oxidation of α-pinene is a valuable transformation for producing pinocarvone, a versatile intermediate used in the synthesis of fine chemicals, advanced polymers, and functional materials [1]. This project investigates new, sustainable strategies for the quantitative oxidation of α-pinene, including photochemical [2,5] and electrochemical approaches [6]. In the photochemical studies, tetraphenylporphyrin (TPP) derivatives were employed as benchmark photocatalysts, while ring-fused chlorins – previously disclosed by our group for their application in photodynamic therapy (PDT) [7,8] – were explored as alternative catalysts. Owing to their enhanced electronic properties and superior light absorption, these chlorins demonstrated potential to improve reaction efficiency and pinocarvone yields. In parallel, electrochemical oxidation was examined as a green, reagent-free method that enables selective ketone formation through controlled potentials, reducing waste and minimizing undesired by-products. By comparing these complementary methodologies in both conventional batch setups and continuous-flow chemistry, the project aimed to optimise reaction conditions, elucidate mechanistic pathways, and assess the scalability and environmental benefits of each oxidation route. Overall, this work contributes to the development of efficient, sustainable, and mechanistically informed oxidation strategies for terpene-derived substrates.



Scheme 1. Schematic routes towards the selective oxidation of α-pinene.

Acknowledgements: CQC-IMS is supported by Fundação para a Ciência e a Tecnologia (FCT) through projects UIDB/00313/2025 and UIDP/00313/2025 and LA/P/0056/2020. The authors also acknowledge **NARES – Resinas Naturais, Lda.** for their support and collaboration, which contributed significantly to the development of this work.

References

[1] Nyamwihura, R. J.; Ogungbe, I. V.; RSC Adv. 2022, 12 (18), 11346-11375.
[2] Miyaji, H.; Satoh, K.; Kamigaito, M.; Angew. Chem. Int. Ed. 2016, 55 (4), 1372-1376.
[3] Maraval, V.; Ancel, J-E.; Meunier, B.; J. Cat. 2002, 206, 349–357
[4] Mihelich, E. D.; Eickhoff, D. J.; J. Org. Chem. 1983,48, 4135-4137
[5] Loponov, K. N.; *et al.*; Org. Process Res. Dev. 2014, 18, 1443−1454
[6] Mateus Afonso, C. A.; Coelho, J.; Martins, I.; ChemRxiv. 2022
[7] Pereira, N. A. M.; Serra, A. C.; Pinho e Melo, T. M. V. D.;Eur. J. Org. Chem. 2010, 6539–6543
[8] Pereira, N. A. M., *et al.*; Eur. J. Med. Chem. 2015, 103, 374 -380

In vitro validation of PARPi derivatives activity for metastatic triple negative breast cancer

Rafaela Silva[1], Leonardo Miranda[2], Miguel A.R.B. Castanho[1,3], Marco Cavaco[1,3]

[1]*Faculdade de Medicina da Universidade de Lisboa, Av Prof. Egas Moniz 1649-028 Lisboa, Portugal ;*

[2]*Instituto Superior Técnico, Av. Rovisco Pais 1, 1049-001 Lisboa, Portugal ;*

[3]*Fundação GIMM -Gulbenkian Institute for Molecular Medicine, Av Prof. Egas Moniz 1649-028 Lisboa, Portugal*

E-mail: rafaelassilva@edu.ulisboa.pt

Triple-negative breast cancer (TNBC) is one of the most aggressive subtypes of breast cancer, characterized by high rates of recurrence and development of distant metastases, typically to the brain, lungs, and bones. Defined by the lack of estrogen and progesterone receptors as well as the absence of HER2 amplification, its molecular profile excludes the use of hormone therapy and HER2-targeted therapies, thereby leaving fewer treatment options. Recently, Poly(ADP-ribose) Polymerase Inhibitors (PARPi) such as Olaparib have shown effectiveness in BRCA-mutated primary TNBC; however, their efficacy against metastases is less consistent [1]. This study aims to develop and validate PARPi derivatives conjugated to a BBB-shuttle peptide (BBBpS) previously characterized by our group, to enhance brain bioavailability while maintaining antitumoral activity. The initial phase of the project involved the design of multiple Olaparib derivatives incorporating linkers with distinct physicochemical properties. These compounds were evaluated for cytotoxicity in endothelial cells and for antitumoral efficacy in several TNBC cell lines with and without BRCA mutations. In parallel, two BBBpS bearing conjugate moieties in different positions were assessed for their ability to retain BBB translocation capacity. Based on these results, two PARPi-BBBpS conjugates were selected for further in vitro evaluation of BBB translocation and anticancer activity, as well as antiproliferation and apoptosis capacity.

Among the Olaparib derivatives tested, compound 73 exhibited biological activity comparable to the parent drug across all TNBC cell lines. The derivatized peptides BBBpS_1A and BBBpS_2A maintained translocation levels similar to their non-derivatized counterparts. The resulting conjugates BBBpS_1A-73 e BBBpS_2A-73, showed a slight reduction in cytotoxic potency relative to Olaparib but preserved effective BBB-crossing capability, representing an improvement over the free drug in terms of brain delivery potential.

Although PARPi-BBBpS conjugation led to a modest decrease in in vitro biological activity, the enhanced BBB permeability constitutes a significant advantage. These results support the continued development of these conjugates, with future biodistribution and efficacy studies planned to determine whether increased brain accumulation can translate into improved therapeutic outcomes for TNBC-derived brain metastases.

Funding: FCT 2023.12099.PEX

References

[1] Kizilbash, S. H., S. K. Gupta, K. Chang, R. Kawashima, K. E. Parrish, B. L. Carlson, K. K. Bakken, A. C. Mladek, M. A. Schroeder, P. A. Decker, G. J. Kitange, Y. Shen, Y. Feng, A. A. Protter, W. F. Elmquist, and J. N. Sarkaria. 2017. "Restricted Delivery of Talazoparib Across the Blood-Brain Barrier Limits the Sensitizing Effects of PARP Inhibition on Temozolomide Therapy in Glioblastoma." Mol Cancer Ther 16 (12):2735-2746. doi: 10.1158/1535-7163.mct-17-0365.

PMC79 derivates for KRAS-mutated cancers: synthesis and characterization

Ana F. Guerreiro[1, 2, 3*], Paulo J. Costa[3], Andreia Valente[1,2]

[1]*Centro de Química Estrutural, Institute of Molecular Sciences, DQB, FCUL;*
[2]*R-nuucell, Edifício Tec Labs, Campus da Fcul - Campo Grande,1749-016 Lisboa, Portugal;*
[3]*BioISI - Instituto de Biossistemas e Ciências Integrativas, DQB, FCUL*
** E-mail: fc49773@alunos.fc.ul.pt*

KRAS mutations are present in 90% of pancreatic cancers [1], as well as in about 45% of all colorectal cancers and 35% of all non-small-cell lung cancers [2]. Although various studies have attempted to create a drug that targets these mutations [3, 4] and despite the existence of two clinically available $KRAS^{G12C}$ inhibitors [5], KRAS mutations are still labelled as undruggable.

In the last few years, a new compound, PMC79 – [Ru(η^5-C_5H_5)(2,2'-bipyridine-4,4'-bis(hydroxymethyl))(PPh_3)][CF_3SO_3], has been found to target three of KRAS most common mutations, namely G12V, G12D and G13D [6]. With this project, we aim to optimize PMC79's structure to enhance the efficacy, selectivity, and pharmacokinetic properties by developing a backup library which will also strengthen R-nuucell's intellectual property portfolio. As a first step, and through conventional organometallic synthesis methods, we synthetised the PMC79 cation bearing different counter-anions. These syntheses were successful, as shown by their respective NMR spectra, with yields of about 66%. The new compounds were then characterized using solubility and stability studies in physiologically relevant conditions.

Funding: Projects UID/00100/2025 and UID/04046/2025 to CQE and BioISI, respectively, and Advanced Computing Project 2023.10475.CPCA to PJC (DOI: 10.54499/2023.10475.CPCA.A2).

References

[1] Zhang, Z.; Zhang, B.; Liao, X.; Tsai, H.; *KRAS mutations: The booster of pancreatic ductal adenocarcinoma transformation and progression*. Front. Cell Dev. Biol., 2023, 11, 1-16
[2] Haigis, K. M. *KRAS Alleles: The Devil Is in the Detail*. Trends in Cancer, 2017, 3(10), 686–697.
[3} Oya, Y.; Imaizumi, K.; Mitsudomi, T.; *The next generation KRAS inhibitors…What comes after sotorasib and agadrasib?* Lung Cancer, 2024, 194 (107886).
[4] Wang, X.; Allen, S.; Blake, J. F.; Bowcut, V.; Briere, D. M.; Calinisan, A.; Dahlke, J. R.; Fell, J. B.; Fischer, J. P.; Gunn, R. J.; Hallin, J.; Laguer, J.; Lawson, D.; Medwid, J.; Newhouse, B.; Nguyen, P.; O'Leary, J. M.; Olson, P.; Pajk, S.; Rahbaek, L.; Rodriguez, M.; Smith, C. R.; Tang, T. P.; Thoma, N. C.; *Identification of MRTX1133, a Noncovalent, Potent, and Selective $KRAS^{G12D}$ Inhibitor*. J. Med. Chem., 2022, 65, 3123-3133.
[5] *FDA grants accelerated approval to sotorasib for KRAS G12C mutated NSCLC*. FDA administration, 2021, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-sotorasib-kras-g12c-mutated-nsclc
[6] Brás, A. R.; Lopes, A.; Mendes, N; Costa, P. J.; Ferreira, A.; Granja, S.; Silva, A. P.; Tortosa, F.; Baltazar, F.; Gärtner, F.; Sousa, M. J.; Valente, A.; Preto, A. *Shifting KRAS hotspot mutations inhibition paradigm in colorectal cancer*. bioRxiv, doi: https://doi.org/10.1101/2023.08.09.552513

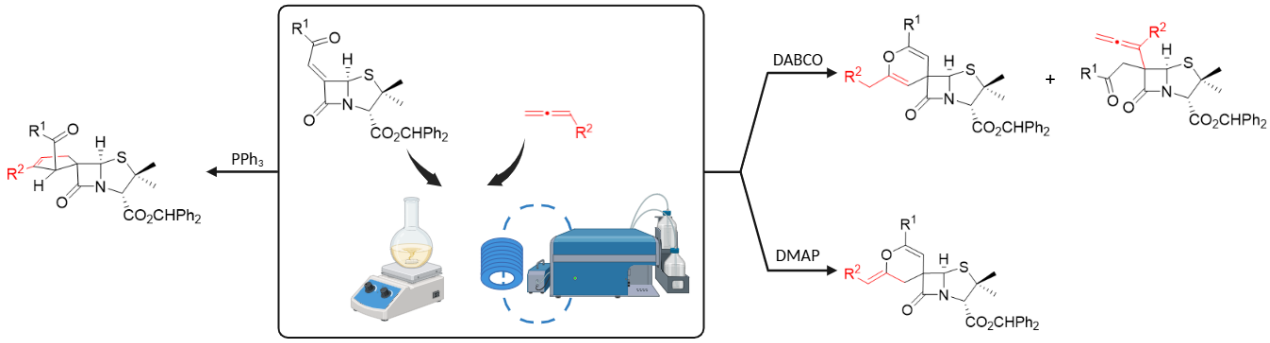
Allene-driven construction of structurally diverse chiral spiro-β-lactams from 6-alkylidenepenicillanates

João P. S. Silva[1], Jéssica Macedo[1], Américo J. S. Alves[1], Inês Bártolo[2,3], Nuno Taveira[2,4], Teresa M. V. D. Pinho e Melo[1,*]

[1]*Department of Chemistry, Coimbra Chemistry Centre – Institute of Molecular Sciences (CQC-IMS), University of Coimbra, 3004-535 Coimbra, Portugal*
[2]*Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, University of Lisbon, 1649-019 Lisbon, Portugal*
[3]*Faculdade de Ciências, Universidade de Lisboa, Campo Grande 1749-016 Lisboa, Portugal*
[4]*Centro de Investigação Interdisciplinar Egas Moniz (CiiEM), Egas Moniz School of Health and Science, 2829-511 Caparica, Portugal*
** E-mail: tmelo@ci.uc.pt*

Influenza, respiratory syncytial virus, and SARS-CoV-2 are high-burden respiratory pathogens that disrupt healthcare systems and devastate economies. Most of the scarcely available drugs for these RNA viruses are virus-specific, leading to drug resistance. The development of broad-spectrum host-directed antivirals offers a promising solution to this challenge, exemplified by the recent discovery of novel spiropenicillanates with a disruptive therapeutic profile by our research team [1,2].

This work focuses on expanding the chemical space of chiral spiro-β-lactams derived from 6-alkylidenepenicillanates. Triphenylphosphine-catalysed formal [3+2] cycloaddition of allenyl ketones and tetrazolyl-allenes afforded spirocyclopentene-β-lactams with a novel substitution pattern. The use of nitrogen-containing bases allowed for divergent annulation pathways, enabling access to previously unexplored spiropyran, spirodihydropyran, and allene-bearing penicillanates (**Scheme 1**).



Scheme 1. Catalysed [3+2] and [4+2] formal cycloaddition reactions and Rauhut-Currier reaction of 6-alkylidenepenicillanates with allenes.

Acknowledgements: CQC-IMS is supported by FCT through projects UIDB/00313/2025 and UIDP/00313/2025 and LA/P/0056/2020. iMed.ULisboa is also supported by FCT through projects UIDB/04138/2020 and UIDP/04138/2020. The authors acknowledge the UC-NMR facility for obtaining the NMR data. Jéssica Macedo thanks FCT PhD fellowship (2024.00332.BDANA). João P. S. Silva thanks FCG for the grant "New Talents 2024".

References

1. Pinho e Melo, Taveira and coworkers: *ACS Infectious Diseases* **2021**, 7, 421-434; *Eur. J. Med. Chem.* **2021**, *219*, 113439; *Front. Chem.* 10:1017250; *Int. J. Mol. Sci.* **2022**, *23*, 14300.
2. WO/2025/104683, Spiro-Penicillanate Compounds for the Treatment of Respiratory Infections, International Filing Date: 15.11.2024

Porphyrin-nanodiamond conjugates for photodynamic therapy and fluorescence imaging

Daniel Cavaco[1,*], Margarida Martins[1], Carla I. M. Santos[1,2], Ermelinda Maçôas[1]

[1] Centro de Química Estrutural and Institute of Molecular Sciences, Departamento de Engenharia Química, Instituto Superior Técnico, Universidade de Lisboa, Lisboa, Portugal; [2] LAQV–REQUIMTE and Department of Chemistry, University of Aveiro, Aveiro, Portugal

** E-mail: danielscavaco@tecnico.ulisboa.pt*

Photodynamic therapy (PDT) is a minimally invasive therapeutic approach that relies on the activation of photosensitizers (PS) by visible or near-infrared light in the presence of molecular oxygen, leading to the generation of cytotoxic reactive oxygen species (ROS) and subsequent cell death. Among the various classes of PS, porphyrins have attracted significant attention due to their quantum high yields of singlet oxygen and favorable photophysical properties. However, their poor aqueous solubility often promotes aggregation, limiting their photodynamic efficiency and biological applicability [1].

To address these limitations, carbon-based nanomaterials have been explored as platforms for PS immobilization [2]. Nanodiamonds are particularly attractive due to their excellent biocompatibility, chemical stability, and versatile surface chemistry [3]. The presence of oxygen-containing functional groups on oxidized nanodiamond surfaces enables efficient covalent conjugation, allowing the formation of stable hybrid systems while reducing porphyrin aggregation.

In this work, two distinct porphyrins were covalently conjugated to carboxylated nanodiamonds through ester and amide bond formation. The resulting nanodiamond-porphyrin conjugates were characterized by spectroscopic and physicochemical techniques to confirm successful functionalization and evaluate their potential as multifunctional platforms for fluorescence imaging and photodynamic therapy.

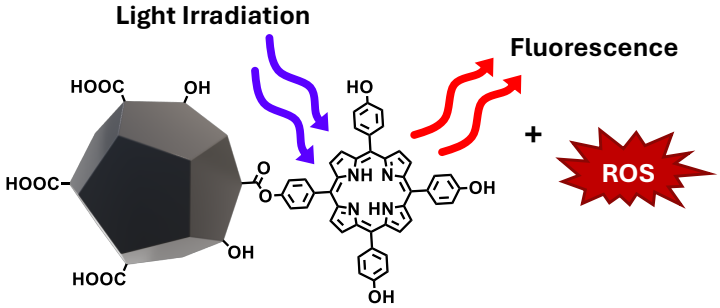


Figure 1. Nanodiamond-porphyrin conjugates for fluorescence imaging and photodynamic therapy.

Acknowledgements: The authors are grateful to Fundação para a Ciência e Tecnologia for the financial support through projects UID/00100/2025, UID/PRR/100/2025, LA/P/0056/2020, and 2022.05950.PTDC and the research contract 2023.08400.CEECIND.

References

[1] A. Akbar et al., J. Photochem. Photobiol. B 2023, 248, 1127966.
[2] C.I.M. Santos et al., ACS Appl. Nano Mater. 2021, 4, 12, 13079-13089.
[3] C.I.M. Santos et al., J. Mater. Chem. B 2023, 11, 675-686.

Butyrolactones from marine-derived *Aspergillus terreus* as anti-aging agents

Elizabeth A. Lopes[1,2], Rebeca André[1,3], Ibrahim Seyda Uras[4], Przemysław Sitarek[5], Belma Konuklugil[6,*], Patrícia Rijo[1,2,3*]

[1]CBIOS – Research Center for Biosciences & Health T echnologies, Universidade Lusófona de Humanidades e Tecnologias, Campo Grande 376, 1749–024 Lisboa, Portugal; [2]Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof Gama Pinto 1649-003, Lisbon, Portugal; [3]Centro de Química Estrutural, Institute of Molecular Sciences, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal; [4]Department of Pharmacognosy, Faculty of Pharmacy, Ağrı İbrahim Çeçen University, 04100, Ağrı, Türkiye; [5]Department of Medical Biology, Medical University of Lodz, Muszyńskiego 1, 90-151 Lodz, Poland; [6]Department of Pharmacognosy, Faculty of Pharmacy, Lokman Hekim University, 06530, Ankara, Türkiye
** E-mail: patricia.rijo@ulusofona.pt; belma.konuklugil@lokmanhekim.edu.tr*

Fungi are prolific producers of secondary metabolites with diverse biological activities and industrial applications. Among them, the genus *Aspergillus* is a major contributor, encompassing approximately 250 species. *Aspergillus terreus*, widely distributed across varied and extreme environments, has evolved genetic and regulatory mechanisms enabling adaptation and the biosynthesis of structurally diverse metabolites, including alkaloids, polyketides, peptides, terpenes, and lignans.[1] In particular, butenolides and terretonins, typical metabolites of this genus, exhibit antibacterial, cytotoxic, anti-inflammatory, antioxidant, and antiviral properties.[2]

In this study, a marine-derived strain of *A. terreus* was explored for its potential in skin aging applications. Two butenolide derivatives, butyrolactones I and III (Figure 1), were isolated and subjected to chemical modification to further assess their biological activity in human neutrophil elastase (HNE), tyrosinase, and collagenase enzymatic assays.

Overall, marine-derived *A. terreus* represents a valuable source of bioactive butenolides with relevance to skin health. Further studies on their mechanisms of action and optimization could support the development of novel anti-aging agents.

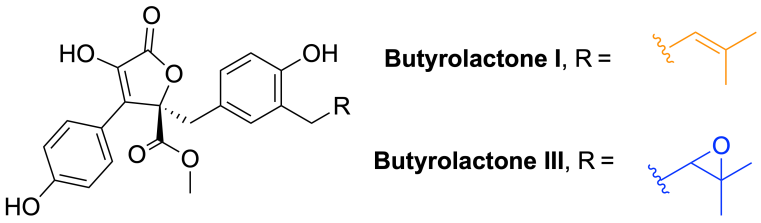


Figure 1. Chemical structures of butyrolactones I and III.

Acknowledgements: This research was funded in part by the Fundação para a Ciência e Tecnologia, I.P. (FCT, https://ror.org/00snfqn58), under Grant UID/04567/2025 (Grant DOI https://doi.org/10.54499/UID/04567/2025).

References

[1] El-hawary, S.S.; *et al.*; RSC Advances 2020, 10, 22058-22079.
[2] Orfali, R.; *et al.*; RSC Advances 2021, 11, 17116-17150.

Increasing aqueous solubility of porphyrins using machine learning and hydrotropy

Ricardo G. Rocha[1,2*], Dinis O. Abranches[1], M. Amparo F. Faustino[2]

[1]*CICECO - Aveiro Institute of Materials, Department of Chemistry, University of Aveiro, Aveiro, Portugal*

[2]*LAQV-REQUIMTE, Department of Chemistry, University of Aveiro, Aveiro, Portugal*

** E-mail: ricardogaspar.r23@ua.pt*

Porphyrins are extensively explored as multifunctional photosensitisers for antimicrobial photodynamic therapy, cancer treatment and theranostic applications; however, their intrinsic hydrophobicity promotes aggregation and poor aqueous solubility, limiting biodistribution, target interaction and overall performance in physiological environments [1].

Hydrotropy offers a potential strategy to overcome this limitation by increasing solubility through the addition of amphiphilic small molecules that interact with the solute while remaining compatible with water. Despite its practical relevance, the molecular determinants governing solubility enhancement by different hydrotropes remain poorly understood [2].

In this work, machine learning models based on Gaussian Processes are employed to predict and rationalise the aqueous solubility increase of porphyrins in the presence of different hydrotropes. Molecular information is encoded using sigma profiles, enabling the transformation of complex molecular structures into numerical descriptors suitable for regression modelling (Figure 1) [3]. The resulting models capture non-linear relationships between porphyrin-hydrotrope interactions and solubility enhancement, allowing comparison across different hydrotropic agents. The approach may guide the rational selection of hydrotropes for porphyrin-based systems, supporting future porphyrin applications.

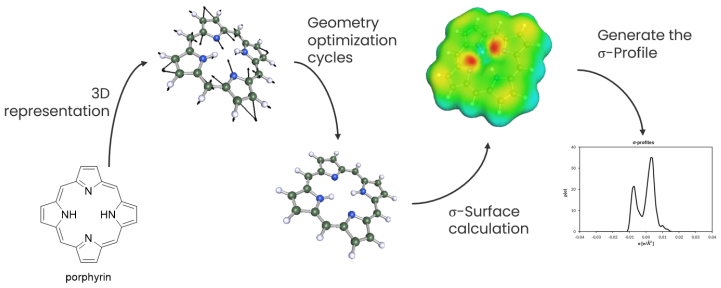


Figure 1. From molecular structure to prediction.

Acknowledgements and Funding: R.G. Rocha thanks Calouste Gulbenkian Foundation the "Novos Talentos 2025" grant.

References

[1] Wainwright M., Maisch T., Nonell S., Plaetzer K., Almeida A., Tegos G.P., Hamblin M.R.; Photoantimicrobials - are we afraid of the light?; Lancet Infect Dis. 2017, Volume 17, pp. e49-e55.

[2] Abranches, Dinis O. et al.; Unveiling the mechanism of hydrotropy: evidence for water-mediated aggregation of hydrotropes around the solute; Chem. Commun. 2020, Volume 56, pp. 7143-7146.

[3] Abranches, Dinis O et al.; Stochastic machine learning via sigma profiles to build a digital chemical space. PNAS, Volume 121, pp. e2404676121

Synthesis and structure elucidation of major metabolites of methylone and pentedrone for further toxicological studies

Ana Sofia Almeida[1,2,3,4], Dália Wang[1], Paula Guedes de Pinho[3,4], Fernando Remião[3,4], Carla Fernandes[1,2,*]

[1]*Laboratório de Química Orgânica e Farmacêutica, Departamento de Ciências Químicas, Faculdade de Farmácia, Universidade do Porto, Porto, Portugal*

[2]*Centro Interdisciplinar de Investigação Marinha e Ambiental (CIIMAR), Universidade do Porto, Porto, Portugal*

[3]*UCIBIO – Applied Molecular Biosciences Unit, laboratory of Toxicology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal*

[4]*Associate Laboratory i4HB - Institute for Health and Bioeconomy, Faculty of Pharmacy, University of Porto, Porto, Portugal*

** E-mail: cfernandes@ff.up.pt*

New psychoactive substances represent a major public health challenge due to their easy accessibility and limited comprehensive toxicological data. Among these substances, synthetic cathinones, such as methylone and pentedrone, are widely abused for their psychostimulant properties [1].

