SOCIEDADE PORTUGUESA DE QUÍMICA

Abstract book

15th National Organic Chemistry Meeting
and
8th National Medicinal Chemistry Meeting

Universidade do Algarve
22-24 January 2024

Title

Abstract book of the 15th National Organic Chemistry Meeting and the 8th National Medicinal Chemistry Meeting

Editor

Diana C. G. A. Pinto

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Acknowledgments and Sponsors

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Welcome

Dear Colleagues,

The Divisions of Organic Chemistry and Medicinal Chemistry&Chemical Biology of the Portuguese Chemical Society (SPQ) and the Faculty of Sciences and Technology of the University of Algarve cordially invite you to attend the 15th National Organic Chemistry Meeting (15ENQO) and the 8th National Medicinal Chemistry Meeting (8ENQT), that will take place on January 22-24, 2024, at the University of Algarve, in Faro, Portugal.

Traditionally, the 15ENQO & 8ENQT biennial meetings gather scientists from all domains of the Organic and Medicinal Chemistry & Chemical Biology areas. Researchers' comprehensive and multidisciplinary approach in these areas plays a pivotal role in developing chemical sciences. As such, vibrant and enlightening scientific discussions on novel developments and innovative ideas are commonly held in the 15ENQO & 8ENQT meetings, which foster new collaborations and expand the boundaries of knowledge.

The venue of the 15ENQO & 8ENQT, Faro, is the main city of Algarve. Not far from Faro, near the southwesternmost point of continental Europe, lies Sagres, a sacred promontory to the Romans. It was in Sagres that, legendarily, Prince Henry the Navigator dreamed and planned the Portuguese discoveries in the 15th century, exploring the unknown and expanding horizons in the quest for a sea route to India. Today, Science is called upon to search for essential tools that enable the sustainable development of societies, striving for global well-being and peace. Chemistry plays an instrumental role in this quest.

The scientific program comprises plenary and keynote lectures spanning advances in Organic and Medicinal Chemistry & Chemical Biology, delivered by national and international scientists, and oral communications and poster presentations.

With an attractive and inspiring scientific program, you will be exposed to Southern Portugal's colours, flavours, tastes, history and traditions.

We hope that you enjoy the 15ENQO & 8ENQT meetings and that we manage to meet the audience´s expectations.

Carlos Afonso, Maria de Lurdes Cristiano & Maria do Amparo F. Faustino
Conference Chairpersons

Scientific Program

Program Overview

Monday, 22 January 2024	
Time (h)	University of Algarve, Grande Auditório Caixa Geral de Depósitos
9:00-10:45	**Registration**
10:45-11:15	**Opening Ceremony** Maria Lurdes Cristiano (UAlgarve) - Chairperson of the 15th National Organic Chemistry Meeting (15th ENQO) and National Medicinal Chemistry and Biological Meeting (8th ENQT) Carlos Afonso (FFUL) - Chairperson & President of the Organic Chemistry Division Maria Amparo F. Faustino (UA) - Chairperson & President of the Medicinal Chemistry Division Joaquim Faria - Presidente da Sociedade Portuguesa de Química Carlos Guerrero - Diretor da Faculdade de Ciências e Tecnologia da Universidade do Algarve Nuno Bicho - Vice-Reitor da Universidade do Algarve
CHAIRS:	Artur M. S. Silva
11:15-12:00	PL1 - Going with the flow – The use of continuous processing in organic synthesis C. Oliver Kappe, *Institute of Chemistry, University of Graz, Heinrichstrasse 28, Graz, Austria*
12:00-12:45	PL2 - New reactions and structures involving main group elements: from hypervalent iodane rearrangements to novel borylated skeletons *Ana B. Cuenca, BISi-Bonds/CRISOL group, Dept. of Organic and Pharmaceutical Chemistry, Institut Químic de Sarrià, Universitat Ramon Llull, Vía Augusta 390, 08017 Barcelona, Spain*
12:45-14:30	**Lunch Break**
CHAIRS:	Emilia Sousa and Rui Moreira
14:30-15:15	PL3 - Chemical biology for drug discovery *Edward Tate, Department of Chemistry, Molecular Sciences Research Hub, London, W12 0BZ and The Francis Crick Institute, 1 Midland Rd, London NW1 1AT, UK*
15:15-15:35	KN1 - Design, synthesis and *in vitro* evaluation of a series of endoperoxide hybrids designed to tackle latent tuberculosis *Patrícia Sofia Menalha Amado, Center of Marine Sciences, University of Algarve, P-8005-039 Faro, Portugal*
15:35-15:55	KN2 - Designing bioconjugates and nanomaterials for enhanced photodynamic therapy *João Paulo Costa Tomé, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1049 001 Lisboa, Portugal*
15:55-16:15	KN3 - Mechanochemistry: in search of sustainable methods for the synthesis of heterocycles *Marta Pineiro, University of Coimbra, Department of Chemistry, 3004-535 Coimbra, Portugal*

16:15-16:35	KN4 - Pyrimido[5,4-*d*]pyrimidines as new tools to tackle old problems: vector-borne parasitic diseases *Maria Alice Carvalho, Centro de Química, Escola de Ciências, Universidade do Minho, Braga, Portugal*		
16:35-17:10	**Coffee break**		
Grande Auditório	Chairs: Paula Branco and Manuela Raposo	Anfiteatro A	Chairs: Pedro Góis and Lucinda Reis
17:10-17:20	OC1 - Plastic depolymerization using commercially available Mo, Zn, Mn catalysts *Ana C. Fernandes, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1049-001 Lisboa, Portugal*	17:10-17:20	OC8 - Wild-type p53 modification by a tryptophanol-derived oxazoloisoindolinone *Ricardo J. F. Ferreira, Faculty of Pharmacy, Universidade de Lisboa. Lisboa, Portugal*
17:20-17:30	OC2 - Active polymeric filtration membranes with siderophore for iron(III) removal from aqueous systems *Ricardo A. L. S. Santos, Chemistry Department, University of Aveiro, Campus Universitário de Santiago 3810-193 Aveiro, Portugal*	17:20-17:30	OC9 - Sphaerococcenol A: Extraction, analogue synthesis, and antitumor assays *Milene A. G. Fortunato, Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003, Lisboa, Portugal*
17:30-17:40	OC3 - Pd-Catalyzed cycloaddition of bicyclic aziridines with isocyanates for imidazolidinone synthesis *Mariana Crespo Monteiro, Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisbon, Portugal*	17:30-17:40	OC10 - Study of the action of a tryptophan metabolite, 8-hydroxyquinoline-2-carboxylic acid, and its Ga(III) complex on microbiota exposed to ionizing radiation *Nádia Ribeiro, Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico, Estrada Nacional 10, km 139.7, 2695-066 Bobadela LRS, Portugal*
17:40-17:50	OC4 - The chemistry of malvidin 3-*O*-glucoside and malvidin 3,5-*O*-diglucoside networks from acidic and basic paradigms. The irreversible reactions. *Joana Oliveira, Faculdade de Ciências, Universidade do Porto, Rua do Campo Alegre, 687, 4169-007 Porto, Portugal*	17:40-17:50	OC11 - Incorporation of unnatural alpha,alpha-dialkylglycines in polymyxins: synthesis and characterization *Susana P. G. Costa, Centre of Chemistry, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal*
17:50-18:00	OC5 - Lewis base-catalyzed reactions of chromans and allenoates: Access to structurally diverse chroman frameworks *Maria I. L. Soares, University of Coimbra, Coimbra Chemistry Centre-Institute of Molecular Sciences and Department of Chemistry, 3004-535 Coimbra, Portugal*	17:50-18:00	OC12 - Searching novel therapeutic targets against MRSA: a mass spectrometry multi-omics approach *Pedro C. Rosado, Centro de Química Estrutural - Institute of Molecular Sciences, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1, 1049-001 Lisboa, Portugal*
18:00-18:10	OC6 - Easy access to functionalized sparteine via electrochemical cyanation in batch and in flow of quinolizidine alkaloids *Raquel M. Durão, Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisbon, Portugal*	18:00-18:10	OC13 - Layer-by-layer supramolecular assembly of alginate/pyranoflavylium -modified chitosan acidochromic biomembranes *Luis Cruz, Faculty of Sciences, University of Porto, Rua do Campo Alegre, s/n, 4169-007, Porto, Portugal*

18:10-18:20	OC7 - Synthesis of new conjugated elongated tryptanthrin derivatives for optoelectronic devices *Vítor A. S. Almodôvar, Faculty of Pharmacy, University of Coimbra, Pólo das Ciências da Saúde, Azinhaga de Santa Coimbra, 3000-548 Coimbra, Portugal.*	18:10-18:20	OC14 - Pharmaceutical ionic (nano)systems: a sustainable approach for infection diseases *Luis C. Branco, FCT NOVA, Universidade NOVA de Lisboa, 2829-516, Caparica, Portugal*
18:20	**Porto de Honra**		

Tuesday, 23 January 2024			
Time (h)	University of Algarve – Grande Auditório Caixa Geral de Depósitos		
CHAIRS:	Vítor Freitas and Uwe Pischel		
9:00-9:45	PL4 – Asymmetric autocatalysis and its implications for symmetry breaking and homochirality Oliver *Trapp, Ludwig-Maximilians-University, Munich/Germany*		
9:45-10:05	KN5 - When less is more: downsizing peptide-ionic liquid conjugates delivers new candidates for topical treatment of skin infections *Paula Gomes, LAQV-REQUIMTE, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade do Porto, Portugal*		
10:05-10:25	KN6 - β-Modifications of *meso*-arylporphyrins: a roadmap to targeted applications *Nuno M. M. Moura, LAQV-Requimte and Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal*		
10:25-10:45	KN7 - Oxindole-small-molecule hybrids in complex diseases *Carolina Silva Marques, LAQV-REQUIMTE, Institute for Advanced Studies and Research (IIFA), University of Évora, Rua Romão Ramalho, 59, 7000-641, Évora, Portugal*		
10:45-11:15	**Coffee break**		
Grande Auditório	Chairs: Mariette Pereira and Nuno Candeias	Anfiteatro A	Chairs: Graça Neves and Maria Manuel Marques
11:15-11:25	OC15 - Radicals at very low temperatures: Monitoring reactions and interactions through IR spectroscopy, *Elisa M. Brás, Universidade de Coimbra, Coimbra, Portugal*	11:15-11:25	OC23 - Bioorthogonal pretargeting for anchoring photoactive BODIPY on the plasma membrane of HER2+ gastric tumours *Sara R. D. Gamelas, LAQV-REQUIMTE, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal*