When evaluating the effects of synthetic cathinones, it is essential to consider not only the parent compounds but also their metabolites, since they may contribute significantly to the overall biological impact or toxicity [2]. Although metabolic pathways of synthetic cathinones have been extensively investigated, including pathways such as *N*-demethylation, *O*-demethylation, and β-keto reduction [3, 4], the specific effects of their metabolites remain largely underexplored. The synthesis of these metabolites is a crucial step to evaluate their effects.

In this work, several synthetic methodologies were employed to obtain major metabolites of methylone and pentedrone, such as nor-metabolites and dihydro-metabolites. Intermediates and metabolites were obtained with high yields and purity, being the structure elucidation carried out using spectroscopic techniques, including IR, and ^{1}H and ^{13}C NMR.

The synthesized metabolites will serve as valuable tools in future studies aimed at understanding the role of metabolites in the toxicological profile of synthetic cathinones. Additionally, metabolomic studies will be performed with parent compounds and metabolites.

Funding and Acknowledgements: This research was supported by national funds by FCT (UIDB/04423/2020, UIDB/MULTI/04378/2020, UIDP/04423/2020 LA/P/0140/2020, PTDC/CTA-AMB/6686/2020 projects). Ana Sofia Almeida acknowledges her PhD grant provided by FCT (project reference 2023.00262.BD and DOI identifier https://doi.org/10.54499/2023.00262.BD).

References

[1] Zawilska, J.B.; Int Rev Neurobiol. 120: Academic Press 2015, p. 273-300.
[2] Kirchmair, J.; Göller, A.H.; Lang, D.; Kunze, J.; Testa, B. Wilson, I.D.; et al.; Nat Rev Drug Discov 2015, 14(6):387-404.
[3] Kamata, H.T.; Shima, N.; Zaitsu, K.; Kamata, T.; Miki, A.; Nishikawa, M.; et al.; Xenobiotica 2006, 36(8):709-23.
[4] Uralets, V.; Rana, S.; Morgan, S.; Ross, W.; J Anal Toxicol 2014, 38(5):233-41.

Synthesis of chitosan-based chiral conjugates for liquid chromatography and biological evaluation

Rita Lima[1,2], Pedro Alexandrino Fernandes[3], Artur M. S. Silva[4], Maria Elizabeth Tiritan[1,2,5], Madalena M. M. Pinto[1,2], Carla Fernandes[1,2*]

[1]Laboratório de Química Orgânica e Farmacêutica, Departamento de Ciências Químicas, Faculdade de Farmácia, Universidade do Porto, Rua de Jorge Viterbo Ferreira, 228, 4050-313 Porto, Portugal; [2]Centro Interdisciplinar de Investigação Marinho e Ambiental (CIIMAR), Edifício do Terminal de Cruzeiros do Porto de Leixões, Av. General Norton de Matos s/n, 4050-208 Matosinhos, Portugal; [3]LAQV, REQUIMTE, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade do Porto, Rua do Campo Alegre, s/n, 4169-007 Porto, Portugal; [4]Departamento de Química & LAQV-REQUIMTE, Universidade de Aveiro, 3810-193 Aveiro, Portugal; [5]UCIBIO-Applied Molecular Biosciences Unit, Translational Toxicology Research Laboratory, University Institute of Health Sciences (1H-TOXRUN, IUCS-CESPU), 1317, 4585-116 Gandra PRD, Portugal

** E-mail: cfernandes@ff.up.pt*

Chitosan is a marine-derived polysaccharide that combines renewable origin, intrinsic biocompatibility, and highly versatile physicochemical properties, which are governed by the amino and hydroxyl groups along its backbone [1]. In addition, these functional groups are reactive sites that can be selectively addressed to modulate solubility, charge density, and intermolecular interactions through targeted derivatization and coupling reactions [2]. This chemical versatility underpins a broad spectrum of applications and biological activities, such as antimicrobial, antitumor, and wound-healing effects, which support its widespread use in drug delivery, tissue engineering, and bioactive coatings. In parallel, chitosan derivatives have emerged as promising chiral stationary phases (CSP) for liquid chromatography (LC), enabling multiple interactions, including hydrogen-bonding, ionic, and hydrophobic, to achieve efficient enantioselective separations [3].

This work describes the synthesis and structure elucidation of a series of chitosan-based chiral conjugates obtained thought diverse synthetic strategies, including Schiff base formation between the chitosan backbone and selected bioactive small molecules. The synthetized conjugates were successfully characterized by spectroscopic methods and elemental analysis. Further studies will include their evaluation as CPS for the LC enantioseparation of representative chiral analytes. Relevant *in vitro* assays will also be performed to evaluate their antimicrobial and antitumor activities.

Acknowledgements: This research was partially supported by national funds by FCT within the scope of Base Funding UIDB/04423/2020 and UIDP/04423/2020 (Group of Marine Products and Medicinal Chemistry – CIIMAR) and the project PTDC/CTA-AMB/0853/2021. Rita Lima acknowledges her Ph.D. research grant provided by FCT 2022.11168 and DOI https://doi.org/10.54499/2022.1168.BD.

References

[1] Periayah, M. H.; Halim, A. S.; Saad, A. Z. M.; Phcog Rev 2016, 10(19), 39.
[2] Lima, R.; Fernandes, C.; Pinto, M. M.; Chirality 2022, 34 (9), 1166-1190.
[3] He, J.; Xi, J.; Han, B.; Xiao, Q.; Guo, D.; Huang, S.; Carbohydr Polym 2025, 359, 123590.

Lysine *N*-acylated dehydropeptides as potential substrates for histone deacetylase-triggered intracellular transformations

Joana Moreira[1,*], David Pereira[2], Paula M. Ferreira[1], José A. Martins[1]

[1]*Chemistry Centre, University of Minho, Gualtar Campus, 4710-057 Braga, Portugal;* [2]*Faculty of Pharmacy, University of Porto, Porto, Portugal*

* *E-mail: joana122rmoreira@gmail.com*

Enzyme-instructed self-assembly (EISA) has emerged in the last decade as a promising disruptive cancer therapy paradigm based on peri- and intracellular formation of toxic nanoaggregates, from soluble precursors, catalysed by enzymes (phosphatases, esterases, proteases, etc) overexpressed by cancer cells [1]. Peptides are privileged building blocks for EISA due to synthetic amenability and modularity and ability to undergo controlled aggregation (self-assembly) mediated by an array of non-covalent interactions such as electrostatic and hydrogen bonding, *van der* Walls and π–π stacking, and hydrophobic forces. Histone deacetylases (HDACs), regulate chromatin condensation by removal of acetyl and succinyl groups from histone and non-histone proteins. HDACs are often overexpressed in several tumours, thus representing potential enzymatic triggers for selective intracellular transformations of exogenous substrates [2,3].

In this project, we aim at developing a new class of minimalist dehydropetides as potential substrates for HDAC-mediated intracellular transformations.

A focused library of lysine N_ε-acylated dehydrotripeptides was synthesised by solution phase methodologies developed by our research group (Figure 1).

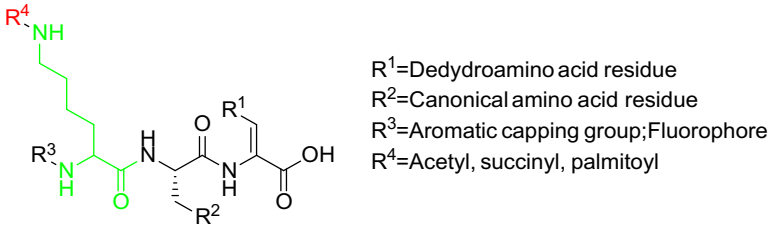


Figure 1. General structure of the Lysine N_ε-acylated dehydrotripeptides library.

The compounds were purified and structurally confirmed by ^{1}H and ^{13}C NMR and mass spectrometry (MS). The self-assembly propensity of the dehydropeptides´ library was determined by fluorescence spectroscopy as the *critical aggregation concentration* (*CAC* values). The proteolytic stability of the peptides towards a panel of proteases was evaluated by HPLC and MS. Preliminary results on the toxicity of the dehydropeptides´ library towards noncancer and a panel of cancer cells known to overexpress HDACs will be reported as well. This study sets the stage for subsequent studies on HDACs-mediated intracellular EISA of Lysine N_ε-acylated dehydrotripeptides as a potential anticancer strategy.

References:

[1] Du, X.; Zhou, J.; Shi, J.; Xu, B. *Chem. Rev.* 2015, *115*, 13165–13307.
[2] Yang, L.; Peltier, R.; Zhang, M.; et al. *J. Am. Chem. Soc.* 2020, *142*, 18150–18159.
[3] Bai, H.; Wang, H.; Zhou, Z.; et al. *Adv. Funct. Mater.* 2023, *33*, 2214025.

Dehydrophenylalanine-driven adaptive peptide dispersions enable controlled encapsulation and adhesion

Mariana Cruz[1,*], Carolina Amorim[1], José A. Martins[1], Paula M. T. Ferreira[1]

[1]*University of Minho, Campos de Gualtar 4710-057, Braga, Portugal;*

** E-mail: pg55649@uminho.pt*

Supramolecular peptide-based materials represent minimalistic plataforms for biomolecule encapsulation, functional surface coatings and bioinspired adhesion. Recent work have demonstrated that short aromatic peptides, including the KYF and KYW motifs, undergo drying-induced phase separation, to form condensed microdomains that sequester biomolecules and produce mechanically stable peptide-based solids [1,2]. Building on these findings, we investigate the incorporation of dehydrophenylalanine (ΔPhe) as a strategy to enhance molecular planarity and π–π interactions, thereby modulating peptide adaptivity, drying behavior, and mechanical properties [3].

In this study, a serie of ΔPhe-containing tri- and tetrapeptides were synthesized and characterized and their behavior was systematically compared with that of the native KYF/KYW motifs to elucidate the role of aromatic interactions and hydrogen bonding. Peptide organisation and condensation during solvent evaporation were analyzed using complementary microscopy and imaging approaches (Figure 1).

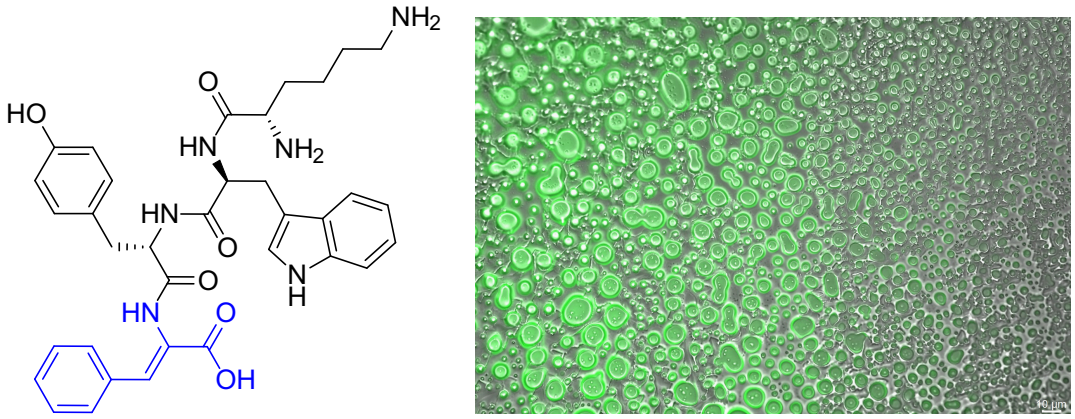


Figure 1. Structure of a dehydropeptide and the corresponding fluorescence microscopy image showing the nanostructures formed upon drying from PBS 7.4.

Overall, peptides incorporating ΔPhe constitute a minimal and well-defined platform for studying adaptive dispersions and peptide self-assembly and show promise for the controlled encapsulation of biomolecules.

References

[1] Dave, D.R.; Kassem, S.; Coste, M.; *et al.* Nat. Mater. 2025,24,1465-1475.
[2] Finkelstein-Zuta, G; Arnon, Z.A.; Vijayakanth, T.; *et al.* Nature 2024, 630, 368-374.
[3] Carvalho, A.; Pereira, T.; Oliveira, C.; Figueiredo, P.; Carvalho, A.; Pereira, D.M.; Hilliou, L.; Bãnobre-López, M.; Xu, B.; Ferreira, P.M.T.; *et al.* Gels 2025, 11, 164.

Structural optimization of BASHY platform for bioimaging

Fábio M.F. Santos[1,*], João M.J.M. Ravasco[1], Christelle Langevin[2], Adelaide Fernandes[1], David Y.W. Ng[3], Jaime A.S. Coelho[4], Uwe Pischel[5], Pedro M.P. Góis[1]

[1]Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Lisbon 1649-003, Portugal; [2]INRAE National Research Institute for Agriculture, Food and Environment, Université Paris-Saclay, Jouy-en-Josas 78350, France; [3]Max Planck Institute for Polymer Research, Mainz 55128, Germany; [4]Centro de Química Estrutural–Institute of Molecular Sciences, Faculty of Sciences, Universidade de Lisboa, 1749-016 Lisboa, Portugal;[5]CIQSO – Centre for Research in Sustainable Chemistry and Department of Chemistry, University of Huelva, Huelva 21071, Spain

** E-mail: fabiosantos1@edu.ulisboa.pt*

Fluorescent molecules are essential tools in biomedicine, enabling sensitive and specific visualization of biological processes [1]. However, optimizing their structures for live-cell and *in vivo* imaging remains challenging due to the complex relationship between structural and photophysical properties [2]. In this study, we applied multivariate linear free-energy relationships (mLFER) to optimize a multicomponent fluorescent platform. A library of boronic-acid-derived salicylidenehydrazone (BASHY) complexes was synthesized and evaluated for chemical stability in aqueous media. These data were used to build an mLFER model that guided the prediction of a new BASHY dye and revealed previously unrecognized factors governing dye stability. The optimized dye was successfully applied in live-cell imaging and zebrafish larvae **Figure 1** [3].

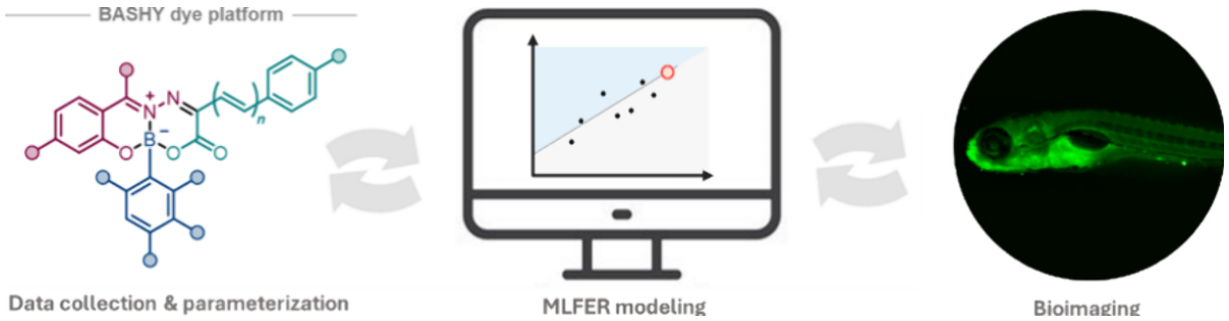


Figure 1. mLFER-Driven Optimization of the BASHY Platform for Bioimaging

Acknowledgements: The authors acknowledge Fundação para a Ciência e a Tecnologia for financial support (2021.04125.CEECIND; 2023.14170.PEX ; PTDC/QUI-OUT/3989/2021 and UID 04138 - Instituto de Investigação do Medicamento.

References

[1] Lavis, L. D.; Raines, R. T. ACS Chem. Biol. 2014, 9, 855–866.
[2] Jun, J. V.; Chenoweth, D. M.; Petersson, E. J.; Org. Biomol. Chem., 2020, 18, 5747–5763.
[3] Ravasco, J. M. J. M.; Felicidade, J.; Pinto, M. V.; Santos, F. M: F.; Campos-González, R.; Arteaga, J. F.; Mehraz, M.; Langevin, C.; Fernandes, A.; Nguyen, H.; Ng, D. Y. W.; Coelho, J. A. S.; Pischel, U.; Gois, P. M. P; JACS Au 2024, 4, 4212–4222

Engineering DAB units as self-immolative modules for ROS responsive linkers

Inês L. Roque[1,*], João P. M. António[1], Pedro M. P. Góis[1]

[1]*Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, 1649-003 Lisbon, Portugal*

** E-mail: miroque@edu.ulisboa.pt*

Cancer is still one of the leading causes of worldwide death, and chemotherapy often faces low selectivity and serious side effects as main limitations. Developing targeted therapies that selectively deliver cytotoxic agents to cancer cells remains one of the most prominent strategies [1]. There are several examples of local prodrug activation using reactive oxygen species (ROS) as stimuli. However, most of the ROS-responsive prodrugs, lack stability to stay in circulation, not having, therefore much use [2].

Our group applied a novel approach with a design of an innovative ROS-responsive prodrug using diazaborines (DABs), aromatic B-N heterocycles. In previous work, we found out that DABs can be stable in circulation while releasing the attached drug in response to ROS [3,4].

Through computational studies, our group identified new lead molecules based on hydrazines to be construct into DABs with different *m-*/*p*-EDG and EWG groups - **Figure 1**. The compounds obtained exhibit an excellent stability under a wide range of pH conditions (5 through 9) for 24 hours showing a half-life of 4 days in pH 7.4. The compounds were also oxidized in the presence of 10 equiv. H_2O_2 at a rate constant of k_{obs} = 0.009 min^{-1} with the best having a half-life of 1h20 at pH 7.4, proving the concept of ROS-responsiveness. *In vitro* results are currently ongoing. All together, these results reveal the possibility of diazaborine-based prodrugs in the selective targeting of cancer cells by ROS-mediated activation.

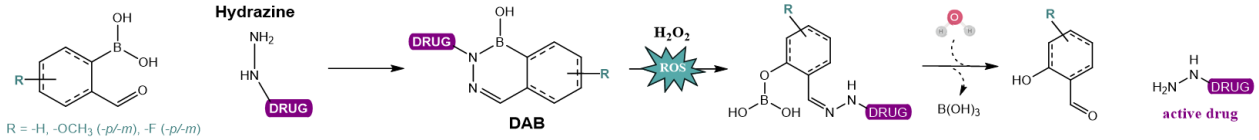


Figure 1. Schematic representation of the formation of a prodrug and its subsequent activation by ROS with the release of the active drug.

Acknowledgements: This research project falls within the scope of the PTDC/QUI-OUT/3989/2021, entitled "SmartBox: Engineering the first generation of ROS responsive ADCs". We thank Fundação para a Ciência e a Tecnologia (2022.06817.CEECIND; *2024.16254.PEX* and UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025) for financial support). We also thank for the PhD fellowship grant 2024.04802.BD awarded to Inês L. Roque.

References

[1] Bhagat SD, Singh U, Mishra RK, Srivastava A. ChemMedChem. 2018; 13(19):2073–2079.
[2] Peiró Cadahía J, Previtali V, Troelsen NS, Clausen MH. Medchemcomm. 2019; 10(9):1531-1549.
[3] António JPM, Russo R, Carvalho CP, Cal PMSD, Góis PMP. Chem Soc Rev. 2019; 48(13):3513-3536
[4] António JPM, Carvalho JI, André AS, Silva FA, Góis PMP. Angew Chemie Int Ed. 2021; 60(49):25914–25921.

Flavonoids as potential antimitotic agents: synthesis, bioactivity evaluation and structure-activity relationship studies

Daniela Pereira[1,2], Henrique Assunção[1,2], Eduarda Alves[3], Lara Cruz[3], Rita Santos[3], Patrícia M. A. Silva[3,4,5], Hassan Bousbaa[3,4,5], Honorina Cidade[1,2,*]

[1]Laboratório de Química Orgânica e Farmacêutica, Departamento de Ciências Químicas, Faculdade de Farmácia, Universidade do Porto, Rua de Jorge Viterbo Ferreira nº 228, 4050-313, Porto, Portugal; [2]CIIMAR/CIMAR LA – Interdisciplinary Centre of Marine and Environmental Research, University of Porto, Terminal de Cruzeiros do Porto de Leixões, Av. General Norton de Matos s/n 4450-208, Matosinhos, Portugal; [3]UNIPRO–Oral Pathology and Rehabilitation Research Unit, IUCS-CESPU, University Institute of Health Sciences, 4585-116 Gandra, Portugal; [4]Associate Laboratory i4HB-Institute for Health and Bioeconomy, University Institute of Health Sciences-CESPU, 4585-116 Gandra, Portugal; [5]UCIBIO-Applied Molecular Biosciences Unit, Translational Toxicology Research Laboratory, 1H-TOXRUN, IUCS-CESPU, University Institute of Health Sciences, 4585-116 Gandra, Portugal

** E-mail: hcidade@ff.up.pt*

Antimicrotubule agents are among the most successful chemotherapeutic agents for treating various types of cancer. However, their clinical application is often constrained by severe side effects and the development of drug resistance, highlighting the demand for novel antimitotic agents [1]. Previously, our research team identified the synthetic prenylated chalcone (PC2) with potent growth-inhibitory effects in several tumour cell lines, associated with mitotic disruption [2]. In this context, and with the aim of enhancing antimitotic potency and conducting structure–activity relationship studies, a series of PC2 analogues, including chalcones, dihydrochalcones and flavones, were synthesised and biologically evaluated. The chalcone derivatives were prepared through Claisen–Schmidt condensation reactions between previously synthesised acetophenones containing prenyl or amine groups and 3,4,5-trimethoxybenzaldehyde under basic conditions. The synthesis of flavones was accomplished by direct thermal cyclocondensation of phloroglucinol and ethyl 3,4,5-trimethoxybenzoylacetate followed by the nucleophilic substitution reaction with 3,3-dimethylallyl bromide. The selective reduction of the double bond of α,β-unsaturated ketone system of an intermediate chalcone carried out by catalytic hydrogenation in a H_2 atmosphere with 10 % Pd/C allowed the synthesis of dihydrochalcones. The antiproliferative effect of all compounds was assessed in three different cancer cell lines using the sulforhodamine B assay, leading to the identification of several flavonoids with noteworthy biological activity. Antimitotic effects, cell death induction, and long-term clonogenic capacity were also assessed, yielding promising results.

Funding: This research was funded by national funds through the FCT–Fundação para a Ciência e a Tecnologia within the scope of the Strategic Funding UIDB/04423/2020 (https://doi.org/10.54499/UIDB/04423/2020), UIDP/04423/2020 (https://doi.org/10.54499/UIDP/04423/2020), and LA/P/0101/2020 (https://doi.org/10.54499/LA/P/0101/2020). This research was also funded by the CESPU—Cooperativa de Ensino Superior Politécnico e Universitário Crl (Grants Ref. FlavScreen_GI2-CESPU-2023; FlavCanAct-GI2-CESPU-2025 and TargetMito-GI2-CESPU-2025).

References

[1] Cermák, V.; Dostál, V.; Jelínek, M.; Libusová, L.; Kovár, J.; Rösel, D.; Brábek, J.; Eur. J. Cell Biol. 2020, 99, 151075.
[2] Fonseca, J.; Marques, S.; Silva, P.; Brandão, P. Cidade, H.; Pinto, M.; Bousbaa, H.; Molecules 2016, 21, 982.

Targeting oxidative stress in Alzheimer's disease: synthesis and neuroprotective potential of novel xanthene derivatives

Inês Costa[1,2,3*], Tiago Gonçalves[1,2,4], Diana Resende[3,4,5], Daniel José Barbosa[6,7], Maria Emília Sousa[3,5], Renata Silva[1,2]

*[1]Laboratório Associado i4HB - Instituto de Saúde e Bioeconomia, Faculdade de Farmácia, Universidade do Porto (FFUP), Porto, Portugal; [2]UCIBIO - Unidade de Biociências Moleculares Aplicadas, Laboratório de Toxicologia, FFUP, Porto, Portugal; [3]CIIMAR - Centro Interdisciplinar de Investigação Marinha e Ambiental, Terminal de Cruzeiros do Porto de Leixões, Matosinhos, Portugal; [4]ICBAS - Instituto Abel Salazar de Ciências Biomédicas, Universidade do Porto, Porto, Portugal; [5]Laboratório de Química Orgânica e Farmacêutica, Departamento de Ciências Químicas, FFUP, Porto, Portugal; [6]Laboratório Associado i4HB - Instituto de Saúde e Bioeconomia, Instituto Universitário de Ciências da Saúde - CESPU, Gandra, Portugal; [7]UCIBIO - Unidade de Biociências Moleculares Aplicadas, Laboratório de Investigação em Toxicologia Translacional, Instituto Universitário de Ciências da Saúde (1H-TOXRUN, IUCS-CESPU), Gandra, Portugal; * E-mail: inessilvacosta@hotmail.com*

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by multiple pathological hallmarks, including amyloid-beta (Aβ) accumulation, oxidative stress, among others. With the global prevalence of AD projected to more than triple by 2050 (more than 100 million), and current therapeutic options offering only symptom relief, there is an urgent need for novel treatments [1]. Xanthenes have been reported to exhibit neuroprotective properties, underscoring their therapeutic potential in AD [2]. In this study, eight xanthene derivatives incorporating dopamine and levodopa moieties were synthesized (Figure 1) and their structures characterized by NMR spectroscopy. The cytotoxicity (0-25 μM) was evaluated in SH-SY5Y cells differentiated into a cholinergic phenotype using MTT reduction and neutral red (NR) uptake assays. Neuroprotective potential was assessed against *tert*-butyl hydroperoxide (*t*-BHP)-induced oxidative stress, using the NR uptake assay and a ROS/RNS-sensitive fluorescent probe. All synthesized derivatives were successfully obtained, structurally characterized, and found to be non-cytotoxic at concentrations up to 10 μM. Several xanthene derivatives markedly attenuated *t*-BHP-induced oxidative stress, as evidenced by significantly reduced ROS/RNS generation and decreased *t*-BHP-induced cell death. These findings support the potential of xanthene derivatives as modulators of oxidative stress. Further studies are required to clarify whether these compounds also modulate other pathological mechanisms of the disease, thereby strengthening their potential as promising drug candidates for AD treatment.

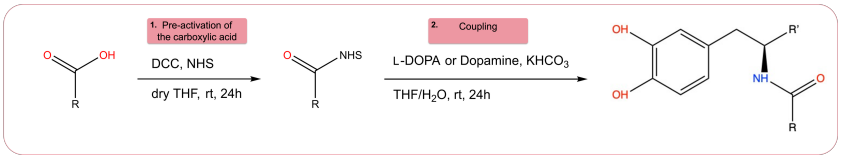


Figure 1: Synthesis of xanthene derivatives (R) incorporating dopamine (R'= H) and levodopa (R'= COOH) moieties.

Funding: FCT/MCTES: UIDP/04378/2020, UIDB/04378/2020, UIDB/04423/2020, UIDP/04423/2020, LA/P/0140/2020 and 2023.04980.BD.

References

[1] Monteiro, A. R.; Barbosa, D. J.; Remião, F.; Silva, R. Alzheimer's Disease: Insights and New Prospects in Disease Pathophysiology, Biomarkers and Disease-Modifying Drugs. Biochem Pharmacol 2023, 211, 115522. DOI: 10.1016/j.bcp.2023.115522 From NLM.

[2] Maia, M.; Resende, D.; Durães, F.; Pinto, M. M. M.; Sousa, E. Xanthenes in Medicinal Chemistry - Synthetic Strategies and Biological Activities. Eur J Med Chem 2021, 210, 113085. DOI: 10.1016/j.ejmech.2020.113085 From NLM.

Design, synthesis, and biological evaluation of triphenylamine-benzothiadiazole derivatives for enhanced photodynamic therapy

Sónia C. S. Pinto[1,2], Lígia C. Gomes-da-Silva[2], João Pina[2], Susana P. G. Costa[1], M. Manuela M. Raposo[1*]

[1] *Chemistry Centre of the University of Minho, Campus de Gualtar, 4710-057, Braga, Portugal.*

[2] *University of Coimbra, CQC-IMS, Department of Chemistry, Rua Larga, 3004-535, Coimbra, Portugal.*

** E-mail: mfox@quimica.uminho.pt*

Photodynamic therapy (PDT) is an effective cancer treatment that uses light-activated photosensitizers to generate reactive oxygen species (ROS) that kill tumor cells. Recent efforts aim to create photosensitizers that produce strong therapeutic effects and work efficiently even under limited oxygen conditions [1-2]. Within this context, benzothiadiazole (BTD) derivatives have stood out because of their visible-light absorption, tunable electronic properties, and high photostability [3-4].

In this study, a new set of BTD-based push-pull molecules was designed by combining a triphenylamine donor moiety with formyl group or cationic heterocyclic salts as acceptors, improving solubility, cellular uptake, and ROS generation. Biological assays in 4T1 cancer cells showed effective internalization and strong production of both type I and type II ROS upon light exposure, leading to notable cancer-cell death. Overall, the new TPA–BTD derivatives show strong potential as photosensitizers for PDT.

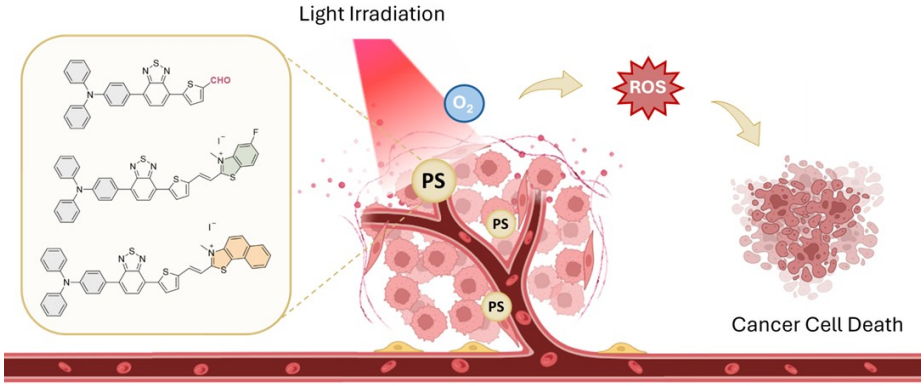


Figure 1. Triphenylamine-benzothiadiazole derivatives studied for PDT application.

Funding: The authors acknowledge the Portuguese Foundation for Science and Technology (FCT), for the Strategic Funding to Centro de Química da Universidade do Minho (CQ-UM, UID/00686/2025), a PhD grant to S.C.S. Pinto (2022.12455.BD) and for funding Coimbra Chemistry Centre projects UIDB/00313/2025 and UIDP/00313/2025. Thanks are also due to the Portuguese NMR Network.

References

[1] Gunaydin, G.; Gedik, M. E.; Ayan, S.; Front. Chem. 2021, 9, 686303.
[2] Pham, T. C.; Nguyen, V.; Choi, Y.; Lee, S.; Yoon, J.; Chem. Rev. 2021, 121, 13454.
[3] Hu, Z.; Feng, L.; Yang, P.; Adv. Funct. Mater. 2024, 34, 2310818.
[4] Boland, M.; Pinto, S.; Gomes-da-Silva, L. C; Pina, J.; Costa, S. P. G.; Raposo, M. M. M.; Dyes Pigm. 2025, 240, 112825.

On the search for TMBIM4 pharmacological inhibitors

Daniel J. V. A. dos Santos[1,*], Nuno Saraiva[1]

[1]*CBIOS, Center for Research in Biosciences and Health Technologies, Universidade Lusófona, Lisboa, Portugal.*

** E-mail: daniel.dos.santos@ulusofona.pt*

The dysregulation of Ca^{2+} homeostasis is crucial in cancer initiation and progression. Cancer cells can establish cancer hallmarks features by manipulating the expression or activity of Ca^{2+} modulators, including pumps, channels, and exchangers.

As an innovative approach, we propose to reprogram Ca^{2+} intracellular fluxes by inhibiting specific endoplasmic reticulum (ER) or Golgi apparatus (GA) Ca^{2+} channels to control glioma progression [1]. In particular, manipulating the expression of the GA Ca^{2+} channel TMBIM4 (transmembrane BAX inhibitor motif containing 4) impacts glioma cell invasion and in vivo tumour growth. Therefore, we aim at finding still unknown pharmacological inhibitors for TMBIM4.

In our recently finished HPC FCT project (CPCA/A1/410638/2021: Fine-tuning TMBIM ion channel activity to control hallmarks of cancer), we used the crystal structures of the TMBIM homolog YetJ from *Bacillus Subtilis* (PDB: 6nq7, 6nq8) as a model for the TMBIM4 channel in the open and closed states [2].

In this communication, we will present molecular dynamics studies extending to the microsecond to clarify the best approach and methodology to be used, by disclosing the behavior of the channel after deprotonation of key residues.

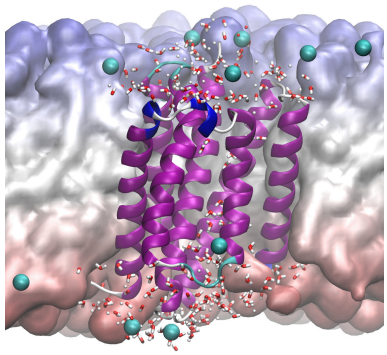


Figure 1. TMBIM4 model embedded in a lipid bilayer, highlighting also the calcium ions and the water molecules near the protein.

Funding: This work was funded by ILIND under projects COFAC/ILIND/CBIOS/2/2023, COFAC/ILIND/CBIOS/2/2024 and FAZER+/ILIND/CBIOS/1/2025, and by FCT (Portugal), through the project with reference UID/04567/2025 and CPCA/A1/410638/2021.

References

[1] M. Martins, A. S. Fernandes, N. Saraiva, GOLGI: Cancer cell fate control, Int. J. Biochem. Cell Biol., 2022, 145, 106174.

[2] G. Guo, M. Xu, Y. Chang, T. Luyten, B. Seitaj, W. Liu, P. Zhu, G. Bultynck, L. Shi, M. Quick, Q. Liu, Ion and pH Sensitivity of a TMBIM Ca2+ Channel, Structure, 2019, 27, 6, 1013.

Catalyst free synthesis of *trans*-3,4,5-triamino-cyclopent-2-enones

Afonso S. G. M. Verde, Tiago M. P. Santos, Sabrina M. E. Cabral, Rafael F. A. Gomes, Carlos A. M. Afonso

Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av.Prof Gama Pinto, 1649-003, Lisboa, Portugal

** E-mail: afonso.verde@farm-id.pt*

Cyclopentenones compose a versatile class of five-membered α,β-unsaturated cyclic ketones whose conjugated structure endows them with distinctive electronic properties and high chemical reactivity. trans-4,5-Diamino-cyclopent-2-enones (DCPs), a versatile motif, can be transformed into various useful cyclopentanone scaffolds, enaminones and it is even involved in the total synthesize of natural product such as Agelastin A [1,2].

DCPs are commonly obtained through a Lewis acid-promoted condensation between furfural and a secondary amine in an organic solvent. Initially, this transformation involves the generation of a Stenhouse Salt intermediate, which subsequently undergoes an electrocyclization process to obtain the desired moiety [1]. We have already reported the synthesis of DCPs using high-pressure promoted Nazarov-like electrocyclization of Stenhouse salts arising from the Sc(III)-catalyzed condensation of furfural with secondary electron-poor anilines [3]. Moreover, 3-acetamido-5-acetyl furan (3A5AF), a *N*-rich furan obtained from chitin biomass, gives us many advantages in the synthesis of bio-derived nitrogen-rich heteroaromatics, in particular, being more reactive towards ring opening/cyclizations [4].

In this context, this work focuses on the establishment of a novel synthetic strategy to obtain CPs from the more reactive 3A5AF, eliminating the need for any catalyst, offering a simpler and potentially more sustainable approach to access these valuable compounds.

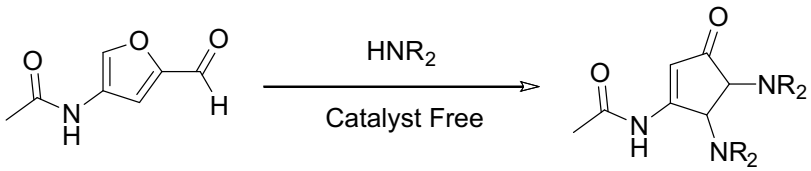


Figure 1. Preparation of trans-3,4,5-triamino-cyclopent-2-enones from furfural derivative

Acknowledgements: We thank the Fundação para a Ciência e a Tecnologia (FCT) for financial support (UID 04138 - Instituto de Investigação do Medicamento. The authors acknowledge FCT to the Project "Ultra-High-pressure as a sustainable tool for tunable chemoselectivity" (2022.08851.PTDC), 2023.11341.PEX and 2024.07129.CBM.

References

[1] R. F. A. Gomes, N. R. Esteves, J. A. S. Coelho**,** C. A. M. Afonso, J. Org. Chem. **2018**, *83*, 14, 7509–7513

[2] R. F. A. Gomes, J. R. Vale, J. G. Pereira, and C. A. M. Afonso, *Organic Letters,* **2023,** *25,* 22, 4188-4192

[3] L. A. S. Cavaca, T. M. P. Santos, J. M. J. M. Ravasco, R. F. A. Gomes, C. A. M. Afonso**,** *J. Org. Chem*. **2024**, *89*, 10, 6677–6683

[4] R. F. A. Gomes, B. M. F. Gonçalves, K. H. S. Andrade, B. B. Sousa, N. Maulide, G. J. L. Bernardes, C. A. M. Afonso, *Angewandte Chemie International Edition* **2023**, *62* (28), e202304449

Abietane diterpenoids from *Plectranthus*: stability, drug-likeness, and anticancer potential

Vera M. S. Isca[1], Elizabeth A. Lopes[1], Milan Nikolić[2] Nenad Filipović[3], Przemysław Sitarek[4], Tomasz Kowalczyk[5], Patricia Rijo[1,6,7],

[1]CBIOS, Center for Research in Biosciences and Health Technologies, Universidade Lusófona, Lisboa, Portugal; [2]Faculty of Chemistry, University of Belgrade, Belgrade, Serbia [3]Faculty of Agriculture, University of Belgrade, Belgrade, Serbia; [4]Department of Medical Biology, Medical University of Lodz, Lodz, Poland; [5]Department of Molecular Biotechnology and Genetics, Faculty of Biology and Environmental Protection, University of Lodz, Lodz, Poland; [6]Center of Structural Chemistry, Institute of Molecular Sciences, University of Lisbon, Lisbon, Portugal; [7]Research Institute for Medicines (iMed.ULisboa), Faculty of Farmacy, Universidade de Lisboa, Lisboa, Portugal.
** E-mail: patricia.rijo@ulusofona.pt*

Cancer remains a major global health challenge, and natural diterpenoids from *Plectranthus* spp. represent promising scaffolds for drug development. Among them, 7α-acetoxy-6β-hydroxyroyleanone (Roy) exhibits notable cytotoxicity and structural versatility for semisynthetic optimization.

This study integrated computational and experimental approaches to explore Roy and derivatives as anticancer candidates.

ADMET and PASS predictions assessed drug-likeness and toxicity, while density functional theory (DFT) provided electronic descriptors. Molecular docking evaluated interactions with apoptosis and cell-cycle regulators. Experimental assays examined aqueous stability and human serum albumin (HSA) binding.

All derivatives displayed favourable pharmacokinetic profiles and strong predicted antineoplastic activity (Pa > 0.8). Docking and MD simulations revealed stable binding to key cancer-related proteins. Roy exhibited moderate affinity for HSA (K_a ≈ 6.5 × 10^4 M^{-1}), enhancing protein thermal stability, and remained chemically stable in aqueous media (pH 7.4, 37 °C).

These findings highlight Roy and selected derivatives as robust, bioactive scaffolds with promising anticancer potential and physicochemical stability, providing a basis for formulation strategies and further biological validation.

Funding: This work was funded by FCT (Portugal) through the project with reference DOI UID/04567/2025 and the PhD grant (SFRH/BD/137671/2018).

References

[1] V.M.S. Isca, et al., Rijo, P., *Chem Biodivers* **2025**, https://doi.org/10.1002/cbdv.202500670.
[2] A. Merecz-Sadowska, V.M.S. Isca, P. Sitarek et al, *Int J Mol Sci* **2024**, 25, 4529, https://doi.org/10.3390/ijms25084529.
[3] V.M.S. Isca, P. Sitarek, A. Merecz-Sadowska, et al., *Molecules* **2024** 16;29(8):1807. doi: 10.3390/molecules29081807.

N-Terminal cysteine bioconjugation enables direct benzodiazaborine formation on peptides

Rafaela A. N. Cavadas [1,*], Rita Padanha [1], J. P. M. António [1], P. M. P. Góis [1]

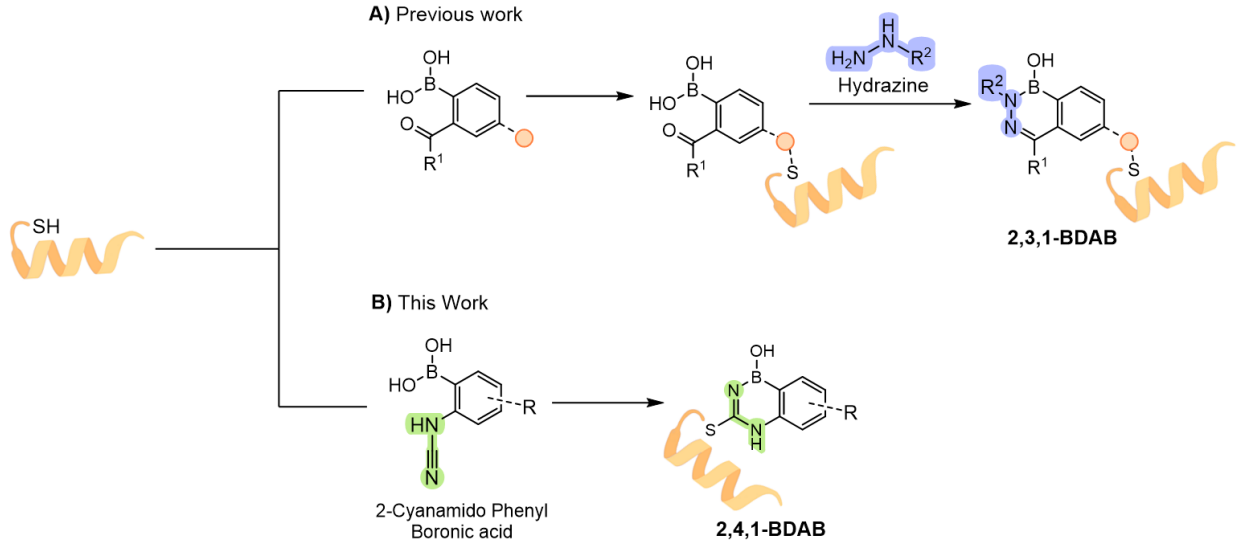
[1] *Research Institute for Medicines (iMed.Ulisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal*

* *E-mail: r.cavadas@edu.ulisboa.pt*

Phenylboronic acids can react with reactive oxygen species (ROS) and act as ROS-responsive units in drug delivery systems. However, their clinical translation is limited by poor physiological stability. Their reactivity with endogenous nucleophiles, such as vicinal diols and proteins, can cause toxicity and a poor pharmacokinetic profile [1].

Diazaborines are B-N heterocycles that are mainly developed to avoid boronic acid off-target reactivity while still maintaining their ability to oxidize. They can be a valuable tool to create functional and stable bioconjugates (e.g., antiboby-drug conjugates) via a click-type transformation (Scheme 1A) [2,3]. However, the current available methods to install them on peptides lack bioorthogonality, limiting their applications.

Here, a novel approach was studied to obtain diazaborines directly on peptides by reacting a cysteine with an aryl cyanamide with a boronic acid in the *ortho* position (Scheme 1B). The resulting diazaborine is stabilized by forming an intramolecular B-N bond. This method was used to selectively modify functional peptides that contained cysteine at their *N*-terminal.



Scheme 1. Methods to form diazaborines. **A)** Previous work – Reaction between hydrazines and phenylboronic acids. **B)** This work - Reaction between (2-Cyanamidophenyl)boronic acid and *N*-terminal cysteine.

Acknowledgements: This work was generously supported by the Portuguese Fundação para a Ciencia e Tecnologia, Ministério da Ciencia e da Tecnologia, Portugal [Grants: PTDC/QUI OUT/3989/2021; 2022.06817.CEECIND; 2024.16254.PEX; 2023.03403.BD, (https://doi.org/10.54499/2023.03403.BD) and Institutional Grants UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025) (iMed.ULisboa)].

References

[1] António J. P. M., Roque I.L., Santos F.M.F., Gois P.M.P.; Acc Chem Res. **2025**, 58, 673-687.
[2] Chio TI, Gu H, Mukherjee K, *et al.*; Bioconjug Chem **2019**, 30, 1554–1564.
[3] António J. P. M., Carvalho J.I., André A. S., *et al.*; Angew. Chem. Int. Ed. **2021**, 60, 2–10

Sphaerococcenol A derivatives for the treatment of Parkinson's disease

Rita D. Felisberto[1,*], Catarina A. Montargil[1,2], Milene A. G. Fortunato[1], Filipa Siopa[1], Carlos A. M. Afonso[1]

*[1]Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal; [2]MARE—Marine and Environmental Sciences Centre/ARNET—Aquatic Research Network, ESTM, Politécnico de Leiria, 2520-614 Peniche, Portugal; * E-mail: ritafelisberto@edu.ulisboa.pt*

The increase in life expectancy has led to a growth in the elderly population, resulting in a higher prevalence of neurodegenerative diseases, such as Parkinson's disease (PD). PD is a chronic disorder that affects more than 6 million people worldwide and for which there is still no known cure, with current treatments only acting on symptomatic relief [1]. Marine Natural Products produce secondary metabolites with unique and highly complex chemical structures, representing a valuable source for Drug Discovery and Development. Particularly, Sphaerococcenol A (SA), isolated from the red algae *Sphaerococcus coronopifolius*, has already demonstrated distinct biological activities [2]. Our interest has been focused on the synthesis of pyrazole derivatives of SA and pyrazoline derivatives of carvones from the photochemical 1,3-dipolar cycloaddition reaction with tetrazoles (**Figure 1**). Moreover, these moieties are frequently found in molecules that have been shown to act on targets involved in PD and have reached different stages of clinical trials [3].

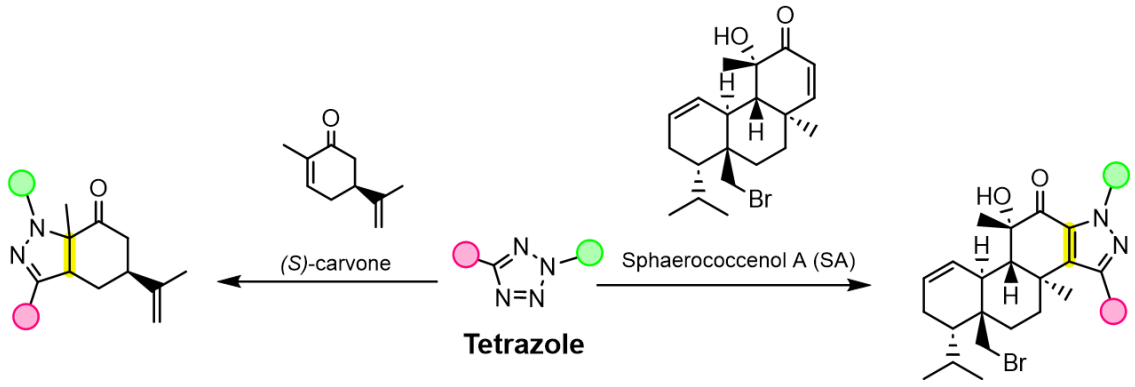


Figure 1. Reaction scheme for the synthesis of pyrazoles and pyrazolines.