11:25-11:35	OC16 - Revealing the potential of phthaloperinones as key optoelectronic components for electronic devices *Ana C. Amorim, University of Coimbra, Coimbra Chemistry Centre – Institute of Molecular Sciences and Department of Chemistry, 3004-535 Coimbra, Portugal*	11:25-11:35	OC24 - Graphitic carbon nitride: new support for glucose oxidase immobilisation towards cancer therapy *Rita A. M. Barros, Faculty of Engineering, University of Porto, Rua Dr. Roberto Frias, 4200-465 Porto, Portugal*
11:35-11:45	OC17 - Synthesis of *C*-glycosyl quinolones, acridones and related compounds: Classical *versus* ohmic heating conditions *Vera Lúcia Marques da Silva, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal*	11:35-11:45	OC25 - Blocking replication of tumour cells with G-quadruplex DNA stabilizing ligands *Catarina I. V. Ramos, LAQV-Requimte and Department of Chemistry, University of Aveiro, 3010-193 Aveiro, Portugal*
11:45-11:55	OC18 - Efficient visible-light-driven imines synthesis using carbon nitride photocatalyst *Joana C. Lopes, Faculty of Engineering, University of Porto, Rua Dr. Roberto Frias, 4200-465 Porto, Portugal*	11:45-11:55	OC26 - Exploring the cytotoxic diterpenoid 7α-acetoxy-6β-hydroxyroyleanone from *Plectranthus* spp. as a PKC-α activator for breast cancer therapy *Vera M. S. Isca, CBIOS – Universidade Lusófona's Research Center for Biosciences & Health Technologies, Lisbon, Portugal*
11:55-12:05	OC19 - Furan-based asymmetric diketopyrrolepyrrole dyes: Optimization of acceptor unit for Dye-Sensitized Solar Cells *João Sarrato, FCT NOVA, Universidade NOVA de Lisboa, 2829-516, Caparica, Portugal*	11:55-12:05	OC27 – Inhibition of G4-helicase interactions: A promising approach for cancer targeting therapy *Israa Aljnadi, Medicinal Organic Chemistry Group, Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal*
12:05-12:15	OC20 - Mechanosynthesis of chiral oligosulfides by inverse vulcanization *Vasco D. B. Bonifácio, Bioengineering Department, Instituto Superior Técnico, Lisboa, Portugal*	12:05-12:15	OC28 - High"light"ing dansylpiperazino-functionalized squaraine dyes for enhanced anticancer photodynamic purposes *Eurico Lima, University of Tras-os-Montes and Alto Douro, Quinta de Prados 5001-801, Vila Real, Portugal*
12:15-12:25	OC21 - Photocatalytic oxidation of bio-based heterocyclic compounds *Késsia H. S. Andrade, Faculdade de Farmácia, Universidade de Lisboa, Lisboa, Portugal*	12:15-12:25	OC29 - Shining against resistance: Photodecontaminant materials for inactivation of bacteria *Carolina V. Domingos, Centro de Química de Coimbra, Departamento de Química, Universidade de Coimbra, Rua Larga, 3004-535 Coimbra, Portugal*
12:25-12:35	OC22 - Degradation products of plastic polymers as markers of microplastics *José P. Da Silva, Centre of Marine Sciences (CCMAR/CIMAR LA), University of Algarve, Campus de Gambelas, 8005-139 Faro, Portugal*	12:25-12:35	
12:35-14:00	**Lunch Break**		
CHAIRS:	Paulo Almeida and António Deométrio Pereira		
14:00-14:45	PL5 - Structure based identification of novel albumin binders for half-life extensions of proteins and peptides *Maria Méndez Pérez, Sanofi, Germany*		

14:45-15:05	KN8 - New dual-color photoinitiators derived from photochromic naphthopyrans for 3D printing *Paulo Jorge dos Santos Coelho, University of Trás os Montes e Alto Douto, 5000-801 Vila Real, Portugal*
15:05-15:25	KN9 - The BASHY dye platform as theranostic tool - from bioimaging to photodynamic therapy *Uwe Pischel, University of Huelva, 21071 Huelva, Spain*
15:25-15:45	KN10 - (Thio)barbiturates combined with fatty acids with potential interest against prostate cancer *Samuel Martins Silvestre, Faculty of Sciences, University of Beira Interior, Covilhã, Portugal*
15:45-16:05	KN11 - C-N and S-N bond formation via hypervalent iodine reagents: the missing link *Maria Manuel B. Marques, School of Science and Technology, Universidade Nova de Lisboa, 2829-516 Caparica, Portugal*
16:05-16:15	SOC - The Elsevier's Chemistry Ecosystem *Marta Da Piana, Elsevier B.V., Radarweg 29, Amsterdam*
16:15-16:35	**Flash Poster Communication in 90 s**
16:35-18:00	**Coffee break & Poster discussion**
18:00-19:00	**Assembleia Geral**
19:45	**Congress Dinner – Eva Sense Hotel**

Wednesday, 24 January 2024	
Time (h)	University of Algarve
CHAIRS:	Teresa Pinho e Melo and Fernanda Proença
9:00-9:45	PL6 - Development of new catalytic systems. Applications in asymmetric catalysis *Rosario Fernández Fernández, Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, Spain*
9:45-10:05	KN12 - The Évora-Coimbra rearrangement: Tales from two (cities) labs *Anthony J. Burke, Faculty of Pharmacy, University of Coimbra, Pólo das Ciências da Saúde, Azinhaga de Santa Coimbra, 3000-548 Coimbra, Portuga*
10:05-10:25	KN13 - Development of synthetic methodologies to obtain dicarboxymethyl cellulose with differentiated structure and properties *Luísa Maria da Silva Pinto Ferreira, Departamento de Química, NOVA School of Science and Technology, Universidade NOVA de Lisboa, 2829-516 Caparica, Portugal*
10:25:10:45	KN14 - Uncovering novel chemotypes targeting the mycobacterial energy metabolism as a strategy to control tuberculosis *Francisca da Conceição Lopes, Faculdade de Farmácia, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal*

10:45-11:15	**Coffee break**		
Grande Auditório	Chairs: Anthony J. Burke and Rita Ventura	Anfiteatro A	Chairs: Maria Alice Carvalho and Paula Gomes
11:15-11:25	OC30 - On the development of novel cellulose derivatives for microplastic flocculation *Bruno Medronho, Faculty of Sciences and Technology (MEDITBIO), University of Algarve, Campus de Gambelas, Ed. 8, 8005-139 Faro, Portugal*	11:15-11:25	OC38 - Total synthesis of marine natural product (-)-agelastatin A: Biological evaluation of N3-alkylation *João R. Vale, Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisbon, Portugal*
11:25-11:35	OC31 - Recent insights on the multifunctional scaffold of chromeno[3,4-*b*]xanthone derivatives against Alzheimer's disease *Daniela Malafaia, LAQV-REQUIMTE and Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal*	11:25-11:35	OC39 - The neurotoxic effects of emerging synthetic cathinones and its metabolites: the role of metabolism *Rita P. Lopes, Instituto Superior Técnico, Departamento de Engenharia Química, Universidade de Lisboa, Portugal*
11:35-11:45	OC32 - Synthesis of 3-(arylamino)thieno[3,2-*b*]pyridines and evaluation of their neuroprotective activity on transgenic *C. elegans* for Machado-Joseph disease *Maria-João R. P. Queiroz, Centre of Chemistry, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal*	11:35-11:45	OC40 - Towards therapeutical applications of camphorimine Ag(I) and Au(I) complexes *Joana P. Costa, Centro de Química Estrutural - Institute of Molecular Sciences, Instituto Superior Técnico, Universidade de Lisboa, Lisboa, Portugal*
11:45-11:55	OC33- Electrochemical oxidation of abietanes using continuous-flow *Inês S. Martins, Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal*	11:45-11:55	OC41 - Antimicrobial evaluation of water-soluble pyrazole-pyridinium zinc(II) phthalocyanines: A promising approach for microorganism eradication *Leandro M. O. Lourenço, LAQV-REQUIMTE, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal*
11:55-12:05	OC34 - Uncovering the origins of supramolecular similarity in a series of benzimidazole structures *Paulo R. S. Salbego, Federal University of Santa Maria (UFSM), 98400-000, Frederico Westphalen Campus, RS, Brazil*	11:55-12:05	OC42 - Bacterial siderophores – iron thievery weapons in environmental research *Diana I. S. P. Resende, Laboratório de Química Orgânica e Farmacêutica, Faculdade de Farmácia, Universidade do Porto, Porto, Portugal*
12:05-12:15	OC35 - Synthesis of amphiphilic di-cationic imidazolyl porphyrins for photoinactivation of bacteria *Madalena F. C. Silva, Coimbra Chemistry Center, Department of chemistry, University of Coimbra, Rua Larga, 3004-535, Coimbra, Portugal*	12:05-12:15	OC43 - Promising antiviral small molecules: from *in silico* studies to effects on cellular infection and cytotoxicity *Francisca Carvalhal, Faculty of Pharmacy, University Porto, 4050-313 Porto, Portugal*
12:15-12:25	OC36 - Nitrogen rich biomass furanics – synthesis and applications *Rafael F. A. Gomes, Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisbon, Portugal*	12:15-12:25	OC44 - Unveiling the COVID impact on biochemical pathways through an integrated omics expedition towards preparedness *Gonçalo C. Justino, CQE - Centro de Química Estrutural – Institute of Molecular Sciences, Instituto Superior Técnico, Univerisdade de Lisboa, 1049-001 Lisboa, Portugal*

12:25-12:35	OC37 - Chan-Lam reaction of arylvinyl boron reagents with (hetero)aromatic amines: application in the synthesis of *N*-heterocycles *Joana R. M. Ferreira, LAQV-REQUIMTE, Department of Chemistry, University of Aveiro, 3010-193 Aveiro, Portugal*	12:25-12:35	OC45 - Exploring the hyaluronidase inhibitory activity of phytosterol derivatives *Gonçalo P. Rosa, LAQV-REQUIMTE, Department of Chemistry, University of Aveiro, Portugal*
12:35-14:00	**Lunch Break**		
CHAIRS:	Carlos A. M. Afonso and Jorge Salvador		
14:00-14:20	KN15 - Perspectives on catalytic continuous flow process in fine chemical industry *Mariette M. Pereira, Universidade de Coimbra, Rua Larga, 3004-535 Coimbra, Portugal*		
14:20-14:40	KN16 - A novel functional assay for the discovery of new drug targets in mycobacteria *Maria Rita Ventura, Instituto de Tecnologia Química e Biológica António Xavier, Universidade Nova de Lisboa, 2780-157 Oeiras, Portugal*		
14:40-15:00	KN17 - Electroorganic oxidation of biorenewable resources into functionalized products *Jaime A. S. Coelho, Centro de Química Estrutural, Institute of Molecular Sciences, Faculty of Sciences, University of Lisbon, Campo Grande, 1749-016 Lisbon, Portugal*		
15:00-15:45	PL7 - Biologically active xanthone and chromone-type compounds and their aza-analogues *Artur M. S. Silva, LAQV-REQUIMTE, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal*		
15:45-16:00	**Closing Ceremony and Best PhD and MSc awards**		