Acknowledgements: We thank the Fundação para a Ciência e Tecnologia (2022.09196.PTDC; UIDP/04292/2020 - MARE—Marine and Environmental Sciences Centre; UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025)) for financial support.

References

[1] Bloem, B. R.; Okun, M. S.; Klein, C. Parkinson's Disease. *The Lancet* **2021**, *397* (10291), 2284–2303.
[2] Sousa, D.; Fortunato, M. A. G.; Silva, J.; Pingo, M.; Martins, A.; Afonso, C. A. M.; Pedrosa, R.; Siopa, F.; Alves, C. Sphaerococcenol A Derivatives: Design, Synthesis, and Cytotoxicity. *Marine Drugs* **2024**, *22* (9), 408.
[3] Sechi, G. P.; Sechi, M. M. Small Molecules, α-Synuclein Pathology, and the Search for Effective Treatments in Parkinson's Disease. *IJMS* **2024**, *25* (20), 11198.

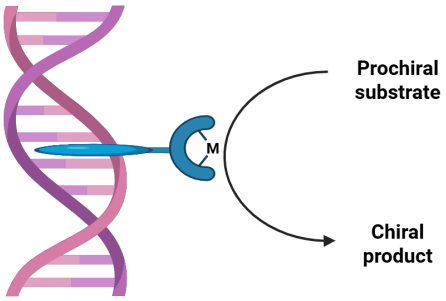
Customized non-conventional solvents for improved solubility and stability of nucleic acids

Bruna F. L. Guerreiro[1,*], Rafaela A. L. Silva[1], Andreia A. Rosatella[1,2], Carlos A. M. Afonso[1]

[1]Research Institute for Medicines (iMed.Ulisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto 1649-003, Lisbon, Portugal; [2]ERISA - Escola Superior de Saúde Ribeiro Sanches, Instituto Politécnico da Lusofonia, R. do Telhal aos Olivais 8, 1950-396, Lisbon, Portugal.
** E-mail: bruna.guerreiro@edu.ulisboa.pt*

Due to their biocompatibility and tunability, non-conventional solvents like Ionic Liquids (ILs) and Deep Eutectic Solvents (DES) have drawn attention as alternative media for biomolecular applications [1]. Notably, compared to aqueous environments, these solvents have been proven to both dissolve DNA and improve its stability [2]. We have been designing and synthesizing ILs and DES that could be used as reaction media in the framework of the European project FUNAMBULIST, which seeks to develop DNA-based asymmetric reactions (**Scheme 1**) by leveraging the intrinsic chirality of DNA. The ability of these solvents to stabilize and solubilize salmon testes DNA (st-DNA) was assessed.

Our findings show that a number of these non-conventional solvents can effectively solubilize st-DNA, achieving concentrations as high as 16.5% w/w while preserving and, in certain circumstances, improving its stability.



Scheme 1. Schematic representation of DNA-based asymmetric catalysis, created in BioRender.com.

Acknowledgements: The project leading to this work has received funding from the European Union's under grant agreement n.º 101099652. We thank the Fundação para a Ciência e a Tecnologia (2024.04361.BDANA and UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025)) for financial support.

References

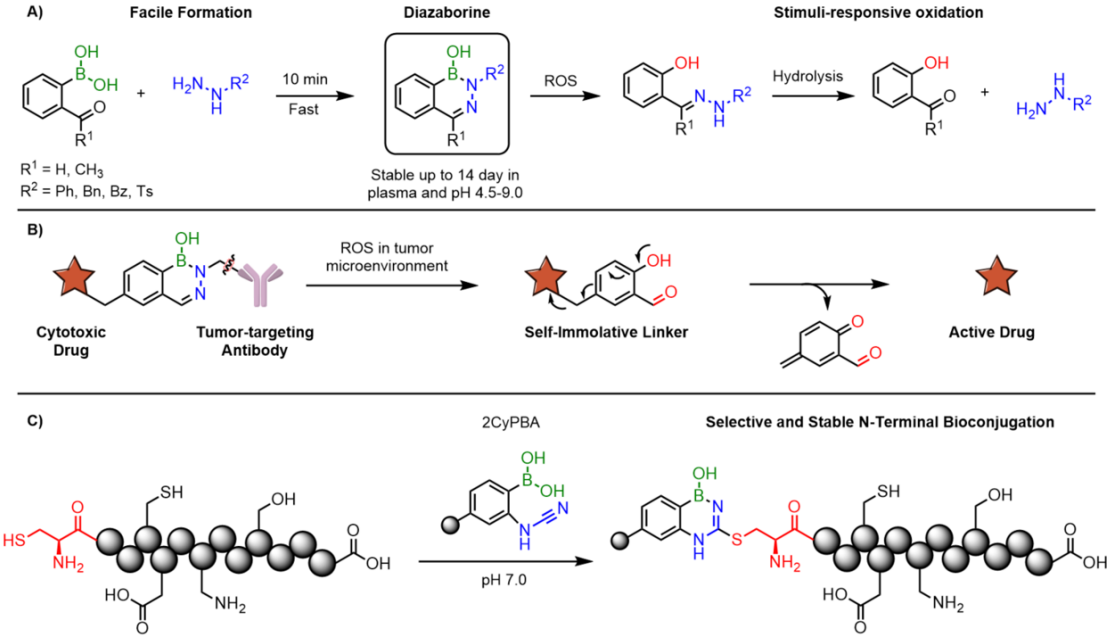
[1] Zhao, H.; J. *Chem. Technol. Biotechnol.* **2015**, *90 (1)*, 19–25.
[2] Vijayaraghavan, R.; Izgorodin, A.; Ganesh, V.; Surianarayanan, M.; MacFarlane, D. R.; *Angew. Chem. Int. Ed.* **2010**, *49 (9)*, 1631–1633.

Click! Bioconjugate! Release!: a unified diazaborine platform for stimuli-responsive therapeutics

João P. M. António,[a] Joana Inês Carvalho,[a] Ana S. André,[b] Gonçalo J. L. Bernardes,[d,e], Rita Padanha[a], Rafaela A. N. Cavadas[a], Frederico A. da Silva,[b] Pedro M. P. Góis[a]

a Research Institute for Medicines (iMed.ULisboa) Faculdade de Farmácia, Universidade de Lisboa. b Faculdade de Medicina Veterinária, Universidade de Lisboa. c Instituto Superior Técnico, Universidade de Lisboa. d Faculdade de Medicina, Universidade de Lisboa. e Department of Chemistry, University of Cambridge
** E-mail: jantonio@ff.ulisboa.pt*

Antibody-drug conjugates (ADCs) are among the most promising therapeutic strategies in oncology. Central to their success is the linker, since it must remain stable in circulation but release the payload selectively within cancer cells [1]. We recently developed diazaborines (DABs) as a novel ROS-responsive motif, exploiting the oxidative microenvironment of tumors to enable the design of a first-in-class ROS-activatable ADC [2]. DABs form rapidly under bioorthogonal conditions (pH 7.4, 10 min), display excellent stability in buffer and plasma (pH 4.5–9.0), and are readily oxidized by H_2O_2 ($t_1/_2$ = 15 min with 100 equiv.). A DAB-based self-immolative linker was incorporated into a homogeneous ADC bearing SN-38 and a B-cell lymphoma-targeting antibody, yielding potent activity (IC_{50} = 54.1 nM) and high selectivity (>100 μM in T-cell lymphoma). To expand the utility of this chemistry, we developed a site-selective strategy for installing DABs directly onto peptides via chemoselective cysteine alkylation. Using (2-cyanamidophenyl)boronic acids (2CyPBAs), DABs can be formed in situ through selective reaction with N-terminal cysteines, guided by an intramolecular B–N bond [3]. The reaction proceeds under mild, aqueous conditions, shows high conversion across diverse peptide sequences, and exhibits strict selectivity over internal cysteines. This method gives new life to DAB chemistry by enabling its direct incorporation without the need for auxiliary bioconjugation handles and opening new opportunities for targeted therapeutics and functional bioconjugates.



***Acknowledgements*:** We thank the FCT for financial support (2022.06817.CEECIND; 2024.16254.PEX and UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025))

References:

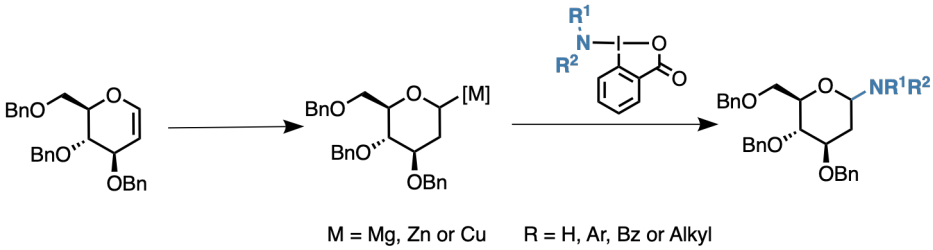
[1] J. P. M. António et al, Chem. Soc. Rev. 2019, 48, 3513.
[2] J. P. M. António et al, Angew. Chem. Int. Ed. 2021, 60, 25914.
[3] J. P. M. António et al, Org. Lett. 2023, 25, 5476–5480

Hypervalent iodine reagents as mediators of *N*-glycosylation

Catarina Cipriano,[a,b] Rafael F. A. Gomes,[b] P. Knochel,[c] M. Manuel B. Marques[a]

[a]*LAQV-REQUIMTE, Department of Chemistry, NOVA School of Science and Technology, Universidade Nova de Lisboa, 2829-516 Caparica, Portugal;*
[b]*Research Institute for Medicines (iMed.Ulisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, Lisboa 1649-003, Portugal*
**Email: ci.cipriano@campus.fct.unl.pt*

N-Glycosides are an important class of carbohydrate derivatives with significant biological relevance, including antineoplastic, antibacterial, immunosuppressive, and antimicrobial activities [1]. While remaining the most common approach to glycoconjugate synthesis, traditional glycosylation methods rely mostly on ionic pathways, often suffering from unstable glycosyl donors, harsh reaction conditions, and limited substrate compatibility [2]. Hypervalent iodine reagents (HIRs) are well-known as oxidation agents, and recently have attracted attention for their potential to transfer functional groups. Particularly, the benziodoxolones and benziodoxoles are attractive due to their enhanced stability compared to acyclic analogues and have been reported to transfer various N-containing moieties [3]. Recently, Marque´s group reported a new class of HIRs capable of transferring amine groups to a variety of nucleophiles [4], including organometallic reagents. Herein we present our latest results on the investigation of the reactivity of these HIRs on the preparation of various N-glycosides. This innovative approach involves the in situ generation of a metal–carbohydrate intermediate, and coupling with N-based HIRs, enabling a straightforward novel access to N-glycans (**Scheme 1**).



Scheme 1. *Synthesis of N-glycosides via metalation of carbohydrates and electrophilic amination using HIRS.*

Acknowledgments: The authors thank the FC&T (fellowship 2022.11378.BD and project 2022.04623.PTDC), and we thank the FC&T (UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025) for financial support. The authors also thank the support by the Laboratório Associado para a Química Verde (LAQV). The National NMR Facility is supported by FCT, ROTEIRO/0031/2013–PINFRA/22161/2016, co-financed by FEDER through COMPETE 2020, POCI, and PORL and FCT through PID-DAC) and CERMAX (022162).

References:

[1] Guimarães, B. M.; De Oliveira Silva, R.; De Sales Barbosa, M. V.; De Freitas, J. J. R.; Freitas, J. C. R.; De Oliveira, R. N.; De Freitas Filho, J. R. *ChemistrySelect* **2023**, 8, e202301417.
[2] Dubey, S.; Azeem, Z.; Mandal, P. K. *Adv. Synth. Catal.* **2024**, 366, 4017–4041.
[3] Macara, J.; Caldeira, C.; Poeira, D. L.; Marques, M. M. B. *Eur. J. Org. Chem.* **2023**, *26*, e202300109.
[4] a) Poeira, D. L.; Negrão, A. C. R.; Faustino, H.; Coelho, J. A. S.; Gomes, C. S. B.; Gois, P. M. P.; Marques, M. M. B. *Org. Lett.* **2022**, *24*, 776–781; b) Negrão, A. C. R.; Cunha, J.; Dedeiras, B.; Santos, F.; Coelho, J. A. S.; Gomes, C. S. B.; Gois, P. M. P.; Knochel, P.; Marques, M. M. B. *Org. Lett.* **2025**, *27*, 9914–9919; c) Cunha, J.; Rocha, G.; Santos, F.; Gois, P. M. P.; Marques, M. M. B. *Chemrxvi.* **2025**, DOI: 10.26434/chemrxiv-2025-18vmh

New sila-based ligands of vitamin D receptor for application in breast cancer therapy

Maria B. Igreja-Cardoso, José E. Rodríguez-Borges, Ivo E. Sampaio-Dias*
LAQV/REQUIMTE, Department of Chemistry and Biochemistry, Faculty of Sciences, University of Porto, 4169-007 Porto, Portugal
** E-mail: ivdias@fc.up.pt*

Vitamin D Receptor (VDR) is a nuclear receptor known for mediating the biological effects of 1,25-dihydroxyvitamin D_3 ($1,25D_3$, calcitriol), including calcium homeostasis, cell proliferation, and differentiation [1, 2]. Calcitriol and several other VDR agonists have demonstrated promising anticancer activity, however, their clinical application is limited by severe hypercalcaemic effects at therapeutic doses [1, 2].

To address this limitation, a carbon-to-silicon bioisosteric strategy was explored for the first time in calcitriol, aiming to reduce the hypercalcaemic effects while also improving VDR binding affinities and metabolic stability. [3]

Six sila-derivatives were synthesised with a silicon atom replacing the C25 side chain carbon starting from the Inhoffen-Lythgoe diol, via a Wittig-Horner strategy. X-ray crystallographic analysis of the VDR ligand-binding domain complexes was performed, showing that the silicon-containing side chains establish additional stabilising interactions within the VDR ligand-binding domain, supporting the receptor's active conformation. Functional studies revealed that sila-derivatives retain VDR binding and transcriptional activity comparable to calcitriol, while markedly reducing hypercalcaemic effects *in vivo*. Biological evaluations also demonstrated that the derivatives exhibited antiproliferative activity in breast cancer cell lines (MCF-7 and MDA-MB-231) at 10^{-7} M and potentiated the efficacy of conventional chemotherapeutics.

These results highlight the carbon-to-silicon bioisosteric approach as a promising strategy for developing non-calcaemic secosteroidal VDR ligands, opening new avenues for applications in both metabolic and cancer-related contexts.

Funding: This work received financial support from FEDER funds (COMPETE 2030), through project COMPETE2030-FEDER-00881500, with operation no. 15152.
Acknowledgements: This work received financial support from PT national funds (FCT/MECI, Fundação para a Ciência e Tecnologia, and Ministério da Educação, Ciência e Inovação) through the project UID/50006/2025 DOI 10.54499/UID/50006/2025 - Laboratório Associado para a Química Verde - Tecnologias e Processos Limpos. I.E.S.-D. thanks FCT for funding through the Individual Call to Scientific Employment Stimulus with reference 2020.02311.CEECIND/CP1596/CT0004 (DOI: 10.54499/2020.02311.CEECIND/CP1596/CT0004). M.B.I.-C. thanks REQUIMTE for the research grant with reference REQUIMTE-2025-42.

References

[1] Maestro, M.A.; Molnar , F.; Carlberg, C.; J. Med. Chem. 2019, 62, 6854-6875.
[2] Carlberg , C.; Nutrients 2022, 14, 1354.
[3] Loureiro, J.; Seoane, S.; Sampaio-Dias, I. E.; Peluso-Iltis, C.; Guiberteau, T., Brito, B.; Gregorio, C.; Pérez-Fernández, F.; Rochel, N.; Mouriño, A.; Rodríguez-Borges, J. E.; J. Med. Chem. 2024, 67, 21505-21519.

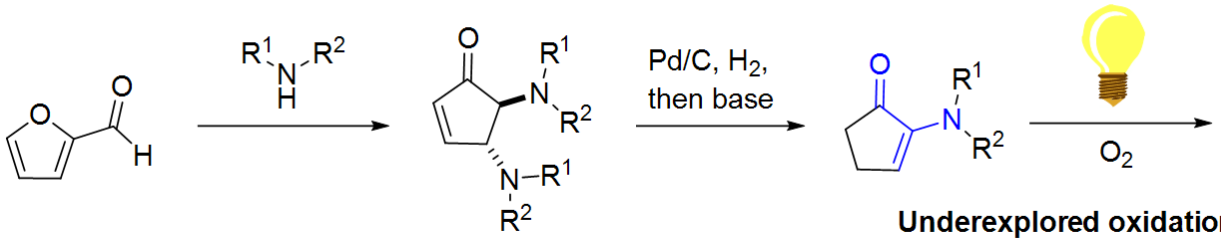
Photochemical oxidation of enaminones

André Peralta,[1*] João R. Vale,[1] Carlos. A. M. Afonso.[1]

[1]*Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisbon, Portugal*

**E-mail: fc57887@alunos.ciencias.ulisboa.pt*

The valorization of biomass-derived platform molecules into structurally complex and functional building blocks represents a key challenge in sustainable organic synthesis. Furfural, a renewable feedstock derived from lignocellulosic biomass, is a particularly interesting synthon and has been used in many useful transformations.[1] In this work, we have synthesized alfa-enaminones starting from furfural and through a sequence of a Nazarov-type electrocyclization, catalytic hydrogenation and β-amine elimination, following a protocol from our group.[2] The resulting alfa-enaminones were subjected to photochemical oxidation with molecular oxygen to obtained added-value oxygen rich compounds (**Scheme 1**). Photocatalytic oxidation using molecular oxygen as the terminal oxidant was explored as it is a green alternative to traditional stoichiometric oxidants, offering mild reaction conditions, operational simplicity, and improved environmental compatibility.[3]



Scheme 1. Synthetic pathway for enaminones and their photochemical oxidation.

Funding: The authors gratefully acknowledge financial support from the Fundação para a Ciência e a Tecnologia (2023.11341.PEX, 2023.09224.CEECIND, UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025) Instituto de Investigação do Medicamento)

References

[1] Mariscal, R.; Maireles-Torres, P.; Ojeda, M.; Sábada, I.; Granados, M. L.; Energy Environ. Sci. 2016, 9, 1144-1189

[2] Lídia, C.; Coelho, J. A. S.; Lucas, S. D., Loureiro, R. M. S.; Gomes, R. F. A.; Afonso, C. A. M.; React. Chem. Eng. 2023, 8, 482-489

[3] DeRosa, M. C.; Crutchley, R. J.; Coord. Chem. Rev., 233-234, 351-371

Chiral sparteine thioureas: synthesis and characterization

Abdullahi A. Muiz[1,*], R. M. Durão[1,2], J. A. S. Coelho[1]

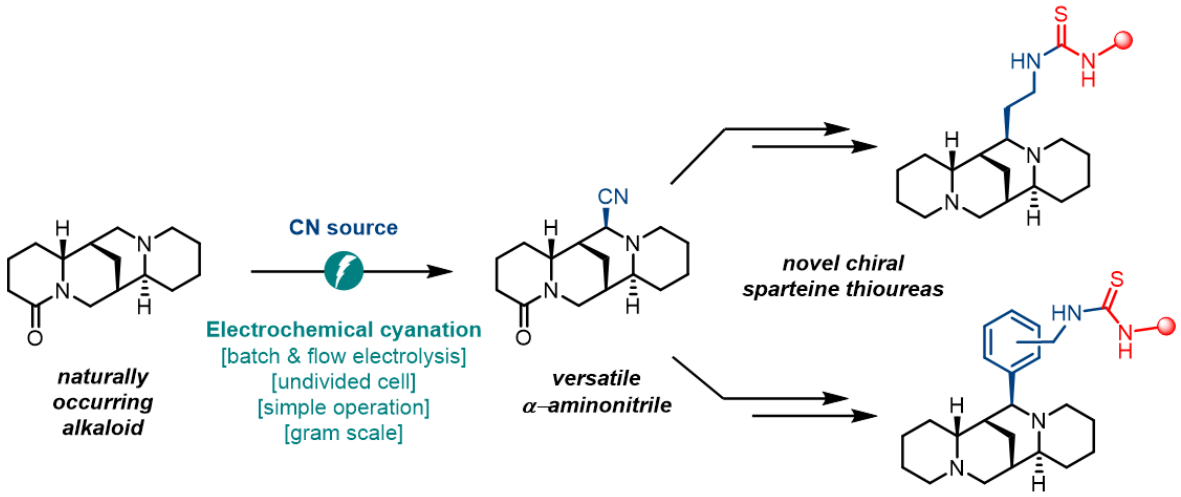
[1]*Centro de Química Estrutural, Institute of Molecular Sciences, Department of Chemistry and Biochemistry, Faculty of Sciences, University of Lisbon, Lisbon, Portugal*

[2]*Research Institute for Medicines, Faculty of Pharmacy, University of Lisbon, Lisbon, Portugal*

** E-mail: aamuiz@ciencias.ulisboa.pt*

Thioureas (thiocarbamides) are an important class of compounds that are widely used as organocatalysts in asymmetric organic synthesis. Their numerous biological activities such as antibacterial, antiviral, anticancer, antifungal, etc, makes them an important candidate for the pharmaceutical industries [1,2]. In addition, their relatively high acidity and strong hydrogen bond donor ability ensures their susceptibility to modifications towards achieving specific reactivity for substrate interactions [2]. Sparteine, a naturally occurring bisquinolizidine alkaloid is an excellent chiral ligand for several metals in asymmetric transformations [3]. It has also demonstrated several pharmacological properties such as antiarrhythmic activity, hypoglycemic effect, diuretic and anti-inflammatory activities [4].

We hereby describe the synthesis of novel chiral sparteine-based thioureas by taking advantage of the recent advances in electrochemical organic synthesis [5] to achieve a site-selective C–H activation of lupanine (2-oxosparteine) [6]. Further functional group transformations afforded the desired sparteine-based thioureas (**Scheme 2**).



Scheme 2. Synthesis of novel chiral sparteine thioureas.

Acknowledgements: We thank the Fundação para a Ciência e a Tecnologia for financial support through PhD studentship 2024.01550.BDANA and projects PTDC/QUI-QOR/1786/2021, UID/00100/2025, UID/PRR/100/2020 and LA/P/0056/2020.

References

[1] Naz, S.; Zahoor, M.; Umar, M.; Alghamdi, S.; Sahibzada, M.; UlBari, W.; *Open Chem*. **2020**, 18, 764. [2] Steppeler, F.; Iwan, D.; Wojaczyńska, E.; Wojaczynski, J.; *Molecules* **2020**, 25, 401. [3] Chuzel, O.; Riant, O.; *Top. Organomet. Chem*. **2005**, 15, 59. [4] Villalpando-Vargas, F.; Medina-Ceja, L.; *Seizure* **2016**, 39, 49. [5] Kärkäs, M.D.; *Chem. Soc. Rev*. **2018**, 4, 5786. [6] Durão, R.M.; Clemente, D.B.; Muiz, A.A.; Lima, S.; Carvalho, D.F.; De Vos, S.; de Jesus, R.; A. Fortuna, A.; Afonso, C.A.M.; Coelho, J.A.S.; *ChemSusChem* **2025**, 18, e202401305.