List of Communications

Plenary Lectures

PL1	C. Oliver Kappe, *Going with the flow – The use of continuous processing in organic synthesis*
PL2	Ana B. Cuenca, *New reactions and structures involving main group elements: from hypervalent iodane rearrangements to novel borylated skeleto*
PL3	Edward Tate, *Chemical biology for drug discovery*
PL4	Oliver Trapp, *Asymmetric autocatalysis and its implications for symmetry breaking and homochirality*
PL5	Maria Méndez Pérez, *Structure based identification of novel albumin binders for half-life extensions of proteins and peptides*
PL6	Rosario Fernández Fernández, *Development of new catalytic systems. Applications in asymmetric catalysis*
PL7	Artur M. S. Silva, *Biologically active xanthone and chromone-type compounds and their aza-analogues*

Keynote Lectures

KN1	Patrícia S. M. Amado, *Design, synthesis and in vitro evaluation of a series of endoperoxide hybrids designed to tackle latent tuberculosis*
KN2	João P. C. Tomé, *Designing bioconjugates and nanomaterials for enhanced photodynamic therapy*
KN3	Marta Pineiro, *Mechanochemistry: in search of sustainable methods for the synthesis of heterocycles*
KN4	M. Alice Carvalho, *Pyrimido[5,4-d]pyrimidines as new tools to tackle old problems: vector-borne parasitic diseases*
KN5	Paula Gomes, *When less is more: downsizing peptide-ionic liquid conjugates delivers new candidates for topical treatment of skin infections*
KN6	Nuno M. M. Moura, *β-Modifications of meso-arylporphyrins: a roadmap to targeted applications*
KN7	Carolina Marques, *Oxindole-small-molecule hybrids in complex diseases*
KN8	Paulo J. Coelho, *New dual-color photoinitiators derived from photochromic naphthopyrans for 3D printing*
KN9	Uwe Pischel, *The BASHY dye platform as theranostic tool – from bioimaging to photodynamic therapy*
KN10	Samuel Silvestre, *(Thio)barbiturates combined with fatty acids with potential interest against prostate cancer*
KN11	M. Manuel B. Marques, *C-N and S-N bond formation via hypervalent iodine reagents: the missing link*
KN12	Anthony J. Burke, *The Évora-Coimbra rearrangement: Tales from two (cities) labs*
KN13	Luísa M. Ferreira, *Development of synthetic methodologies to obtain dicarboxymethyl cellulose with differentiated structure and properties*
KN14	Francisca Lopes, *Uncovering novel chemotypes targeting the mycobacterial energy metabolism as a strategy to control tuberculosis*
KN15	Mariette M. Pereira, *Perspectives on catalytic continuous flow process in fine chemical industry*

KN16	M.R. Ventura, *A novel functional assay for the discovery of new drug targets in mycobacteria*
KN17	Jaime A. S. Coelho, *Electroorganic oxidation of biorenewable resources into functionalized products*

Sponsor Oral Communication

SOC	**Marta Da Piana, *The Elsevier's Chemistry Ecosystem***

Oral Communications

OC1	Ana C. Fernandes, *Plastic depolymerization using commercially available Mo, Zn, Mn catalysts*
OC2	Ricardo A. L. S. Santos, *Active polymeric filtration membranes with siderophore for iron(III) removal from aqueous systems*
OC3	Mariana Crespo Monteiro, *Pd-Catalyzed cycloaddition of bicyclic aziridines with isocyanates for imidazolidinone synthesis*
OC4	Joana Oliveira, *The chemistry of malvidin 3-O-glucoside and malvidin 3,5-O-diglucoside networks from acidic and basic paradigms. The irreversible reactions.*
OC5	Maria I. L. Soares, *Lewis base-catalyzed reactions of chromans and allenoates: Access to structurally diverse chroman frameworks*
OC6	Raquel M. Durão, *Easy access to functionalized sparteine via electrochemical cyanation in batch and in flow of quinolizidine alkaloids*
OC7	Vítor A. S. Almodôvar, *Synthesis of new conjugated elongated tryptanthrin derivatives for optoelectronic devices*
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OC14	Luis C. Branco, Pharmaceutical ionic (nano)systems: a sustainable approach for infection diseases
OC15	Elisa M. Brás, *Radicals at very low temperatures: Monitoring reactions and interactions through IR spectroscopy*
OC16	Ana C. Amorim, *Revealing the potential of phthaloperinones as key optoelectronic components for electronic devices*
OC17	Vera L. M. Silva, *Synthesis of C-glycosyl quinolones, acridones and related compounds: Classical versus ohmic heating conditions*

OC18	Joana C. Lopes, *Efficient visible-light-driven imines synthesis using carbon nitride photocatalyst*
OC19	João Sarrato, *Furan-based asymmetric diketopyrrolepyrrole dyes: Optimization of acceptor unit for Dye-Sensitized Solar Cells*
OC20	Vasco D. B. Bonifácio, *Mechanosynthesis of chiral oligosulfides by inverse vulcanization*
OC21	Késsia H. S. Andrade, *Photocatalytic oxidation of bio-based heterocyclic compounds*
OC22	José P. Da Silva, *Degradation products of plastic polymers as markers of microplastics*
OC23	Sara R. D. Gamelas, *Bioorthogonal pretargeting for anchoring photoactive BODIPY on the plasma membrane of HER2+ gastric tumours*
OC24	Rita A. M. Barros, *Graphitic carbon nitride: new support for glucose oxidase immobilisation towards cancer therapy*
OC25	Catarina I. V. Ramos, *Blocking replication of tumour cells with G-quadruplex DNA stabilizing ligands*
OC26	Vera M. S. Isca, *Exploring the cytotoxic diterpenoid 7α-acetoxy-6β-hydroxyroyleanone from Plectranthus spp. as a PKC-α activator for breast cancer therapy*
OC27	Israa Aljnadi, *Inhibition of G4-helicase interactions: A promising approach for cancer targeting therapy*
OC28	Eurico Lima, *High"light"ing dansylpiperazino-functionalized squaraine dyes for enhanced anticancer photodynamic purposes*
OC29	Carolina V. Domingos, *Shining against resistance: Photodecontaminant materials for inactivation of bacteria*
OC30	Bruno Medronho, *On the development of novel cellulose derivatives for microplastic flocculation*
OC31	Daniela Malafaia, *Recent insights on the multifunctional scaffold of chromeno[3,4-b]xanthone derivatives against Alzheimer's disease*
OC32	Maria-João R. P. Queiroz, *Synthesis of 3-(arylamino)thieno[3,2-b]pyridines and evaluation of their neuroprotective activity on transgenic C. elegans for Machado-Joseph disease*
OC33	Inês S. Martins, *Electrochemical oxidation of abietanes using continuous-flow*
OC34	Paulo R. S. Salbego, *Uncovering the origins of supramolecular similarity in a series of benzimidazole structures*
OC35	Madalena F. C. Silva, *Synthesis of amphiphilic di-cationic imidazolyl porphyrins for photoinactivation of bacteria*
OC36	Rafael F. A. Gomes, *Nitrogen rich biomass furanics – synthesis and applications*
OC37	Joana R. M. Ferreira, *Chan-Lam reaction of arylvinyl boron reagents with (hetero)aromatic amines: application in the synthesis of N-heterocycles*
OC38	João R. Vale, *Total synthesis of marine natural product (-)-agelastatin A: Biological evaluation of N3-alkylation*
OC39	Rita P. Lopes, *The neurotoxic effects of emerging synthetic cathinones and its metabolites: the role of metabolism*
OC40	Joana P. Costa, *Towards therapeutical applications of camphorimine Ag(I) and Au(I) complexes*
OC41	Leandro M. O. Lourenço, *Antimicrobial evaluation of water-soluble pyrazole-pyridinium zinc(II) phthalocyanines: A promising approach for microorganism eradication*

OC42	Diana I. S. P. Resende, *Bacterial siderophores – iron thievery weapons in environmental research*
OC43	Francisca Carvalhal, *Promising antiviral small molecules: from in silico studies to effects on cellular infection and cytotoxicity*
OC44	Gonçalo C. Justino, *Unveiling the COVID impact on biochemical pathways through an integrated omics expedition towards preparedness*
OC45	Gonçalo P. Rosa, *Exploring the hyaluronidase inhibitory activity of phytosterol derivatives*

Poster Communications

P1	Rodrigo Barriga, *TIGIT/PD-L1 dual inhibition: finding small molecules to fight cancer*
P2	***Selected for Flash Communication*** Mélanie Fonte, *Cinnamic acid-acridine hybrids as multi-stage antiplasmodial leads*
P3	M.V. Rodrigues, *Development of AI-2 chemical probes for the identification and characterisation of novel AI-2 receptors*
P4	João C.S. Simões, *Novel trans-A2B2 porphyrins: from oxime/hydrazone α-substituted dipyrromethanes to meso-substituted functionalized macrocycles*
P5	Ana Margarida Janeiro, *Using the Passerini multicomponent reaction as a tool to access small-libraries of oxindole-type hybrids as promising anticancer agents*
P6	Lúcia Melo, *Building novel amyloid probes featuring D-A-D architectures*
P7	***Selected for Flash Communication*** Ana Teresa Silva, *"Seasoning" antimalarial drugs action: chloroquine bile salts as novel triple-stage antiplasmodial hits*
P8	***Selected for Flash Communication*** Iago C. Vogel, *Quinic acid: A new framework for α-glucosidase inhibitors*
P9	***Selected for Flash Communication*** Gonçalo F. Oliveira, *Synthesis and functionalization of non-symmetrical N-alkyl diketopyrrolopyrroles*
P10	Américo J. S. Alves, *Continuous flow phosphine-catalyzed [3+2] annulation of allenoates: Towards efficient synthesis of chiral spirocyclopentene-penicillanates*
P11	***Selected for Flash Communication*** Pedro Sobral, *Novel semisynthetic A-ring-cleaved glycyrrhetinic acid derivatives as potential anticancer agents*
P12	Rita I. Oliveira, *Towards the discovery of novel ubiquitin specific protease 7 (USP7) Inhibitors: an integrated protocol of pharmacophore modelling and virtual screening*
P13	D. Nunes, *Antituberculosis agents multitargeting the electron transport chain of Mycobacterium tuberculosis*
P14	C. Henriques, *Pharmacokinetic profile of selenochrysin: a promising anticancer scaffold*
P15	Paula M. Marcos, *Hexahomotrioxacalix[3]arene-based receptors containing naphthalene, anthracene and pyrene fluorophores*
P16	Catarina A. Montargil, *Synthesis of isatin-based macrocycles for treating Alzheimer's disease*