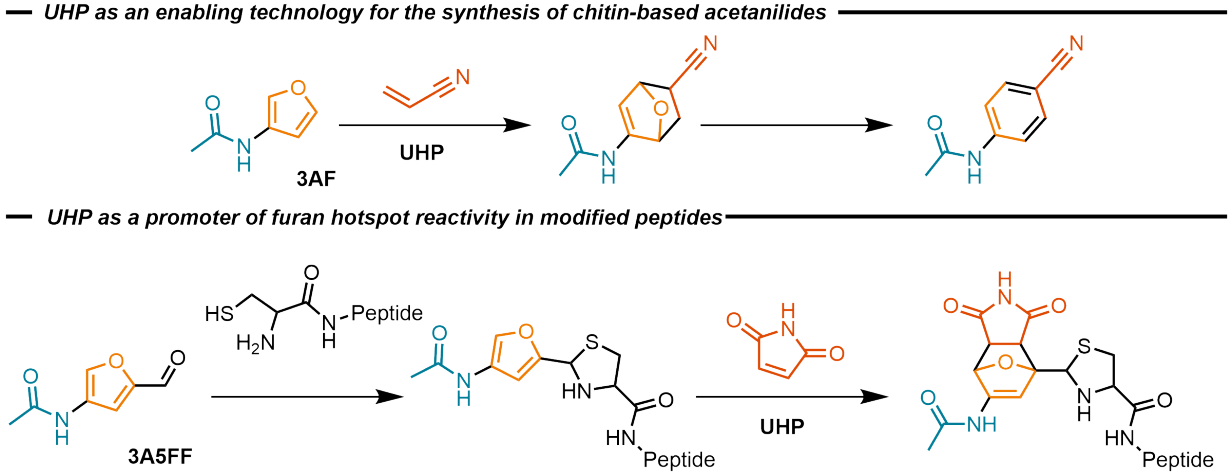
Emerging technologies for the transformation of biomass-derived nitrogen-rich furans

Tiago M. P. Santos[1,2,*], Sabrina M. E. Cabral[1], Jaime A. S. Coelho[2], Rafael F. A. Gomes[1], Carlos A. M. Afonso[1]

[1]Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649- 003 Lisboa, Portugal; [2]Centro de Química Estrutural, Institute of Molecular Sciences, Faculty of Sciences, Universidade de Lisboa, Lisboa, Portugal.

** E-mail: tiagomsantos1@edu.ulisboa.pt*

N-Acetylglucosamine (**NAG**), produced through the hydrolysis of chitin, serves as a precursor for the synthesis of various nitrogen-containing furan derivatives [1]. These electron-rich furans have been reported to participate in Diels-Alder reactions with maleimides, yielding stable cycloadducts [2]. However, their reactivity toward other dienophiles has remained largely unexplored. In this study, chitin-derived 3-acetamidofuran (**3AF**) was investigated as a diene in Diels–Alder cycloaddition reactions, which are strongly promoted under ultra-high-pressure (**UHP**) conditions due to their negative activation volumes [3]. Under **UHP** conditions, novel **3AF** cycloadducts with otherwise challenging dienophiles were successfully synthesized at room temperature without the use of catalysts. Biomass-derived aniline building blocks were then obtained under basic aromatization conditions. **UHP** was also applied to the modification of furan-containing peptides, via N-terminal cysteine modification with **3A5FF** [4], to perform Diels-Alder under bioconjugation conditions (**Scheme1**).



Scheme 1. UHP cycloadditions with challenging dienophiles and as a promoter of peptide modifications.

Acknowledgements: We thank the Fundação para a Ciência e a Tecnologia (FCT) for financial support (UID 04138 - Instituto de Investigação do Medicamento; UID/00100 – Centro de Química Estrutural). The authors acknowledge FCT to the Project "Ultra-High-pressure as a sustainable tool for tunable chemoselectivity" (2022.08851.PTDC), 2023.11341.PEX and 2024.07129.CBM.

References

[1] Bossons, N.; Gomes, R. F. A. Current Opinion in Green and Sustainable Chemistry **2024**, *49*, 100961.
[2] Pereira, J. G., *et al*. Green Chemistry **2022**, *24*, 7131–7136.
[3] Chataigner, I.; Maddaluno, J. in Activation Methods, Wiley **2019** 95–149.
[4] Gomes, R. F. A. *et al*. Angewandte Chemie International Edition **2023**, *62*, e202304449.

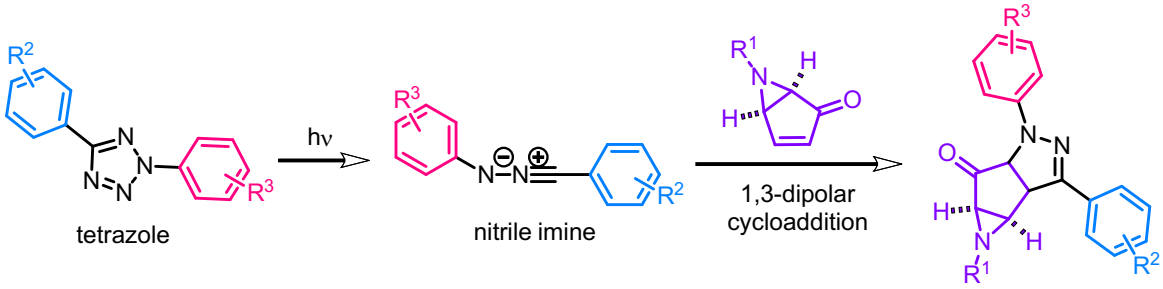
Synthesis of new pyrazoline derivatives via photoinduced 1,3-dipolar cycloaddition

Mariana C. Monteiro[1], Sara O. Antunes[1,2], Filipa Siopa[1*], Carlos A. M. Afonso[1]

[1]Research Institute for Medicines (iMed.ULisboa), Faculdade de Farmácia, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal; [2]Department of Chemistry, NOVA School of Science and Technology, Universidade Nova de Lisboa, 2829-516 Caparica, Portugal

** E-mail: filipasiopa@ff.ulisboa.pt*

Nitrogen-containing heterocycles can have several applications in the pharmaceutical industry since they contain a wide spectrum of biological activities. Furthermore, they are of great usefulness as synthetic intermediates [1,2]. Among them, pyrazolines, five-membered nitrogen containing rings, are known for their anticancer [3], anti-inflammatory [4], and antimicrobial activities [5]. The substituted pyrazoline scaffold can be synthesized through 1,3-dipolar cycloaddition of unsaturated systems with nitrile imines generated photochemically from tetrazoles [6, 7]. In previous works, we have studied the photoreaction of pyridinium salts into the corresponding bicyclic aziridines, under continuous-flow conditions, allowing us to overcome the scalability issues associated with batch photochemical transformations [8,9]. In this work, we report the photoinduced cycloaddition between α,β-unsaturated carbonyl bicyclic aziridines and tetrazoles for the obtention of new pyrazoline derivatives (**Scheme 1**). Moreover, this transformation was also implemented in substrates derived from marine biorenewable sources.



Scheme 1. Synthesis of pyrazolines *via* photoinduced 1,3-dipolar cycloaddition of α,β-unsaturated aziridine and tetrazoles.

Acknowledgements: We thank the Fundação para a Ciência e a Tecnologia (UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025); 2023.03748.BD (https://doi.org/10.54499/2023.03748.BD); 2022.09196.PTDC, DOI: https://doi.org/10.54499/2022.09196.PTDC); for financial support.

References

[1] Kerru N.; Gummidi L.; Maddila S.; Gangu K. K.; Jonnalagadda S. B. Molecules 2020, 25, 1909.
[2] Ebenezer O.; Shapi M.; Tuszynski J. A., Biomedicine 2022, 10, 1124.
[3] Matiadis D.; Sagnou M., Int. J. Mol. Sci. 2020, 21, 5507.
[4] Priya D.; Gopinath P.; Dhivya L. S.; Vijaybabu A.; Haritha M.; Palaniappan S.; Kathiravan M. K. Chem. Select. 2022, 7, e202104429.
[5] Hassan S. Y. Molecules 2013, 18, 2683–2711.
[6] Labassi C.; Fournier-le-Ray N.; Gauffre F.; Fillaut J.; Gatri R. Eur. J. Org. Chem. 2023, 26, e202300911.
[7] Kumar G. S.; Lin Q. Chem. Rev. 2020, 121, 6991–7031.
[8] Siopa F.; António J. P. M.; Afonso C. A. M. Org. Process. Res. Dev. 2018, 22, 551-556.
[9] Fortunato M. A. G.; Ly C. P.; Siopa F.; Afonso C. A. M. Methods Protoc. 2019, 2, 67-75.

DFT insights into the electrochemical 1,4-dicyanation of abietanes

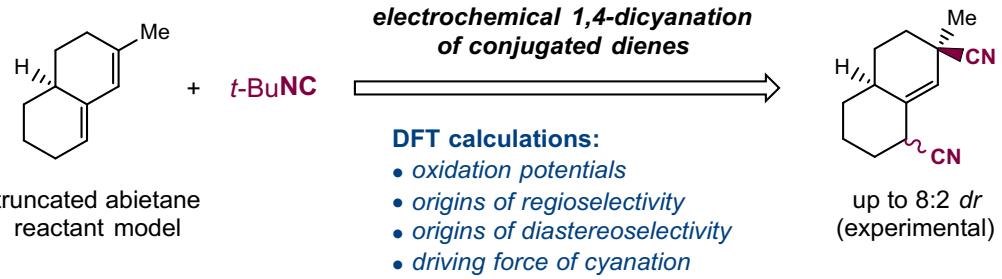
Francisco P. Nascimento[1,*], Inês S. Martins[1,2], Daniel F. Carvalho[2], Jaime A. S. Coelho[2]

[1]*Instituto de Investigação do Medicamento (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal;* [2]*Centro de Química Estrutural, Institute of Molecular Sciences (CQE-IMS), Faculty of Sciences, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal.*

** E-mail: francisco.nascimento@edu.ulisboa.pt*

Abietanes are a group of diterpenes found in colophony that exhibit a wide range of biologically relevant activities, including antimicrobial, antiviral, antitumoral, and anti-inflammatory effects.[1,2]

We recently discovered that direct electrochemical 1,4-dicyanation of the conjugated dienes system in abietanes (e.g., abietic acid and methyl abietate) can be achieved via anodic oxidation of the abietanes followed by addition of tert-butyl isocyanide.[3] To the best of our knowledge, although tert-butyl isocyanide has previously been reported as a source of cyanide,[4] little is known about the reaction mechanism. Here, we elucidate the mechanism of this transformation by means of density functional theory (DFT) calculations (Scheme 1).



Scheme 1: DFT investigation of the electrochemical 1,4-dicyanation of conjugated dienes.

Acknowledgements: We thank the Fundação para a Ciência e a Tecnologia (FCT) through projects 2022.04623.PTDC, PTDC/QUI-QOR/1786/2021 (https://doi.org/10.54499/PTDC/QUI-QOR/1786/2021), UID/00100/2025, UID/PRR/100/2020, LA/P/0056/2020 (https://doi.org/10.54499/LA/P/0056/2020), UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025) for financial support.

References

[1] M.A. González *et al. Eur. J. Med. Chem.* **2009**, 44, 2468–2472.
[2] G. Eksi *et al.* Analysis of diterpenes and diterpenoids. *Recent Advances in Natural Products Analysis*, S. M. Nabavi, M. Saeedi, S. F. Nabavi, A. T. S. Silva, Eds., Elsevier Inc., **2020**, 313–345.
[3] I. S. Martins *et al.*, *unpublished results*.
[4] S. Tang, *et al. Org. Lett.* **2022**, 24, 2125–2130.

A green and scalable strategy for the multigram synthesis of (hydroxyethyl)sulfonamide peptidomimetics

Xavier C. Correia[1,*], Ivo E. Sampaio-Dias[1]

[1]*LAQV/REQUIMTE, Department of Chemistry and Biochemistry, Faculty of Sciences, University of Porto, 4169-007 Porto, Portugal.*

** E-mail: xavier.correia.sc@gmail.com*

Highly active antiretroviral therapy (HAART) is the most effective pharmacological treatment available to fight infections by the human immunodeficiency virus (HIV) [1]. This combination therapy successfully suppresses the replication of HIV, resulting in reduced morbidity and mortality associated with HIV infection, as well as improving the lifespan of patients [1]. Protease inhibitors (PI; e.g., Amprenavir and Darunavir) are a class of antiretroviral drugs used in HAART that prevent the maturation of viral particles by inhibiting the viral enzyme protease, thereby suppressing the reassembly of viral proteins [1]. However, the crescent use of PI in chronic therapy induces mutations in the virus, resulting in the development of drug-resistant strains [2]. As such, there is a constant need for the discovery of novel antiretroviral pharmaceuticals to fight resistant strains of the virus [2].

A common research approach in this regard is the design and synthesis of Amprenavir and Darunavir analogues by strategic chemical modifications, conserving the (hydroxyethyl)sulfonamide structural motif [3], which is relevant for the pharmacological properties of these compounds. In the literature, different methodologies are reported for the synthesis of the (hydroxyethyl)sulfonamide pharmacophore; the majority use disconnective approaches, hazardous solvents, and are limited to small-scale synthesis.

In this work, an innovative and practical multi-gram one-pot methodology is presented for the preparation of the (hydroxyethyl)sulfonamide structural motif. The key steps of this novel protocol are the preparation of the amino alcohol precursor in ethanol as the solvent and the sulfonamide synthesis in an aqueous medium, offering high global yields (88-94%) and chemical purity (>98%, HPLC). Moreover, this methodology avoids chromatography techniques, thus offering a more sustainable approach for the preparation of this structural motif, boosting the HIV drug research of structure-related Amprenavir and Darunavir analogues.

Funding: This work received financial support from PT national funds (FCT/MCTES, Fundação para a Ciência e a Tecnologia and Ministério da Ciência, Tecnologia e Ensino Superior) through project 2023.14440.PEX (DOI: 10.54499/2023.14440.PEX).

Acknowledgements: FCT is also acknowledged for supporting the project UID/50006/2025 DOI 10.54499/UID/50006/2025 - Laboratório Associado para a Química Verde - Tecnologias e Processos Limpos. I.E.S.-D. thanks FCT for funding through the Individual Call to Scientific Employment Stimulus with reference 2020.02311.CEECIND/CP1596/CT0004 (DOI: 10.54499/2020.02311.CEECIND/CP1596/CT0004). X.C.C. thanks FCT for the Ph.D. grant 2024.02245.BD.

References

[1] Cunha, J.; Maselli, L.M.F.; Stern, A.C.B.; Spada, C.; Bydlowski, S.P.; *World J. Virol*. 2015, 4, 56.

[2] Lu, Z.; *Expert Opin. Drug Discov*. 2008, 3, 775.

[3] Ghosh, A.K.; Nyalapatla, P.R.; Kovela, S.; Rao, K.V.; Brindisi, M.; Osswald, H.L.; Amano, M.; Aoki, M.; Agniswamy, J.; Wang, Y.F.; Weber, I.T.; Mitsuya, H.; *J. Med. Chem*. 2018, 61, 4561.

Cispentacin-based melanostatin peptidomimetics as ago-allosteric modulators of the dopamine D_2 receptors

Hugo F. Costa-Almeida[1,2,*], Xavier C. Correia[1], Sara C. Silva-Reis[1,2], Beatriz L. Pires-Lima[1], Vera M. Costa[2,3], José E. Rodríguez-Borges[1], Ivo E. Sampaio-Dias[1]

[1]LAQV/REQUIMTE, Department of Chemistry and Biochemistry, Faculty of Sciences University of Porto, 4169-007, Porto, Portugal; [2]UCIBIO – Applied Molecular Biosciences Unit, Laboratory of Toxicology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, 4050-313, Porto, Portugal; [3]Associate Laboratory i4HB – Institute for Health and Bioeconomy, Laboratory of Toxicology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, 4050-313, Porto, Portugal;

** E-mail: up201805208@up.pt*

Melanostatin (MIF-1) is an endogenous hypothalamic positive allosteric modulator (PAM) of the dopamine D_2 receptors (D_2R) and a promising lead compound against dopamine-related CNS disorders, such as Parkinson's disease. In this work, we report the design, synthesis, and biological evaluation of a new series of MIF-1 peptidomimetics bearing the alicyclic β-amino acids cispentacin and its synthetic precursor 2-aminocyclopent-3-ene-1-carboxylic acid as proline surrogates. Six derivatives were obtained and fully characterized. Functional assays in transfected human D_2R in CHO cells showed that only cispentacin-based analogs **8b** and **9b** retained activity, significantly enhancing dopamine (DA) potency by 4.2- and 4.3-fold at 0.01 nM, while MIF-1 was inactive at this concentration. At 1 nM, while compound **9b** showed a comparable reduction of EC_{50} to that of MIF-1 (3.8- versus 3.7-fold), compound **8b** reduced the EC_{50} of DA by 9.2-fold, significantly surpassing MIF-1. Furthermore, in the absence of DA, compound **8b** displayed intrinsic agonist activity, establishing the first MIF-1-based compound with ago-allosteric activity. Cytotoxicity assays in differentiated SH-SY5Y cells using the MTT reduction assay confirmed that **8b** and **9b** are non-toxic at 100 μM. Overall, these findings uncover alicyclic β-amino acids as powerful scaffolds for next-generation MIF-1-based D_2R modulators and identify **8b** as a promising, potent, safe, and mechanistically distinct lead for therapeutic development in Parkinson's disease and other DA-related disorders.

Funding: This work received financial support from PT national funds (FCT/MCTES, Fundação para a Ciência e a Tecnologia and Ministério da Ciência, Tecnologia e Ensino Superior) through project 2023.14440.PEX (DOI: 10.54499/2023.14440.PEX).

Acknowledgements: FCT is also acknowledged for supporting the project UID/50006/2025 DOI 10.54499/UID/50006/2025 - Laboratório Associado para a Química Verde - Tecnologias e Processos Limpos. I.E.S.-D. thanks FCT for funding through the Individual Call to Scientific Employment Stimulus with reference 2020.02311.CEECIND/CP1596/CT0004 (DOI: 10.54499/2020.02311.CEECIND/CP1596/CT0004). B.L.P.-L., X.C.C., and H.F.C.-A. thank FCT for the Ph.D. grants 2022.14060.BD (DOI: 10.54499/2022.14060.BD), 2024.02245.BD, and UI/BD/154888/2023 (DOI: 10.54499/UI/BD/154888/2023), respectively. S.C.S.-R. thanks REQUIMTE for the post-doc contract with reference REQUIMTE 2025-43.

Bioactive potential of pomegranate peel: from food waste to functional extracts

Ana Rita Pereira[1,*], Patrícia Correia[1], Ana Fernandes[2], Iva Fernandes[2], Victor de Freitas[2]

[1]LAQV-REQUIMTE, Porto, Portugal; [2]Faculdade de Ciências da Universidade do Porto, Portugal

** E-mail: anarita@fc.up.pt*

Food waste is a pressing global challenge, with fruits and vegetables representing a large proportion of discarded food. Among fruit by-products, pomegranate peel is a rich source of bioactive compounds with potential applications in food preservation and health [1]. In this study, pomegranate peel was freeze-dried, milled, and extracted with water and hydroalcoholic solutions (50:50, v/v). Extracts were characterized for their phenolic and flavonoid content, antioxidant activity, and antibacterial properties. Hydroalcoholic extracts showed the highest total phenolic content (up to 236 mg EA/g DW for methanol and 205.7 ± 8.5 mg EA/g DW for ethanolic extract) and flavonoid content (81.3 ± 1.7 and 77.1 ± 9.1 mg CE/g DW, respectively, for methanol and ethanol extracts), which correlated with the strong reducing capacity in the FRAP assay. All extracts exhibited comparable DPPH scavenging activity with IC_{50} values of 5.942 µg/mL (H_2O), 5.807 µg/mL (EtOH), and 5.172 µg/mL (MeOH). Phenolic compounds were further quantified by HPLC, showing lower values compared to those obtained by the colorimetric method. LC–MS analysis revealed β-punicalagin and α-punicalagin as the major constituents, together with other punicalagin derivatives. A significant presence of ellagic acid aglycone and its glycosylated derivatives (with glucose, pentose, or rhamnose) was detected. Hydroalcoholic extracts also showed the distinctive presence of HHDP-D-glucose, a hydrolysable tannin characteristic of pomegranate. The stability of the extracts under different conditions of temperature, light exposure, and pH was also assessed to evaluate their behaviour in diverse matrices and storage environments. Antibacterial activity was evaluated using the reference strain *Staphylococcus aureus* ATCC 29213. All pomegranate peel extracts exhibited antibacterial activity, with the aqueous extract showing comparable effectiveness to the ethanolic and methanolic extracts. At concentrations of 4 and 8 g/L, the extracts promoted reductions of 4 and 6 $\log_{10}$ (CFU/mL) in bacterial growth, respectively, highlighting the feasibility of choosing water as a green solvent, compatible with technological applications.

Funding: This work received financial support from the IDfoods project - Food System of The Future - Investigação e Desenvolvimento em Sistemas Agroalimentares Sustentáveis e Nutrição Saudável - POCI-01-0247-FEDER-182848.

References

[1] Giri, N.A.; Gaikwad, N.N.; et al. Curr Nutr Rep, 2023, 12, 270–289.

Late-stage hydroxylation of agrochemical active ingredients using commercial continuous flow electrochemical cells

Rodrigo S. Gomes[a], Duarte B. Clemente[a], Carlos M. Monteiro[b], Jaime A. S. Coelho[a]

[a] *Centro de Química Estrutural, Institute of Molecular Sciences, Department of Chemistry and Biochemistry, Faculty of Sciences, University of Lisbon, Lisbon, Portugal.*
[b] *ASCENZA Agro, S.A., Setúbal, Portugal.*
E-mail: rodrigomes@alunos.fc.ul.pt

The development of agrochemicals requires the evaluation of the safety profile of their active ingredients, including the toxicity determination of their metabolites. Hydroxylation is a very common phase-one metabolism reaction, which is catalyzed by cytochrome P450 enzymes [1]. Thus, the preparation of hydroxylated metabolites of agrochemical active ingredients (AAI) is of great importance to agrochemical producing companies, such as Ascenza Agro [2], for safety evaluation purposes. However, the late-stage preparation of AAI metabolites remains challenging due to the structural complexity of these compounds. Synthetic organic electrochemistry allows for highly chemoselective C-H activation reactions under mild conditions [3], and the use of continuous flow methodologies leads to enhanced reactivity, selectivity and reproducibility of these electrochemical transformations [4,5]. Herein, we describe the preparation and characterization of hydroxylated metabolites of several AAIs, using commercially available continuous flow electrochemical cells, based on methodologies described by Xu [6] and Ošeka [7] (**Figure 1**). These methods allow for the preparation of trifluoroacetate derivatives of the AAIs, which yield the phenol metabolites upon hydrolysis.

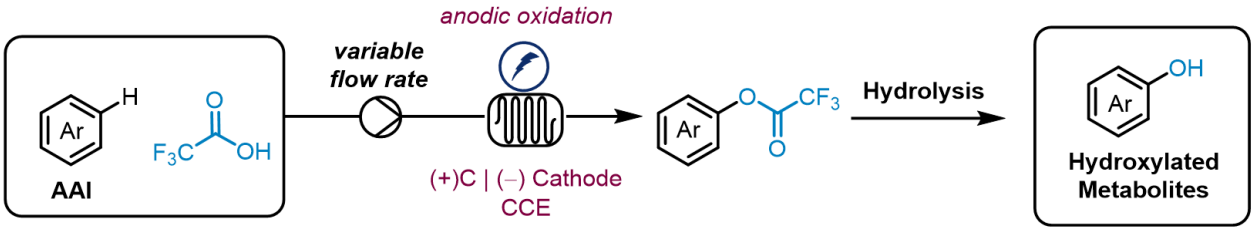


Figure 3: Electrochemical hydroxylation of AAIs in continuous flow [6,7].

Acknowledgments: We thank FCT for financial support (UID/00100/2025, UID/PRR/100/2025, LA/P/0056/2020). We thank Fundação Calouste Gulbenkian for financial support (Novos Talentos 2024 Nº 328964).

References:

[1] *Regulatory Toxicology*, 2nd ed., F.-X. Reichl, M. Schwenk, Eds., Springer Nature Switzerland AG: Cham, Switzerland, **2021**.
[2] https://www.ascenza.pt/ *(accessed 2025-12-12)*.
[3] Y. Wang, S. Dana, H. Long, Y. Xu, Y. Li, N. Kaplaneris, *Chem. Rev.* **2023**, *123*, 11269.
[4] T. Noël, Y. Cao, G. Laudadio, *Acc. Chem. Res.* **2019**, 52, 2858.
[5] M. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796.
[6] H. Long, T.-S. Chen, J. Song, S. Zhu, H.-C. Xu, *Nat. Commun.* **2022**, *13,* 3945.
[7] A. Kooli, L. Wesenberg , M. Beslać, A. Krech, M. Lopp, T. Noël, M. Ošeka, *Eur. J. Org. Chem.* **2022**, e202200011.