P17	***Selected for Flash Communication*** Raquel Eustáquio, *Inexpensive small molecules as promising fluorescent labels for biomolecules*
P18	Diana C. G. A. Pinto, *Lipophilic profile of the Salicornia alpini growing in different salt marshes of the Ria de Aveiro*
P19	Vânia M. Moreira, *Design and synthesis of 12-thiazole abietanes as selective inhibitors of the human metabolic serine hydrolase hABHD16A*
P20	***Selected for Flash Communication*** Inês C. C. Costa, *Amplifying the library of thio-linked pyrimidine-based conjugates*
P21	Manuel J. Verganista, *Iron-catalysed transfer hydrogenation of shikimic acid derivatives*
P22	Patrícia Rijo, *Halimane derivatives from Plectranthus ornatus Codd. demonstrate anti-cancer activity*
P23	B. Bahls, *c-MYC G-quadruplex stabilization by 5-amino-8-chloro-11H-indolo[3,2-c]isoquinoline derivatives: in vitro and in silico studies*
P24	***Selected for Flash Communication*** J. da Cunha, *Synthesis of sulfonamides via electrophilic amination mediated by hypervalent iodine(III) reagents*
P25	Josélia C. Sousa, *Mechanochemistry: a way to improve sustainability of furans' transformations*
P26	Daiane N. Maronde, *Synthesis and characterization of mono- and di-aminopyrazine precursors for the preparation of zinc(II) phthalocyanine derivatives*
P27	***Selected for Flash Communication*** Maria F. Martins, *Synthesis of Sonogashira coupling products in the thieno[2,3-b]pyrazine series and cyclizations to tricyclic lactones*
P28	João R. Costa, *Biocatalytic approach for sustainable esterification*
P29	Maria B. V. Moura, *Multicomponent synthesis of chiral spiro-oxindoles-hydantoins for leishmaniasis treatment*
P30	V. Maciel, *Synthesis and computational modelling of naturally occurring sucrose-based phytochemicals as lead pharmaceutics*
P31	Ana C.S. Veríssimo, *Valorization of thistles from Beira Baixa through the study of the biochemical profile and potential bioactivities*
P32	Nádia E. Santos, *Ru-HKUST: Combining the drug loading and release ability of metal-organic frameworks (MOFs) with ruthenium*
P33	Maria Graça P. M. S. Neves, *Antimicrobial potential of nitrogen-substituted Zn(II)-porphyrins as photosensitizers against Staphylococcus aureus*
P34	M. M. M. Raposo, *Biological activity of bis(indolyl)methanes functionalized with different hetero(aromatic) moieties*
P35	P. Almeida, *Exploring novel anticancer agents by the coupling of (thio)barbiturates with mono- and trimethinecyanine dyes*
P36	L. Pinheiro, *Synthesis of floridoside phosphotriesters*
P37	***Selected for Flash Communication***

	João Braz, *Oxime-functionalized trans-A2B-corroles as promising photosensitizers for photodynamic therapy of lung cancer*
P38	Lara Mingatos, *Synthesis of carvone derivatives and screening of anti-inflammatory activity*
P39	V. Ledesma-Martin, *Structure and ligand-based strategies to discover novel orexin receptor modulators: targeting the circadian clock and Alzheimer's disease*
P40	Emília Sousa, *Novel synthetic cinnamic acid-flavonoid hybrids with multifunctional properties*
P41	Diana L. Assis, *Revolution in neuroscience: Innovating Alzheimer's treatment with photoswitchable molecules*
P42	***Selected for Flash Communication*** Flávia Leitão, *Quinonemethides: Synthesis and electrochemical studies of potential new organic redox mediators*
P43	Latimah Bustillo, *Exploration of electrocatalytic reactivity using electrochemistry in combination with computational tools*
P44	Susana M. M. Lopes, *Hetero-Diels-Alder reactions of a novel steroidal nitrosoalkene*
P45	M.B. Antunes, *Light driven modifications in quinic acid derivatives*
P46	Tiago G. Paiva, *Novel methodologies for dicarboxymethyl cellulose preparation*
P47	A. Varges, *Substituted carbocyanine dyes: synthesis and antiproliferative evaluation*
P48	I. Carvalho, *Decoding drug targets: An innovative strategy for protein binding pocket exploration*
P49	Joana F. D. Duarte, *Optimization of enzymatic kinetic resolution for scale-up production of (-)- agelastatin A*
P50	Inês Falcato Santos, *Photochemical cysteine modification*
P51	Filipe G. A. Estrada, *Reaching important objectives in the difficult fight against lung cancer: a knowledgeable in silico strategy*
P52	***Selected for Flash Communication*** Camila Q. V. Costa, *Photodegradation of microplastics: Role of adsorbed contaminants*
P53	Inaiá O. Rocha, *Synthesis and optical properties of 2-(((4-(trifluoromethyl)quinolin-6-yl)amino)methyl)phenols*
P54	M. Matias, *(Thio)barbiturate-dehydroepiandrosterone hybrids with potential anticancer properties: Synthesis, biological evaluation and pharmacokinetic predictions*
P55	M. Amparo F. Faustino, *Exploring the reactivity of β-vinylporphyrins with α,α'-dioxothione*
P56	Ivo E. Sampaio-Dias, *Synthesis and structural analysis of cyclic aza-amino acid derivatives for the assembly of azapeptides*
P57	Marta Correia-da-Silva, *Environmental benign antifouling agent, developed employing the tactics of medicinal chemistry, moved to "clinical" trials*
P58	Maria M. M. Santos, *Mechanistic insights on the reactivation of wild-type activity of mutants p53 by tryptophanol-derived small molecules*
P59	Custódia Fonseca, *Compounds with biological activities on Ca^{2+}-ATPases*