Designing smart linkers for next-generation antibody-drug conjugates

Catarina A. R. Vilão[1,*], Rafaela A. N. Cavadas[1], João P. M. António[1]

[1] *Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Portugal. Av. Prof. Gama Pinto, 1649-003, Lisboa.*

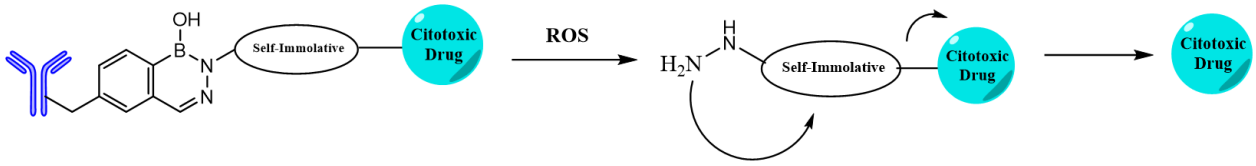
** E-mail: cvilao@edu.ulisboa.pt*

The development of therapeutic targets has revolutionized cancer treatment. Antibody-drug conjugates are among the most promising therapeutic strategies, as they enable cancer treatment through the direct delivery of potent drugs to diseased cells, thus protecting healthy tissues.[1]

One of the important aspects of ADCs for them to be successful is the linker, the small molecular bridge that connects the cytotoxic payload to the antibody. The linker must be stable in circulation, yet release the drug selectively into cancer cells when a specific stimuli, such as Reactive Oxygen Species (ROS), are elevated.[2]

A new class of ROS-responsive linkers based on diazoborines (DABs) is being developed to enable selective drug release in ROS-rich tumor microenvironments.[3] To ensure the release of the active drug, these systems require self-immolative spacers that fragment cleanly upon activation. However, these spacers have some limitations, such as limited stability, low kinetics, and poor compatibility with the chemical structures of existing therapeutic agents.

This project aims to address these limitations by designing and synthesizing two distinct families of self-immolative linkers, based on rational structural features that promote rapid intramolecular cyclization and release, evaluating the chemical stability and release kinetics of each linker family under simulated physiological and oxidative conditions (ROS- triggered environments).



Scheme 1. ROS-mediated cytotoxic drug release mechanism via a self-immolative spacer.

Acknowledgements: We thank Fundação para a Ciência e a Tecnologia (2022.06817.CEECIND; 2024.16254.PEX and UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025)) for financial support.

References

[1] J. P. M. António et al, Chem. Soc. Rev. 2019, 48, 3513
[2] J. P. M. António et al, Acc. Chem. Res. 2025, 58, 5, 673–687
[3] J. P. M. António et al, Angew. Chem. Int. Ed. 2021, 60, 25914

Design, synthesis and biological evaluation of novel carnosic acid derivatives with anticancer activity

Sara P. S. P. Moura[1,2,3*], Marta Cascante[4,5], Ismael Rufino[6], Rita C. Guedes[6], Silvia Marin[4,5], Jorge A. R. Salvador[1,2,3]

[1]Laboratory of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Coimbra, 3000-548 Coimbra, Portugal; [2]Center for Neuroscience and Cell Biology (CNC), University of Coimbra, 3004-504 Coimbra, Portugal; [3]Centre for Innovative Biomedicine and Biotechnology (CIBB), University of Coimbra, 3004-504 Coimbra, Portugal; [4]Department of Biochemistry and Molecular Biomedicine, Faculty of Biology, University of Barcelona, 08028 Barcelona, Spain; [5]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Instituto de Salud Carlos III (ISCIII), 28029 Madrid, Spain; [6]Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, University of Lisbon, 1649-003 Lisboa, Portugal

** E-mail: spmoura17@gmail.com*

Carnosic acid **1** is an abietane-type diterpenoid found in rosemary leaves (*Rosmarinus officinalis)* and common sage (*Salvia officinalis*), with recognized anticancer activity [1,2]. Although carnosic acid **1** has demonstrated promising anticancer activity, chemical modifications of its backbone are required to enhance its potency. Thus, novel derivatives of carnosic acid **1** with ester or carbamate groups at C-20 and derivatives with these functional groups combined with benzylic modifications (C-7) were synthesized and evaluated in a colorectal cancer cell line (HCT116) [3]. Compound **8**, which featured a butyl ester at C-20 and a carbonyl group at C-7, and compound **17**, which featured a 2-methylpropyl carbamate at C-20, achieved the best results in HCT116 cells. Compounds **8** and **17** also demonstrated better ability to inhibit the growth of other cancer cell lines than CA **1**. In general, the best results were achieved with compound **17**, which exhibited higher potency against SW480 cells (IC_{50} = 6.3 µM). This compound also showed selectivity for cancer cells compared to normal cells. Compound **17** was subjected to additional studies to elucidate the mechanism responsible for its antiproliferative activity in SW480 cells. At 24 h, compound **17** arrested the cell cycle at the G0/G1 phase by decreasing the CDK4/CDK6 levels. It also reduced ROS levels by increasing the expression of SOD2/MnSOD. However, at 48 h, compound **17** induced cell cycle arrest in the S phase and increased ROS levels. At 72 h, compound **17** elevated the ROS levels without inducing cell cycle arrest. Additionally, molecular docking studies showed that compound **17** establishes several interactions with the amino acids of the CDK6 active site. In conclusion, compound **17** has potential as a lead compound for the development of novel anticancer drugs and merits further investigation.

Acknowledgements: Sara P.S.P. Moura and Ismael Rufino acknowledge FCT for funding the research grants SFRH/BD/138674/2018 and 2024.05709.BDANA, respectively.

References

[1] Bahri, S.; Jameleddine, S.; Shlyonsky, V.; Biomed Pharmacother 2016, 84, 569-582.
[2] Acquaviva, R.; Malfa, G.A.; Loizzo, M.R; Xiao J.; Bianchi, S.; Tundis, R.; Molecules 2022, 27, 4791.
[3] Moura, S. P. S. P.; Cascante, M.; Rufino I.; Guedes, R. C.; Marin, S.; Salvador, J. A. R.; *RSC Adv* 2025, 15, 36861-36878.

pH-Sensitive boron based platform (AZABY) for biological applications

Rafael F. P. Mascarenhas[1*] Eduardo F.F. Reis[1],Pedro M.P. Góis[1],Uwe Pischel[2], David Ng[3] and Fábio M.F. Santos[1]

[1] Research Institute for Medicines (iMed.ULisboa) Faculdade de Farmácia, Universidade de Lisboa, Portugal [2] CIQSO-Centre for Research in Sustainable Chemistry and Department of Chemistry University of Huelva, Spain [3] Max Plank Institute for Polymer Research, Germany

** E-mail: rafaelmascarenhas@edu.ulisboa.pt*

To achieve the UN's goal of reducing cancer mortality by 2030, it is essential to develop more precise therapies. The azaboron-oxy (AZABY) platform proposes a new generation of boron-based ligands for antibody-drug conjugates (ADC). The clinical success of ADCs requires a delicate balance between stability in the systemic circulation and efficient release in the tumour. [1] The AZABY platform addresses this challenge by exploiting the adjustable electronic properties of B-O bonds, which promote rapid cleavage in the acidic conditions of tumour lysosomes.[2] A distinctive feature of this technology is the incorporation of a self-immolative mechanism. This mechanism ensures that the cleavage process triggers the spontaneous elimination of the spacer, allowing the "trace-free" release of the cytotoxic molecule and maximising the therapeutic index.[3] Recent studies have evaluated the release of the self-immolative module, with different alcohols being used to study their respective hydrolysis and its influence on the mechanism of release of the payload.

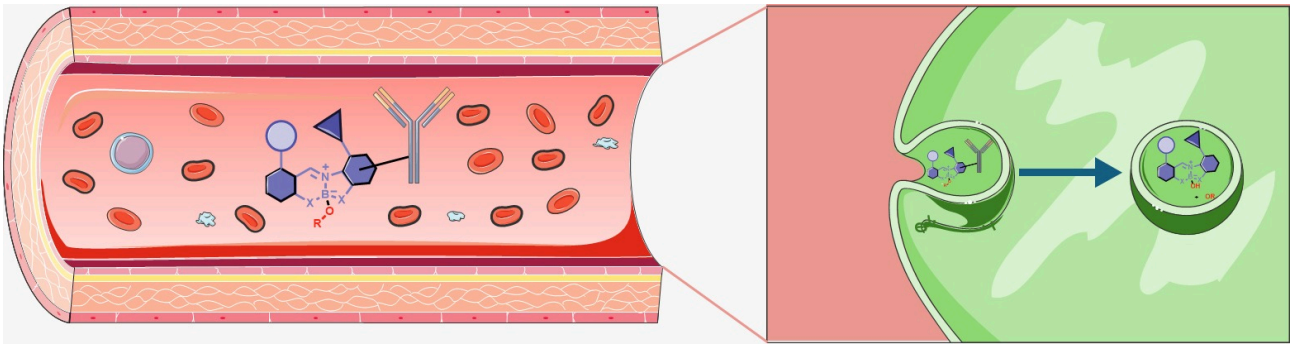


Figure 1. AZABY Platform: pH-Responsive, Self-Immolating Boron-ADC Release for Targeted Cancer Therapy

Acknowledgements: *Agradecemos à Fundação para a Ciência e Tecnologia pelo apoio financeiro. (2021.04125.CEECIND; 2023.14170.PEX https://doi.org/10.54499/2023.14170.PEX. ; PTDC/QUI-OUT/3989/2021 and UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025)).*

References

[1] Santos, F. M. F.; Matos, A. I.; Ventura, A. E.; Gonçalves, J.; Veiros, L. F.; Florindo, H. F.; Gois, P. M. P. Angew. Chem., Int. Ed. 2017, 56 (32), 9346–9350.
[2] António, J. P. M.; Russo, R.; Carvalho, C. P.; Cal, P. M. S. D.; Gois, P. M. P. Chem. Soc. Rev. 2019, 48 (13), 3513–3536.
[3] Marvin, C. C.; et al. . Bioconjugate Chem. 2023, 34 (10), 1835–1850.

Electrochemical lactonization of ketones through anodic oxidation of benzoate anions

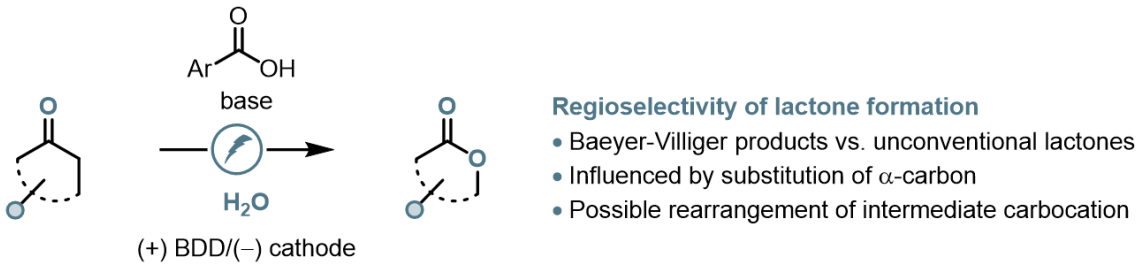
Duarte B. Clemente*, Jaime A.S. Coelho

Centro de Química Estrutural, Institute of Molecular Sciences, Department of Chemistry and Biochemistry, Faculty of Sciences, University of Lisbon, Lisbon, Portugal.

** E-mail: dbclemente@fc.ul.pt*

The Baeyer-Villiger oxidation is a key reaction in organic synthesis, involving the conversion of ketones into esters, typically using peracids as oxidants [1,2]. Despite its synthetic relevance, only a limited number of electrochemical approaches to the Baeyer-Villiger reaction have been described. In particular, simple, general, and stoichiometric-oxidant-free electrochemical protocols remain underdeveloped, despite their potential to provide more sustainable and efficient synthetic strategies [3–6].

A simple protocol for the electrochemical lactonization of cyclic ketones was developed. The method relies on the electrochemical oxidation of benzoates to generate perbenzoic acids *in situ* using a commercially available boron-doped diamond (BDD) anode, capable of generating hydroxyl radicals [7], followed by ketone lactonization. The regioselectivity for the formation of unconventional lactones versus ring-expanded Baeyer-Villiger products is directly influenced by substitution on the α-carbon, suggesting that the reaction proceeds through a carbocation intermediate capable of undergoing rearrangement (**Scheme 1**).



Scheme 1. Proposed strategy for the electrochemical lactonization reaction.

Acknowledgements: We acknowledge FCT for the Doctoral Research Studentship 2023.01672.BD. This work was supported by FCT (UID/00100/2025, UID/PRR/100/2025 and LA/P/0056/2020).

References

[1] Baeyer, A.; Villiger, V. *Ber. Dtsch. Chem. Ges*. **1899**, 32, 3625–3633.
[2] Siengalewicz, P.; Mulzer, J.; Rinner, U. Synthesis of Esters and Lactones. In *Comprehensive Organic Synthesis*, 2nd ed.; Knochel, P., Molander, G. A., Eds.; Elsevier: Oxford, UK, **2014**; Vol. 6, pp 355–410.
[3] Hu, Y. L.; Xie, Y. B.; Li, D. J. *Bull. Chem. Soc. Eth*. **2016**, 30, 297–306.
[4] Maalouf, J. H.; Jin, K.; Yang, D.; Limaye, A. M.; Manthiram, K. *ACS Catal*. **2020**, 10, 5750–5756.
[5] Mu, Y.; Chen, B.; Zhang, H.; Fei, M.; Liu, T.; Mehta, N.; Wang, D. Z.; Miller, A. J. M.; Diaconescu, P. L.; Wang, D. *J. Am. Chem. Soc*. **2024**, 146, 13438–13444.
[6] Cha, S.; Chen, Y.; Du, W.; Wu, J.; Wang, R.; Jiang, T.; Yang, X.; Lian, C.; Liu, H.; Gong, M. *JACS Au* **2024**, 4, 3629–3640.
[7] Lips, S.; Waldvogel, S. R. *ChemElectroChem* **2019**, 6, 1649–1660.

HQ-BASHYs as an innovative multimodal platform for advanced photodynamic therapy

João F. Felicidade[1*], Fábio M.F. Santos[1], Pedro M.P. Góis[1,] Uwe Pischel[2], Gilles Gasser[3]

[1] *Research Institute for medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Lisbon 1649-003, Portugal;*

[2] *CIQSO-Centre for Research in Sustainable Chemistry and Department of Chemistry, University of Huelva, Campus de El Carmen s/n, Huelva 21071, Spain.*

[3] *Chimie ParisTech, PSL University, CNRS, Institute of Chemistry for Life and Health Sciences, Laboratory for Inorganic Chemical Biology, Paris F-75005, France.*

** E-mail: felicidade@edu.ulisboa.pt*

Despite considerable progressions in cancer therapy, glioblastoma persists as a lethal disease, explained by its high rate of recurrence and resistance to conventional treatments [1]. Photodynamic therapy (PDT) has emerged as a promising complementary approach, enabling spatiotemporal control of treatment and circumventing classical resistance mechanisms [1]. Photodynamic therapy (PDT) is a therapeutic that uses light-activated photosensitizers (PSs) to generate reactive oxygen species, inducing cell death [2]. However, current PSs still limitations such as photobleaching, complex synthesis, and reliance on scarce metals [2]. Boronic-acid salicylidenehydrazones (BASHYs) have been identified as a modular and synthetically accessible fluorescent platform, that exhibits favorable photophysical properties and have proven bioimaging applications [3]. Recently, cyanine-like BASHYs (Cy-BASHYs) have demonstrated exceptional singlet oxygen generation and phototoxicity, surpassing clinically used PSs [3]. However, they suffered from photobleaching, low hydrophilicity, and suboptimal absorption wavelengths [3]. To surpass these limitations, we proposed the development of hydroxyquinone (HQ)-BASHYs, representing a new BASHY subclass designed with increased structural rigidity to enhance photostability and photophysical performance. The objective of this study is to establish HQ-BASHYs as a new generation of efficient and affordable organic photosensitizers for PDT in glioblastoma.

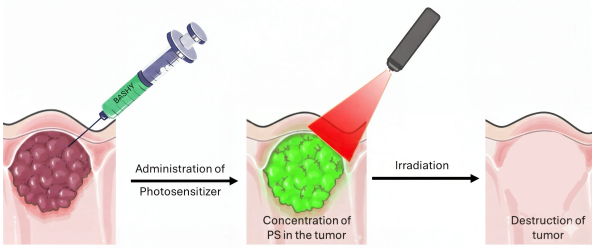


Figure 2. Representation of PDT clinical application

Acknowledgements: Agradecemos à Fundação para a Ciência e Tecnologia pelo apoio financeiro. (2024.05331.BD; 2021.04125.CEECIND; 2023.14170.PEX https://doi.org/10.54499/2023.14170.PEX. ; PTDC/QUI-OUT/3989/2021 and *UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025)*).

References

[1] Van Solinge, T. S., Nieland, L., Chiocca, E. A. *Nature Reviews Neurology* 2022, **18**, 221–236;
[2] Cramer, S. W., Chen, C. C. *Frontiers in Surgery* 2020,**6**, 81;
[3] Silva, M. J. S. A., Yiyi, Z. *Bioconjugate Chemistry* 2023, **34**, 2337–2344;

BLOCKBI Platform: multifunctional and fluorescent constructs for bioimaging and therapeutics

João E. Leite[1,*], Fábio M.F. Santos [1], Pedro M.P. Góis [1]

[1] *Research Institute for Medicines (iMed.ULisboa) Faculdade de Farmácia, Universidade de Lisboa, Portugal*

** E-mail: leite.joao@edu.ulisboa.pt*

Multicomponent reactions (MCRs) provide substantial structural diversity, making them a powerful strategy for the discovery of new fluorescent platforms. A notable example is the family of boronic acid–derived salicylidenehydrazone (BASHY) dyes, recently developed by Gois and co-workers [1]. In BASHY dyes, the boronic acid moiety plays a central role by enabling structural diversity, stimuli responsiveness, and rich coordination chemistry, which collectively serve to lock the molecular framework.

Inspired by the pivotal role of boronic acid in BASHY dyes, this project aims to exploit this functional group as a stimuli-responsive building block and conformational lock in the modular synthesis of benzylidene imidazolones—the fluorescent core of green fluorescent protein (GFP) [2]. This boron-based "B-lock" is expected to enhance the photophysical properties of the resulting dyes by restricting rotation around the aryl–alkene bond. Further structural diversification will focus on tuning the push–pull electronic system to achieve red-shifted emission of the B-lock GFP core, as well as introducing bioconjugation handles for the development of therapeutic bioconjugates.

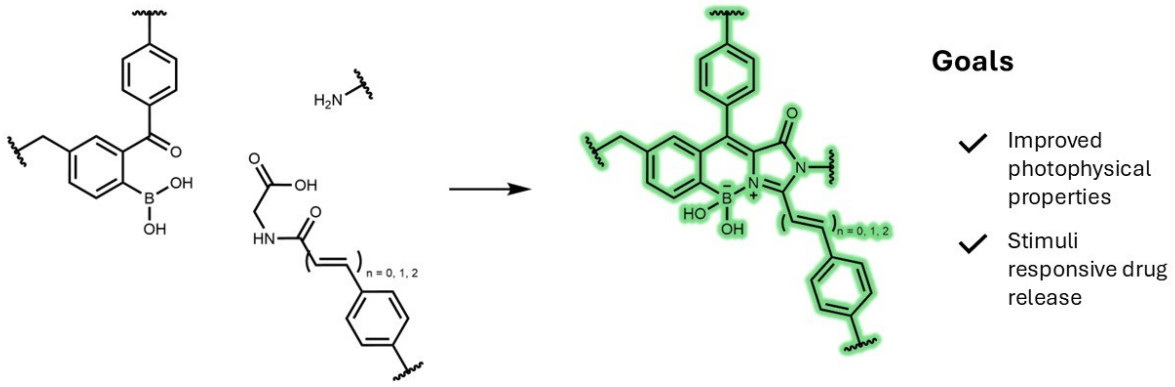


Figure 3: Engineering the BLOCK-BI platform

Acknowledgements: Agradecemos à Fundação para a Ciência e Tecnologia pelo apoio financeiro. (2021.04125.CEECIND; 2023.14170.PEX https://doi.org/10.54499/2023.14170.PEX. ; PTDC/QUI-OUT/3989/2021 and *UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025)*).

References

[1] Santos, F. M. F., Rosa, J. N., Candeias, N. R., Carvalho, C. P., Matos, A. I., Ventura, A. E., Florindo, H. F., Silva, L. C., Pischel, U., & Gois, P. M. P. (2016). Chemistry – A European Journal, 22(5), 1631–1637.

[2] Ferreira, J. R. M., Esteves, C. I. C., Marques, M. M. B., & Guieu, S. (2023) Molecules, 28(1), 234.

Development and evaluation of new depigmenting agents using a Safe and Sustainable by Design approach

Sandra Mota[1,2], Abigail Rodrigues[3], Smeera Ratanji[2,4], Sónia A. Pinho[5,6], Clara Quintas[2,4], Maria T. Cruz[5,6], Isabel F. Almeida[1,2], Emília Sousa[3,7*]

[1]UCIBIO—Applied Molecular Biosciences Unit, Laboratory of Pharmaceutical Technology, Faculty of Pharmacy, University of Porto, Portugal, 4050-313; [2]Associate Laboratory i4HB, Faculty of Pharmacy, University of Porto, Portugal, 4050-313; [3]Laboratório de Química Orgânica e Farmacêutica, Faculdade de Farmácia, Universidade do Porto, Portugal, 4050-313; [4]UCIBIO–Applied Molecular Biosciences Unit, Laboratory of Pharmacology, Department of Drug Sciences, Faculty of Pharmacy, University of Porto, Rua Jorge Viterbo Ferreira 228, 4050-313 Porto, Portugal; [5]Faculty of Pharmacy, University of Coimbra, Portugal, 3000-548; [6]Centre for Innovative Biomedicine and Biotechnology and Center for Neuroscience and Cell Biology, Coimbra, Portugal, 3000-548; [7]CIIMAR–Centro Interdisciplinar de Investigação Marinha e Ambiental, Portugal, 4450-208;
**E-mail: esousa@ff.up.pt*

Cosmetic ingredients are increasingly recognized as emerging environmental contaminants, with resorcinol-based depigmenting agents raising particular concern due to their ecotoxicological profiles [1]. The Safe and Sustainable by Design (SSbD) framework offers an integrated strategy to develop functional cosmetic ingredients with improved safety and environmental performance [2].

In this study, SSbD principles guided the design of new resorcinol-based depigmenting agents. An initial library of derivatives was screened *in silico* for tyrosinase inhibition, biodegradability, aquatic toxicity, and topical ADMET properties. Five promising compounds – three esters and two amines – were synthesized via green methodologies, namely Fischer esterification and reductive amination and characterized using spectroscopic techniques. These compounds were assessed for chemical stability (photo-, thermo-, and pH stability) and *in vitro* tyrosinase inhibition. The most promising candidates were further tested for cytotoxicity in relevant skin cell models, such as melanocytes (B-16V), keratinocytes (HaCaT), and fibroblasts (NHDF). Biodegradation studies in seawater are currently ongoing to further assess their environmental fate. The results showed that ester compounds combine favourable photo- and thermostability, as well as stability at different pH conditions. These esters also presented relevant tyrosinase inhibition in mushroom tyrosinase with an IC_{50} ranging from 370 nM to 23 µM and did not affect cell viability up to 100 µM (B-16V) and up to 200 µM (HaCaT and NHDF). Overall, this work showed the practical application of the SSbD framework in the experimental development of new cosmetic depigmenting agents, highlighting its potential to guide the cosmetics industry toward safer, effective, and more environmentally sustainable ingredients.

Funding: FCT - Fundação para a Ciência e a Tecnologia, I.P., 10.54499/LA/P/0140/2020, 10.54499/UIDB/04378/2020, 10.54499/UIDP/04378/2020, UIDB/04539/2020, UIDP/04539/2020, LA/P/0058/2020, https://doi.org/10.54499/UIDB/04423/2020, https://doi.org/10.54499/UIDP/04423/2020, https://doi.org/10.54499/LA/P/0101/2020 and https://doi.org/10.54499/2022.12487.BD.

References

[1] Mota S.; Rego L.; Sousa E.; Cruz M.T.; Almeida I.M. Pharmaceuticals. 2025, 18(3):368.

Structure-neurotoxicity relationships of pyridine-based melanostatin derivatives for application in Parkinson's disease

Beatriz L. Pires-Lima,[1,2,*] Xavier C. Correia,[1] Hugo F. Costa-Almeida,[1] Nuno Vale,[2,3,4] Xerardo García-Mera,[5] José E. Rodríguez-Borges,[1] Ivo E. Sampaio-Dias[1]

[1]LAQV/REQUIMTE, Department of Chemistry and Biochemistry, Faculty of Sciences, University of Porto, Porto, Portugal; [2]PerMed Research Group, RISE-Health, Faculty of Medicine, University of Porto, Portugal; [3]Laboratory of Personalized Medicine, Department of Community Medicine, Health Information and Decision (MEDCIDS), Faculty of Medicine, University of Porto, Portugal; [4]RISE-Health, Department of Community Medicine, Health Information and Decision (MEDCIDS), Faculty of Medicine, University of Porto, Portugal; [5]Department of Organic Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, Santiago de Compostela, Spain.

** E-mail: beatriz.lp.lima@outlook.com*

In Parkinson's disease (PD), degeneration of dopaminergic neurons in the substantia nigra leads to dopamine deficiency and the characteristic motor symptoms associated with this disorder.[1,2] Although levodopa remains the first-line treatment, its long-term use results in dyskinesias and fluctuating symptom control, underscoring the need for alternative pharmacological strategies.[2,3] Melanostatin (MIF-1), an endogenous neuropeptide, modulates dopaminergic neurotransmission through positive allosteric modulation of D_2 receptors.[2,3] However, its peptide nature limits its clinical use, prompting the design of new analogs with improved pharmacokinetic properties.[2,3] In this work, pyridine-based scaffolds were used to synthesize twelve novel analogs. Neurotoxicity assays performed in differentiated SH-SY5Y cells showed that methyl ester derivatives exhibited marked cytotoxicity at 100 µM, whereas the amide counterparts showed safer profiles. This structure-cytotoxicity relationship supports further optimization of pyridine-based MIF-1 derivatives and highlights their potential as safer and more effective therapeutic candidates for PD.

Funding: This work received financial support from PT national funds (FCT/MECI, Fundação para a Ciência e a Tecnologia and Ministério da Educação, Ciência e Inovação) through project 2023.14440.PEX (DOI: 10.54499/2023.14440.PEX).

Acknowledgements: FCT is also acknowledged for supporting the project UID/50006/2025 DOI 10.54499/UID/50006/2025 - Laboratório Associado para a Química Verde - Tecnologias e Processos Limpos. I.E.S.-D. thanks FCT for funding through the Individual Call to Scientific Employment Stimulus with reference 2020.02311.CEECIND/CP1596/CT0004 (DOI: 10.54499/2020.02311.CEECIND/CP1596/CT0004). B.L.P.-L., X.C.C., and H.F.C.-A. thank FCT for the Ph.D. grants 2022.14060.BD (DOI: 10.54499/2022.14060.BD), 2024.02245.BD, and UI/BD/154888/2023 (DOI: 10.54499/UI/BD/154888/2023), respectively. N.V. thank FCT for funding through projects IF/00092/2014/CP1255/CT0004, PRR-09/C06-834I07/2024.P11721, 2024.18026.PEX, and the Chair in Onco-Innovation at the FMUP. X.G.-M. thanks Xunta de Galicia for financial funding with reference GPC2020/GI1597. X.G.-M. thanks Consellería de Cultura, Educación e Ordenación Universitaria of the Galician Government (grant: ED431B 2023/25) and Ministerio de Ciencia e Innovación – Agencia Estatal de Investigación (PID2021-124010OB-100) for the financial support.

References

[1] Balestrino R. and Schapira A.H.V., Eur. J. Neurol., 27 (2020), 27.
[2] Dorszewska J., et al., Curr. Genom., 15 (2014), 11.
[3] Sampaio-Dias, I. E., et al., J. Med. Chem., 64 (2021), 6209.

Pharmaceutical ionic systems for drug delivery applications

F. Faisca[1], M. José[1], L. Filipe[1], D. Madeira[1], S. Gago[1], A. A. Ricardo[1], Luís C. Branco[1]

[1] *LAQVREQUIMTE, Department of Chemistry, NOVA School of Science and Technology, NOVA University of Lisbon, 2819-516 Caparica, Portugal*

E-mail: l.branco@fct.unl.pt

Over recent decades, ionic liquids (ILs) have attracted considerable attention across a wide range of chemical and biological research fields, including pharmaceutical sciences, owing to their highly tunable physicochemical properties. Within the pharmaceutical domain, ILs have emerged as environmentally friendly solvents for the preparation, purification, and crystallization of active pharmaceutical ingredients (APIs) [1]. In addition, the combination of ionizable APIs with biocompatible organic counter-ions has proven to be an effective strategy for enhancing the bioavailability of drugs with limited aqueous and/or lipid solubility. This approach also contributes to the reduction or elimination of polymorphism, thereby fa- cilitating the development of more robust and effective pharmaceutical formulations [1].

Our research group has recently reported a series of pharmaceutical ionic systems, in- cluding ionic liquids and organic salts derived from anti-inflammatory, antibiotic, antitumoral, antiviral, and antidiabetic agents, which exhibited significant performance enhancements compared to their parent APIs [2–5]. Building on these findings, the present work describes recent advances in the synthesis and characterization of pharmaceutical ionic systems based on streptomycin [6] and metformin as representative examples of established drugs repurposed to address emerging challenges. These ionic salts were incorporated into lipid nanoparticles and dry powder formulations, with the aim of improving therapeutic efficacy and optimizing drug delivery systems.

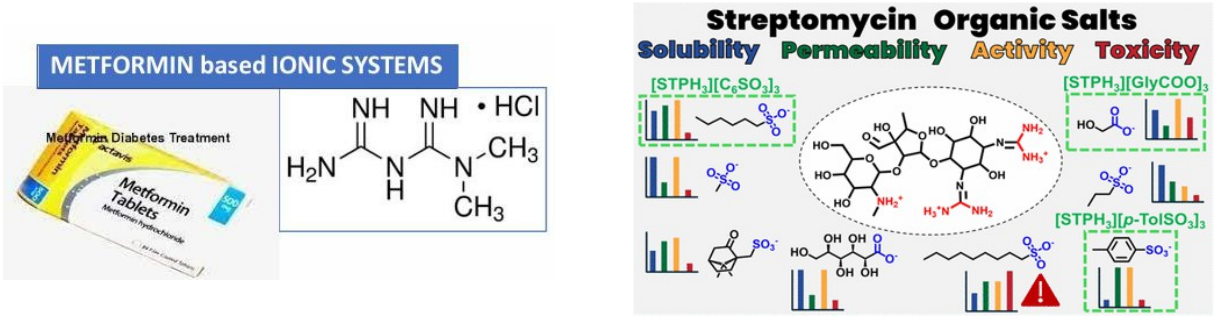


Figure 1. Metformin and Streptomycin Ionic Systems

Acknowledgements: This work was supported by the InsectERA – Novo sector bioindustrial Project (nº C644917393-00000032), co-financed by PRR - Recovery and Resilience Plan of the European Union (Next Generation EU). The authors also thank the support from FCT/MCTES (UIDB/50006/2020, LA/P/0008/2020 and UIDP/50006/2020 of the Associate Laboratory for Green Chemistry – LAQV).

References

[1] J. L. Shamshina, R. D. Rogers, Chem. Rev. 2023, 123, 11894.
[2] M. M. Santos, L. R. Raposo, G. V. S. M. Carrera, A. Costa, M. Dionísio, P. V. Baptista, A. R. Fernandes, L. C. Branco, ChemMedChem 2019, 14, 907.
[3] S. Teixeira, M. M. Santos, L. C. Branco, J. Costa-Rodrigues, Int. J. Pharm. 2021, 610, 121262.
[4] I. C. B. Martins, A. Forte, H. P. Diogo, L. R. Raposo, P. V. Baptista, A. R. Fernandes, L. C. Branco, M. T. Duarte, Chemistry Methods 2022, 2, e202100104.
[5] D. Silva, S. Cordeiro, P. V. Baptista, A. R. Fernandes, L. C. Branco, RSC Med. Chem., 2025, 16, 3593.
[6] F. Faísca, A. F. M. Santos, M. Ferreira, P. Gameiro, S. A. C. Lima, L. C. Branco, Mol. Pharmaceutics 2025, 22, 5361.

Study of the chemical profile of the alga *Rugulopteryx okamurae*

Ana M. Faisca Phillips[1,*], Patrícia Máximo[1], Paula S. Branco[1], Luísa M. Ferreira[1], Ana Lourenço[1], Pedro Lima[2], Diego O. Hartmann[2], Patrícia Sequeira[2]

[1]*LAQV-REQUIMTE, Department of Chemistry, NOVA School of Science and Technology, Universidade Nova de Lisboa, Caparica 2829-516, Portugal*
[2] *Sea4Us - Biotecnologia e Recursos Marinhos, S.A, Sagres, Portugal*
** E-mail: ana.faisca@fct.unl.pt*

The macroalga *Rugulopteryx okamurae,* native to Japan and Korea, appeared recently in the south coast of Europe, including in Portugal and the Azores islands, where it is becoming a truly invasive species [1]. It propagates rapidly forming dense layers of biomass, thus posing a threat to marine diversity, with a serious impact on the local ecosystems. The residues also accumulate on the local shores, threatening tourism and public health, thus creating the need for continuous removal at large costs.

Aiming to transform this problem into an opportunity by finding new marketable products, a few research projects have been started. We are studying the alga chemical profile to identify bioactive secondary metabolites or potential nutraceuticals. The presence of such substances is obvious, since the alga requires chemical defenses to be able to propagate and compete favorably with the local species. We have so far determined the presence of several terpenes, steroids, retinols, carbohydrates, besides fatty acids and some hydrocarbons. Amongst the terpenes, diterpenoids and sesquiterpenoids were the most common, e.g. spatanes, secospatanes, cubebanes. Their biological activity is being determined, and some neurological effects have been detected. Some of the results obtained are presented here.

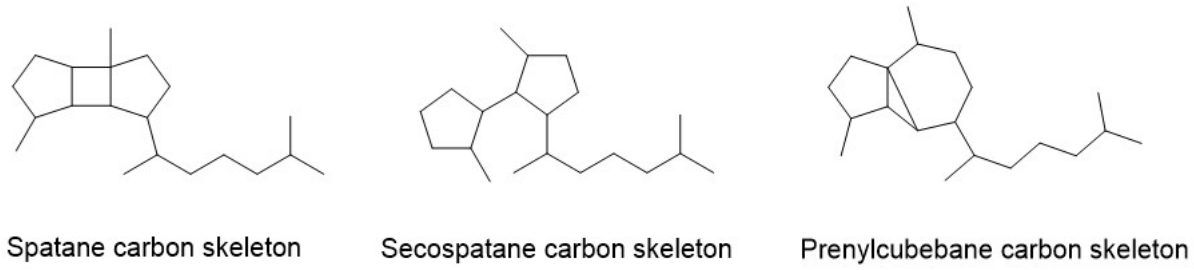


Figure 1. Some terpenoids found in *Rugulopteryx okamurae*.

Funding: This work was supported by "Pacto de Bioeconomia Azul" (Project No. C644915664-00000026) within the WP5 Algae Vertical, funded by Next Generation EU European Fund and the Portuguese Recovery and Resilience Plan (PRR) This work was also supported by national funds from FCT - Fundação para a Ciência e a Tecnologia, I.P., under the scope of the project UID/50006/2023 of the Associate Laboratory for Green Chemistry - LAQV REQUIMTE.

Reference

[1] Barcellos, L.; Pham, C.K.; Menezes, G.; Bettencourt, R.; Rocha, N.; Carvalho, M.; Felgueiras, H.P.: Mar. Drugs 2023, 21, 40.

Rational identification of novel ubiquitin specific protease 7 (USP7) inhibitors through chemoinformatics and high-throughput screening

Rita I. Oliveira[1,2,3*], Caio Franco[3], Miguel Mano[2,3], Ana Leal[4], Karen Liby[4], Jorge A. R. Salvador[1,2,3]

[1] *Laboratory of Pharmaceutical Chemistry, Faculty of Pharmacy - University of Coimbra*
[2] *Centre for Innovative Biomedicine and Biotechnology - University of Coimbra, Coimbra, Portugal*
[3] *Center for Neuroscience and Cell Biology - University of Coimbra, Coimbra, Portugal*
[4] *Indiana University School of Medicine, Indianapolis, IN, USA*
** E-mail: rita.oliveira@cnc.uc.pt*

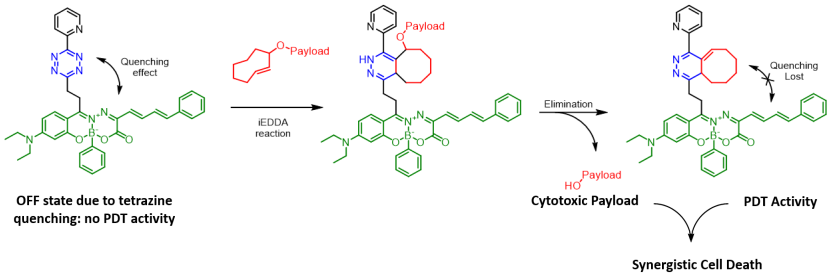
Ubiquitin-Specific Protease 7 (USP7) is a member of one of the most largely studied families of deubiquitylating enzymes, proteases that play a key role in controlling the dynamics of ubiquitination within the cellular ubiquitome. USP7 plays a pivotal role in modulating the levels of multiple proteins, including tumor suppressors, transcription factors, epigenetic modulators, DNA repair proteins, and regulators of the immune response. This suggests USP7 as a promising druggable target that offers interesting new avenues for cancer therapy. Wherefore, the main goal of this study was the identification of promising small molecules that inhibit USP7 enzymatic activity. The work was conducted according to an integrated workflow combining Computer-Aided Drug Discovery (CADD) and High-Throughput Screening (HTS) of chemical libraries to discover and characterize selective USP7 inhibitors with new chemotypes and adequate pharmacological properties as potential drug candidates to be used for anticancer therapy. Such protocol screened a large set of databases, disclosing 9 novel USP7 hit compounds with in vitro USP7 inhibitory activities against both USP7 full-length and USP7 catalytic domain, displaying IC50 values between 4.5 μM to 33 μM. The dose-response curves of these compounds tested against cancer cell lines showed promising selective cytotoxicity in breast and lung cancer cells, with IC50 values ranging from low nanomolar to micromolar. These results highlight the utility of using CADD and HTS in the early steps of drug discovery and pave the way for the identification of novel USP7 inhibitors that might represent a steppingstone for cancer treatment.

A novel click-to-kill dual strategy based on oxygen and light: modified BASHY dyes as smart photosensitizers

Ana M. Marques[1,*], João Felicidade[1], Pedro M. P. Góis [1], João P. M. António [1]

[1]*Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Portugal. Av. Prof. Gama Pinto, 1649-003, Lisboa.*
**E-mail: a.maria@edu.ulisboa.pt*

Photodynamic therapy (PDT) is an emerging non-invasive light-activated therapy in which photosensitizers (PS) generate reactive oxygen species (ROS) in the presence of endogenous oxygen, resulting in tumor cell-death. Despite its advantages, PDT is limited by photosensitivity-related off-target effects and poor performance under hypoxic tumor microenvironments. To address these limitations, we recently developed new modified boronic-acid derived salicylidenehydrazone (BASHY) dyes, which can act as photosensitizers [1], displaying an OFF-ON mechanism in PDT. These BASHYs contain a tetrazine group, which promotes their intramolecular quenching, effectively blocking photodynamic activity. Upon their inverse Electron-Demand Diels-Alder (iEDDA) reaction with *trans*-cyclooctene (TCO), the quenching effect disappears, successfully reactivating the PS. To enable synergistic cell-damage under hypoxic conditions, a cytotoxic payload (SN-38) is incorporated into the TCO for controlled release upon the iEDDA reaction [2]. This method opens new avenues for safer and more effective treatment strategies for highly aggressive tumors, including glioblastoma, overcoming the classical limitations of traditional PDT.



Scheme 1. Mechanism of novel modified BASHYs in PDT employing an OFF-ON strategy.

Funding: We thank Fundação para a Ciência e a Tecnologia (2022.06817.CEECIND; 2024.16254.PEX and UID/04138/2025 (https://doi.org/10.54499/UID/04138/2025)) for financial support.

References

[1] M. J. S. A. Silva, Y. Zhang, R. Vinck, F. M. F. Santos, J. P. M. António, L. Gourdon-Grünewaldt, C. Zaouter, A. Castonguay, S. A. Patten, K. Cariou, F. Boscá, F. Nájera, J. F. Arteaga, G. Gasser, U. Pischel, P. M. P. Gois, *Bioconjugate Chemistry* **2023**, 34, 2337–2344.
[2] D. Kang, S. Lee, J. Kim, *Chem* **2022**, 8, 2260–2277.

Insights into the electrochemical reactions of aryl ketones

Carolina M. Catarino[1,*], C. M. Monteiro[2], J. A. S. Coelho[1]
[1]*Centro de Química Estrutural-Institute of Molecular Sciences, Department of Chemistry and Biochemistry, Faculty of Sciences, University of Lisbon, Lisbon, Portugal.*
[2]*ASCENZA Agro, S.A., Screening & Synthesis Laboratory, Setúbal, Portugal.*
**E-mail: cmcatarino@fc.ul.pt*

In conventional organic synthesis, the preparation of benzaldehyde derivatives from toluene-based substrates typically involves multistep sequences, such as oxidation of benzylic methyl groups to carboxylic acids using strong oxidants (e.g., $KMnO_4$), followed by reduction to benzyl alcohols with stoichiometric hydride reagents (e.g., $LiAlH_4$) and subsequent reoxidation (e.g., PCC) to the benzaldehyde.[1] Although effective, these routes rely on hazardous reagents, generate significant waste, and require multiple synthetic steps.

In this context, organic electrosynthesis emerges as a potentially more viable alternative, enabling direct oxidation of benzylic methyl groups in a single step by using electricity as the sole redox agent, without the need for external oxidants, enabling efficient redox transformations under mild and sustainable conditions.[2]

The objective of this work is to develop an electrochemical methodology to achieve this transformation, enabling the oxidation of benzylic methyl groups (**Figure 1. A**).

In collaboration with ASCENZA Agro, this approach was specifically applied to metrafenone (**Figure 1. B**), a fungicidal active ingredient, as a representative and industrially relevant substrate.

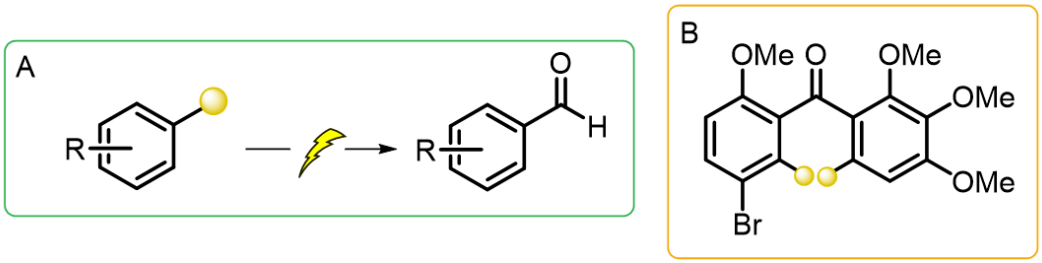


Figure 1. General scheme for benzylic oxidation of methyl (A) groups. Structure of metrafenone with positions susceptible to oxidation (B).

Acknowledgements: Centro de Química Estrutural, a Research Unit funded by Fundação para a Ciência e a Tecnologia through projects UID/00100/2025, UID/PRR/100/2025 and LA/P/0056/2020, for financial support.

References

[1] Popovsky et al. *Russ. Chem. Bull.* **2012**, 61, 1616.
[2] M. C. Leech, K. Lam, *Nat. Rev. Chem.* **2022**, 6, 275.

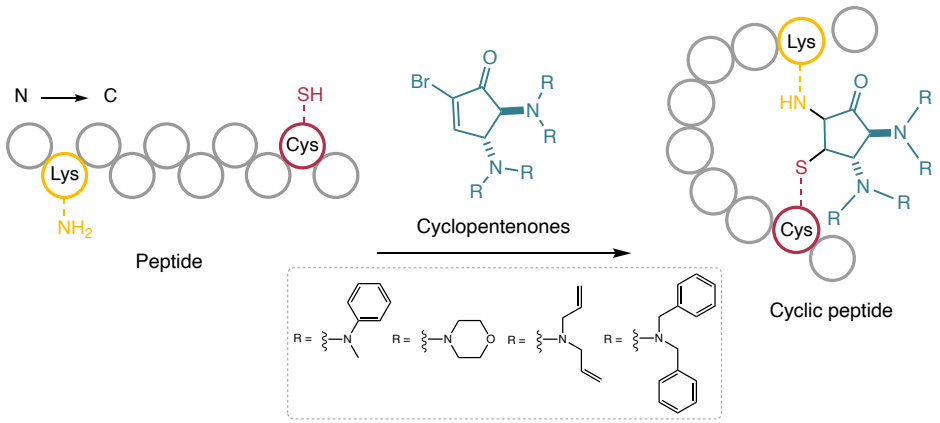
A novel macrocyclization strategy for antimicrobial peptides using cyclopentenones

Inês M. F. Santos[1*], Tiago M. P. Santos[1], Bruna F. L. Guerreiro[1], Ana M. Madureira[1], Carlos A. M. Afonso[1], Pedro M. P. Góis[1], Rafael F. A. Gomes[1]

[1]*Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, University of Lisbon, Av. Prof. Gama Pinto, 1649- 003 Lisbon, Portugal*

** E-mail: inesfalcatosantos@gmail.com*

The cyclopentenone scaffold has been widely studied in medicinal chemistry due to its antibacterial, antifungal, and antitumor properties [1,2]. Cyclopentenones also exhibit selective reactivity toward cysteine residues in peptides, even in the presence of other nucleophilic amino acids [3]. Peptide cyclization is a powerful strategy for expanding peptide chemical space, as cyclic peptides often reveal enhanced conformational rigidity, metabolic stability, bioavailability, and cellular permeability compared to their linear counterparts [4]. In this study, bromo-diamino-cyclopentenones were explored as novel agents for the macrocyclization of antibacterial peptides, aiming to stabilize peptide three-dimensional structure and potentially enhance antibacterial activity through a synergistic contribution of the cyclopentenone scaffold. Four bromo-diamino-cyclopentenone derivatives and a series of peptide sequences were synthesized to probe the influence of reactive residue spacing on cyclization efficiency. The resulting cyclic peptides were evaluated against gram-positive and gram-negative bacterial strains, showing measurable antibacterial activity, particularly against gram-positive bacteria, and highlighting cyclopentenone-mediated macrocyclization as a promising strategy for novel antimicrobial agent development (**Scheme 1**).



Scheme 1. Cyclopentenone-mediated macrocyclization of antimicrobial peptides.

Funding and Acknowledgements: We thank the Fundação para a Ciência e Tecnolgia for financial support (UID 04138 - Instituto de Investigação do Medicamento; 2023.11341.PEX – Photochemical Reduction of Proteins).

References

[1] Gomes, R. F. A., Isca, V. M. S., Andrade, K., Rijo, P. & Afonso, C. A. M. *ChemMedChem*,2021, **16**, 2781–2785.
[2] T. Matsumoto, T. Hosoya, H. Tomoda, M. Shiro, H. Shigemori, *Chem.Pharm. Bull*. 2011, 59, 1559–61.
[3] Gomes, R. F. A.; Ravasco, J. M. J. M.; Andrade, K. H. S.; Coelho, J. A. S.; Moreira, R.; Nogueira, F.; Afonso, C. A. M.; *ChemSusChem*, 2022, 15, e202102204.
[4] Whitty, A.; Zhong, M.; Viarengo, L.; Beglov, D.; Hall, D.R.; Vajda, S.; *Drug Discov Today*, 2016, 21, 712–717.

Porphyrin-carbon dots conjugates: enhancing the photodynamic performance of tetrapyrrolic photosensitizers

Carla I. M. Santos[1,2*], Daniel S. Cavaco[1], José M. G. Martinho[1], M. Amparo Faustino[2], M. Graça P. M. S. Neves[2], Ermelinda M. S. Maçôas[1]

[1]*Centro de Química Estrutural, Institute of Molecular Science and Departamento de Engenharia Química, Instituto Superior Técnico, Universidade de Lisboa, 1049–001 Lisboa, Portugal*
[2] *LAQV-REQUIMTE, Department of Chemistry of University of Aveiro, 3810-193 Aveiro, Portugal*
** E-mail: carla.santos@tecnico.ulisboa.pt*

Photodynamic therapy (PDT) is a minimally invasive treatment that has gained attention due to its reduced systemic toxicity compared with conventional cancer therapies. PDT relies on the light-induced activation of photosensitizers which, in the presence of molecular oxygen, generate reactive oxygen species capable of inducing oxidative damage in malignant cells. Its clinical efficiency strongly depends on the physicochemical properties of the photosensitizers, including low dark toxicity, photostability, and adequate dispersibility in aqueous media.

Porphyrins are among the most widely studied photosensitizers owing to their strong absorption in the visible region, high singlet oxygen generation, and structural versatility. However, their limited water solubility and tendency to aggregate under physiological conditions often impair both photophysical and biological performance [1].

Carbon dots (CDs) have emerged as attractive nanomaterials to address these limitations. CDs display excellent water dispersibility, high chemical and photostability, low intrinsic toxicity, and favourable optical properties. Moreover, the abundance of surface functional groups on carbon dots enables efficient conjugation with porphyrins, allowing the formation of hybrid systems with improved colloidal stability and controlled photophysical properties. [2].

In this work, porphyrins were conjugated with carbon dots to obtain hybrid nanomaterials designed to improve the photodynamic performance of porphyrin-based photosensitizers. The resulting conjugates were structurally and optically characterized, and preliminary biological studies, including cellular uptake and intracellular localization assessed.

Acknowledgements: Authors are grateful to University of Aveiro, Instituto Superior Técnico (IST, Portugal) and FCT/MCTES (Fundação para a Ciência e a Tecnologia and Ministério da Ciência, Tecnologia e Ensino Superior) for the support to LAQV-REQUIMTE, CQE- IST and the projects: 2022.05950.PTDC (DOI: 10.54499/2022.05950.PTDC), 2022.03596.PTDC (DOI: 10.54499/2022.03596.PTDC) through national funds, where applicable, co-financed by European Union, FEDER, QREN, and COMPETE within the PT2020 Partnership Agreement, and to the Portuguese NMR Network. C. I. M. Santos is also grateful to her research contract (2023.08400.CEECIND; https://doi.org/10.54499/2023.08400.CEECIND/CP2830/CT0013).

References

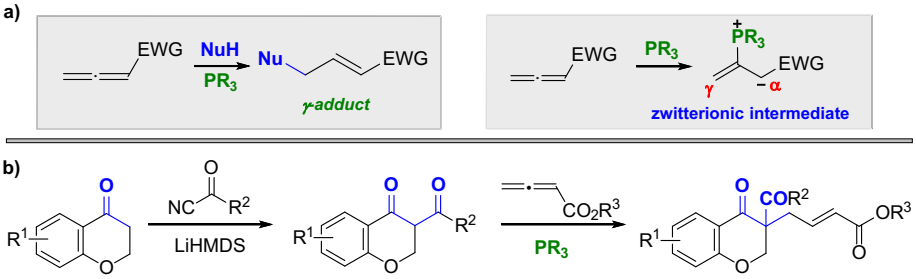
[1] Santos, C. I. M.; Rodrigues-Perez, L.; ACS Appl. Nano Mater. 2021, 4, 13079–13089.
[2] Santos, C. I. M.; Almeida, A. C; Nanoscale, 2025,17, 12554-12579.

Synthesis of chromanones with a quaternary carbon center via phosphine-catalyzed inverse conjugate addition

Tiago P. dos Santos*, Maria I. L. Soares, Teresa M. V. D. Pinho e Melo
University of Coimbra, Coimbra Chemistry Centre - Institute of Molecular Sciences (CQC-IMS), Department of Chemistry, 3004-535 Coimbra, Portugal
** E-mail: tiagopdsantos77@gmail.com*

Allenes are versatile building blocks due to their two cumulated orthogonal π-bonds. Among the rich chemistry of allenes, electron-deficient allenes have emerged as attractive electrophiles in organic synthesis [1]. In reactions with nucleophiles, addition usually occurs at the electrophilic α,β-double bond to form Michael-type β-adducts. However, the presence of a phosphine catalyst enables nucleophiles to add to the β,γ-double bond of allenes via the formation of a zwitterionic intermediate, yielding γ-adducts (**Scheme 1a**).

Our research group has been interested in the Lewis base-catalyzed reactions of allenic esters and chromene-based substrates for the construction of chromane scaffolds [2]. Building on our previous work on the stereoselective nucleophilic addition of carbonucleophiles to electron-deficient allenes [3], we now aim to explore the reactivity of allenic esters with chromane-based substrates acting as carbon pronucleophiles. In this communication, we report our recent studies on the phosphine-catalyzed inverse conjugate addition of 3-acyl-4-chromanones to allenic esters, enabling the synthesis of chromanones bearing a quaternary carbon center (**Scheme 1b**).



Scheme 1. Phosphine-catalyzed inverse conjugate addition of nucleophiles to allenes.

Funding: CQC-IMS is supported by the Fundação para a Ciência e a Tecnologia (FCT), Portuguese Agency for Scientific Research. CQC is funded by FCT through projects UID/PRR/00313/2025 (DOI: 10.54499/UID/PRR/00313/2025) and UID/00313/2025 (DOI: 10.54499/UID/00313/2025) and IMS through special complementary funds provided by FCT (project LA/P/0056/2020 DOI: 10.54499/LA/P/0056/2020).
Acknowledgements: The authors acknowledge the UC-NMR facility for obtaining the NMR data (www.nmrccc.uc.pt).

References

[1] a) Ma, S. *Aldrichim. Acta* **2007**, *40*, 91; b) Pinho e Melo, T. M. V. D. *Monatsh. Chem*. **2011**, *142*, 681.
[2] a) Soares, M. I. L.; Gomes, C. S. B.; Nunes, S. C. C.; Pais, A. A. C. C.; Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem*. **2019**, 5441. b) Soares, M. I. L.; Gomes, C. S. B.; Oliveira, M. C.; Marçalo, J.; Pinho e Melo, T. M. V. D. *Org. Biom. Chem*. **2021**, *19*, 9711.
[3] Cardoso, A. L.; Beja, A. M.; Silva, M. R.; de los Santos, J. M.; Palacios, F.; Abreu, P. E.; Pais, A. A. C. C.; Pinho e Melo, T. M. V. D. *Tetrahedron* **2010**, *66*, 7720.

Facile epimerization of (+)-sclareolide: a versatile experiment for laboratory education

Florence O'McCarthy[1], Jukka Saarinen[2], Amit Upadhyay[1,3] Chiara Zanetti[3], Emily A. Collins[1,3] Michelle O'Driscoll[1,3] Orla M. Lynch[1,3] Michael f. Cronin[3], Tobias Rüffer[4], Olha Antoniuk[5,6,7] Jari Yli-Kauhaluoma[2], Vânia M. Moreira[2,5,6,7, *]

[1]School of Chemistry and Analytical Biological Chemistry Research Facility (ABCRF), University College Cork, Western Road, Cork, Ireland T12K8AF; [2]Drug Research Program, Division of Pharmaceutical Chemistry and Technology, Faculty of Pharmacy, University of Helsinki, Viikinkaari 5 E, P.O. Box 56, 00014 Helsinki; [3]School of Pharmacy, University College Cork, Ireland, T12K8AF; [4]Inorganic Chemistry, Faculty of Natural Sciences, Institute of Chemistry, Technische Universität Chemnitz, 09107 Chemnitz, Germany; [5]Faculty of Pharmacy, University of Coimbra, Pólo das Ciências da Saúde, Azinhaga de Santa Comba, 3000-548 Coimbra, Portugal; [6]Centre for Neuroscience and Cell Biology (CNC-UC), University of Coimbra, 3004-504 Coimbra, Portugal; [7]Centre for Innovative Biomedicine and Biotechnology (CIBB), 3004-504 Coimbra, University of Coimbra, Portugal
** E-mail: vmoreira@ff.uc.pt*

An experiment to teach the concept of epimerization has been designed and developed starting from the naturally occurring sesquiterpene lactone (+)-sclareolide and made available to the general community [1]. The parent compound suffered epimerization at position 8, under catalytic conditions, upon treatment with bismuth(III) triflate, in refluxing acetonitrile (Figure 1). The facile experimental setup allowed the implementation of the experiment at two different locations, namely, the School of Pharmacy at the University College Cork (UCC), in Ireland and the Faculty of Pharmacy at the University of Helsinki (UHEL), in Finland. At both locations, students with only basic knowledge of stereochemistry and analytical techniques were able to prepare and isolate the epimer of (+)-sclareolide. Problem set questions helped the students to learn important concepts beyond epimerization, including carbocation-mediated reaction mechanisms and catalysis, as well as to apply the most current analytical techniques for structural elucidation, i.e., Nuclear Magnetic Resonance, High-Resolution Mass Spectrometry and X-Ray Crystallography. Overall, the students assessed the work positively and felt more confident to explore the concept of epimerization which can be challenging to grasp thorough theory alone. This presentation will provide an overview of the experiment which we hope will inspire the teaching of this topic by the broader community of educators in the field.

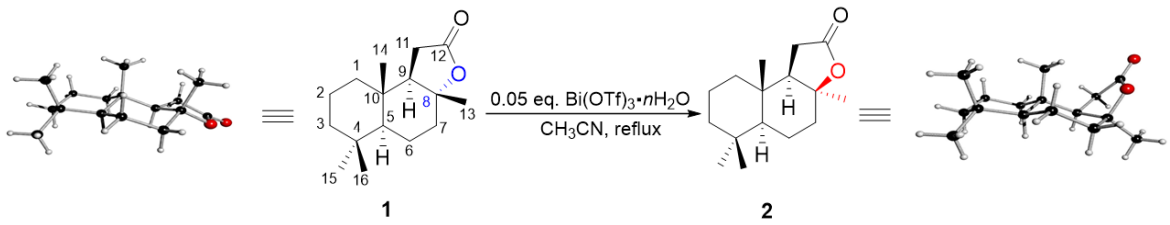


Figure 1. Bismuth triflate-promoted epimerization of (+)-sclareolide 1.

References

[1] F. O. McCarthy, J. Saarinen, A. Upadhyay, C. Zanetti, E. A. Collins, M. O Driscoll, O. M. Lynch, M. F. Cronin, T. Rüffer, O. Antoniuk, J. Yli-Kauhaluoma, V. M. Moreira, J. Chem. Educ. 2025, 102, 2, 556–562. https://doi.org/10.1021/acs.jchemed.4c00763

Synthesis of (-)-agelastatin A

Adriana G. Casteleiro[1*], João R. Vale[1], Rafael F. T. A. Gomes[1], Carlos A. M. Afonso[1]

[1]*Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, University of Lisbon, Av. Prof. Gama Pinto, 1649- 003 Lisbon, Portugal*

** E-mail: adrianacasteleiro@edu.ulisboa.pt*

Agelastatin alkaloids have been the subject of interest by the scientific community since their first reported isolation from *Agelas dendromorpha* sponges. In fact, this natural product has been shown to have high toxicity against tumor cells, it also can inhibit neoplastic transformation and metastasis, generating interest for its continued exploration [1].
This synthesis will be based on a flow photorearrangement of a pyridinium salt, in this case allyl pyridinium bromide, due to its compatibility with photochemical reactions. In this way, it is possible to obtain the desired cyclopentene structure, which is a highly functionalized ring. A flow enzymatic kinetic resolution will be performed in early stages of this synthesis allowing the enantiopure precursor to the natural product [1] (**Figure 1**).
Following this synthesis, the activity of the natural product, (-) – Agelastatin A, will be further investigated with some biological assays to test its anticancer activity.

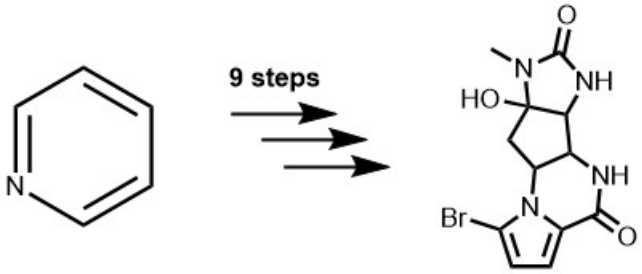


Figure 1. Synthetic route.

Funding and Acknowledgements: We thank the Fundação para a Ciência e Tecnologia for financial support (2023.11341.PEX, UIDB/04138/2025 - Instituto de Investigação do Medicamento.)

References

[1] Vale, J. R.; Fortunato, M. A. G.; Andrade, K. H. S.; Rocha, Â. M. R.; Afonso C. A. M.; Siopa, F.; *Advanced Synthesis and Catalysis* 2023,365, 2240-2247.

LIST OF AUTHORS

List of authors

(presenting author in bold)

	P91	183
	P110	202
	P114	206
Carlos Baleizão	**IL1**	36
Carlos M. M. Afonso	OC4	65
Carlos M. Monteiro	**IOC8**	59
	P96	188
	P109	201
Carmen Fernandez Becerra	P34	126
Carmen Ramos Martín	F7	82
Carolina Amorim	KN7	49
	P73	165
Carolina Canilho	P29	121
Carolina M. D. Catarino	IOC8	59
	P109	201
Carolina Marques	P43	135
Cassandra Spinosa	IOC4	55
Catarina A. Montargil	P13	105
	P83	175
Catarina A. R. Vilão	**P97**	189
Catarina Alexandra Aires Henriques	**P12**	104
Catarina Amorim	F5	80
Catarina Cipriano	**P86**	178
Catarina Cunha	OC10	71
Catarina Maria	**P49**	141
Cátia Vieira	F16	91
	P7	99
Cecília R.C. Calado	OC13	74
Celine	P60	152
Celso Alves	F14	89
Chiara Zanetti	P113	205
Christelle Langevin	P74	166
Christopher D. Maycock	P31	123
Clara Quintas	P103	195
Cláudia Alves	**P9**	101
Cláudia C. Miranda	P30	122
Claudia Nastasi	IOC4	55
Cláudia P. S. Ribeiro	P17	109
Cláudio Leal	P30	122
Cristiana P. Von Rekowski	OC13	74
Cristina Moiteiro	P44	136
Cristina Visentin	IOC4	55
Daiane Nascimento Maronde	**P7**	99

Emília Sousa	OC11	72
	P45	137
	P55	147
	P77	169
	P103	195
Emily A. Collins	P113	205
Emre Ergene	F13	88
Ermelinda M. S. Maçôas	P67	159
	P111	203
Esther Calvino-Sanles	**F12**	87
Eugénia Pinto	P55	147
Eurico Lima	**F3**	78
Fábio M. F. Santos	P26	118
	P74	166
	P99	191
	P101	193
	P102	194
Fátima Maria de Souza Pereira	P1	93
Fernanda Marques	P27	119
Fernando Remião	P70	162
Festus O. Ogungbemiro	**P61**	153
Filipa Marcelo	**IL2**	37
Filipa Mendes	P5	97
	P27	119
Filipa Pires	F5	80
Filipa Siopa	F14	89
	P83	175
	P91	183
Filipe Teixeira	P36	128
Florbela Pereira	P23	115
Florence O'McCarthy	P113	205
Francisca Almeida-Pinto	**P4**	96
Francisco Faisca	P105	197
Francisco P. Nascimento	**P92**	184
Francisco Ribeiro	P25	117
Frederico A. da Silva	P85	177
Gabriel Vitor de Lima Marques	**P45**	137
Gang Zheng	P35	127
Gil Martins	P28	120
Gilles Gasser	P101	193
Giorgia Torello	F7	82
Girolamo Calò	OC11	72
Gonçalo Almeida	F2	77

Iva Fernandes	F8	83
	F9	84
	P15	107
	P95	187
Ivo E. Sampaio-Dias	**IL4**	39
	P87	179
	P93	185
	P94	186
	P104	196
J. Sérgio Seixas de Melo	OC2	63
	F5	80
	F10	85
	F11	86
	P9	101
Jaime A. S. Coelho	IOC8	69
	F1	76
	P5	97
	P6	98
	P53	145
	P74	166
	P89	181
	P90	182
	P92	184
	P96	188
	P100	192
	P109	201
Jakob Frey	IOC6	57
Jari Yli-Kauhaluoma	P113	205
Jennifer Noro	P56	148
Jennifer Szilagyi	P42	134
Jessica Baiget	**IOC5**	56
Jéssica Macedo	**P46**	138
	P54	146
	P66	158
Joana Cardoso	P55	147
Joana Deyse Lima Agostinho	**P16**	108
Joana Ferreira	F14	89
Joana Filipa Alves Martins	F14	89
Joana Inês Carvalho	P85	177
Joana L. C. Sousa	OC10	71
Joana Martins	OC5	66
Joana Moreira	**P72**	164
Joana Oliveira	F8	83

Marta Cascante	P98	190
Marta M. Alves	OC6	67
Marta P. Carrasco	P14	106
Marta Piñeiro	OC2	63
	F10	85
	F11	86
	P57	149
Massimo Zuchetti	IOC4	55
Mathilde L. Boland	**P21**	113
Matilde Simão	P60	152
Mattia Mason	IOC4	55
Maurizio Viale	P23	115
M. B. T. Ferreira	IOC8	59
Melani J. A. Reis	OC9	70
Meltem Avci-Adali	F13	88
Michael f. Cronin	P113	205
Michelle O'Driscoll	P113	205
Miguel A. R. B. Castanho	OC3	64
	P64	156
Miguel Machuqueiro	**IL3**	38
Miguel Mano	P107	199
Milan Nikolić	P81	173
Milene A. G. Fortunato	**F14**	89
	P83	175
Miljan Ćorović	P51	143
Miloš Vavrík	**IOC6**	57
Mpanzu Nelo	**P38**	130
Nádia Senhorães	P22	114
Nahyun Kwon	P35	127
Nenad Filipović	P81	173
Nicholas Bossons	**OC7**	68
Nina Wang	**P40**	132
Nuna Ramos	**P48**	140
Nuno Basílio	**OC5**	66
Nuno Ferreira	**P36**	128
Nuno M. M. Moura	**OC9**	70
	P23	115
Nuno Manuel Xavier	F2	77
	P38	130
	P42	134
	P49	141
Nuno Mateus	F8	83
	F9	84

Nuno Maulide	IOC6	57
Nuno R. Candeias	**KN5**	47
Nuno R. Neng	P58	150
Nuno Santarém	P25	117
Nuno Saraiva	P79	171
Nuno Taveira	P66	158
Nuno Vale	P104	196
Octávio Ferreira	F3	78
Olga Genilloud	F7	82
Olha Antoniuk	**P113**	205
Orla M. Lynch	P113	205
Patrícia Correia	**F8**	83
	P15	107
	P95	187
Patrícia M. A. Silva	P76	168
Patrícia Máximo	P106	198
Patricia Remón	P14	106
Patrícia Rijo	**IOC9**	60
	P61	153
	P81	173
	P68	160
Patrícia Sequeira	P106	198
Paul Knochel	P86	178
Paula A. Oliveira	OC10	71
Paula B. Andrade	IL5	40
Paula Gameiro	P15	107
Paula Gomes	F6	81
	P15	107
Paula Guedes de Pinho	P70	162
Paula M. Marcos	**P47**	139
Paula M. T. Ferreira	**KN7**	49
	P72	164
	P73	165
Paula S. Branco	**P62**	154
	P106	198
Paulo Almeida	F3	78
	F4	79
	P16	108
	P33	125
Paulo D. Nunes Barradas	F5	80
	P9	101
Paulo J. Costa	P3	95
	P11	103

	P65	157
Paulo J. G. Coutinho	F15	90
	P22	114
Paulo J. Gavaia	P28	120
Paulo Pereira	P22	114
Pedro Alberto Pavão Pessôa	P1	93
Pedro Alexandrino Fernandes	P71	163
Pedro Cruz	P43	135
Pedro Lima	P106	198
Pedro M. O. Gomes	IL5	40
Pedro M. P. Góis	OC7	68
	F12	87
	P26	118
	P74	166
	P75	167
	P82	174
	P85	177
	P99	191
	P101	193
	P102	194
	P108	200
	P110	202
Pedro M. R. Paulo	P29	121
Pedro Pinheiro	P51	143
Pedro Santos	**P35**	127
Pedro V. Baptista	P60	152
Philipp Spieß	IOC6	57
Przemysław Sitarek	P68	160
	P81	173
R. Gomes	OC7	68
Radek Jorda	F2	77
	P38	130
Rafael F. A. Gomes	**KN1**	43
	F12	87
	P80	172
	P86	178
	P90	182
	P110	202
	P114	206
Rafael Ferrer Pires Mascarenhas	**P99**	191
Rafaela A. L. Silva	P84	176
Rafaela A. N. Cavadas	**P82**	174
	P85	177

	P97	189
Rafaela Silva	**P64**	156
Raquel M. Durão	**P6**	98
	P89	181
Raquel Nunes da Silva	**F9**	84
Rebeca André	P68	160
Redouane Er-raqioui	P23	115
Renata Barbosa de Oliveira	P45	137
Renata Silva	P77	169
Renato Boto	F3	78
Ricardo Chagas	**F13**	88
Ricardo Dias	P37	129
Ricardo Ferraz	**F6**	81
Ricardo G. Rocha	**P69**	161
Ricardo J. F. Ferreira	P20	112
	P32	124
Ricardo M. Gomes	**P63**	155
Ricardo Ribeiro	P55	147
Rita D. Felisberto	**P83**	175
Rita Guedes	P98	190
Rita I. Oliveira	**P107**	199
Rita Lima	**P71**	163
Rita Padanha	P82	174
	P85	177
Rita Padinha Lopes	**P30**	122
Rita Santos	P76	168
Rita Silva-Reis	**OC10**	71
Rita Sobreiro-Almeida	IOC3	54
Roberta Frapoli	IOC4	55
Rodrigo de Almeida	P49	141
Rodrigo S. Gomes	IOC8	59
	P96	188
Romeu A. Videira	IL5	40
Rosario Fernández Godino	F7	82
Rúben Araújo	OC13	74
Ruben Valente	P60	152
Rui Brito	P43	135
Rui Moreira	**PL6**	34
	F7	82
	P2	94
	P4	96
	P14	106

Vânia M. Moreira	**KN4**	46
	P113	205
Vasco Branco	F7	82
Vasco Cachatra	P44	136
Vasco D. B. Bonifácio	OC6	67
Vasco M. S. Castanheira	**F16**	91
Vera Alves	P33	125
Vera L. M. Silva	**IL5**	40
	P59	151
Vera M. Costa	P94	186
Vera M. S. Isca	P61	153
	P81	173
Vera Sousa	IOC3	54
Victor de Freitas	F8	83
	F9	84
	P37	129
	P95	187
Vítor Almodovar	P9	101
Vítor Félix	P59	151
Xavier C. Correia	IL4	39
	P93	185
	P94	186
	P104	196
Xerardo Garcia-Mera	IL4	39
	P104	196
Yaryna S. Buzan	**P28**	120
Yasmine Fernine	**P43**	135
Zayra Victória Barros da Silva	**P1**	93