P60	Daniel Raydan, *Practical palladium-catalyzed switchable access to imines and amines from secondary alcohols*
P61	Anja Udundzic, *Identification of bacterial strains competent in biodegrading carbamazepine, diclofenac, and 17-α-ethinylestradiol–preliminary results*
P62	Terver J. Sase, *Novel chiral organocatalysts for the asymmetric synthesis of 2-(tetrazol-5-yl)-2H-azirines*
P63	Cristiano A. Conceição, *Exploring a novel functional assay for investigating the efficacy of anti-tuberculosis drugs targeting arabinofuranosyltransferases*
P64	Carina J. N. Caires, *Photocatalytic transformations of quinic acid*
P65	Bruno C. Guerreiro, *Pyridyl-saccharinates: synthesis, structure and chelating properties*
P66	Luísa M. Ferreira, *Development of synthetic methodologies to obtain dicarboxymethyl cellulose with differentiated structure and properties*
P67	Oliviero Cini, *Innovative probes for imaging tumor-associated cathepsins through Positron Emission Tomography (PET)*
P68	M. Margarida Martins, *One-pot synthesis of aromatic aminopropyl lactams as potential agents for Alzheimer's disease*
P69	Pedro M. R. Santos, *Glyco-porphyrin based gold nanoplatforms for combined cancer photodynamic and photothermal therapies*
P70	Cláudia P. S. Ribeiro, *The synthesis of BODIPY-tetrazine and its potential application in gastric cancer cells via click chemistry*
P71	Juliana R. Lopes, *Synthesis and evaluation of boronic-chalcone derivatives as anti-cancer and anti-inflammatory agents*
P72	Volodymyr V. Tkach, *The theoretical description for omeprazole and diclophenac cathodic electrochemical determination by poly(tartrazine) modified carbon electrode*
	Selected for Flash Communication
P73	Catarina Maria, *New purine nucleosides against Alzheimer's disease: Cholinesterase inhibitors and metal chelators*

Plenary Lectures

Going with the flow – The use of continuous processing in organic synthesis

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Continuous flow processes form the basis of the petrochemical and bulk chemicals industry where strong competition, stringent environmental and safety regulations, and low profit margins drive the need for highly performing, cost effective, safe and atom efficient chemical operations. In contrast to the commodity chemical industry, however, the fine chemical industry primarily relies on its existing infrastructure of multipurpose batch or semi-batch reactors. Fine chemicals, such as drug substances and active pharmaceutical ingredients (APIs), are generally considerably more complex than commodity chemicals and usually require numerous, widely diverse reaction steps for their synthesis. These requirements generally make versatile and reconfigurable multipurpose batch reactors the technology of choice for their preparation. However, the advantages of continuous flow processing are increasingly being appreciated also by the pharmaceutical industry and, thus, a growing number of scientists, from research chemists in academia to process chemists and chemical engineers in pharmaceutical companies, are now starting to employ continuous flow technologies on a more routine basis [1].

Flow technology has considerable advantages in mass- and heat transfer, safety and ease of scale-up, when compared to traditional batch reactions. Furthermore, hazardous chemistries such as highly exothermic reactions, or those involving unstable or toxic intermediates can be operated safely in flow, whereby this technology acts as a powerful route-enabler. In this lecture, contributions from our research group in the field of continuous flow processing in the areas shown in Figure 1 will be highlighted.

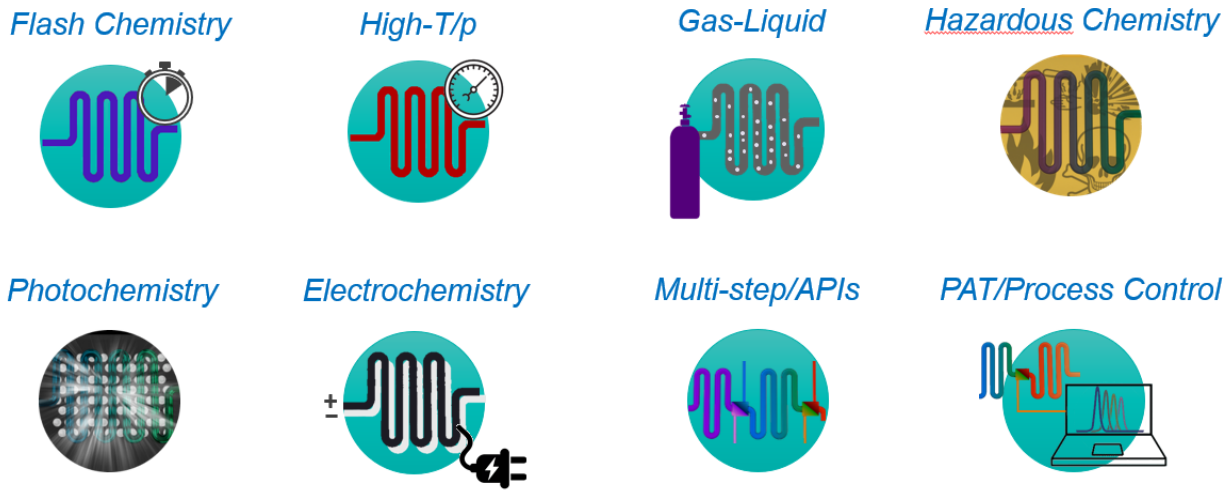

Figure 1: Examples of flow chemistry applications presented in this lecture

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New reactions and structures involving main group elements: from hypervalent iodane rearrangements to novel borylated skeletons

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In recent years our team has developed a series of transformations that reveal the great potential held by the ability of the iodine atom in a λ^3-iodane to undergo iodine-to-arene group transfer, *e.g. via* iodonio-assisted sigmatropic rearrangements [1,2]. We became particularly interested in the reaction between aryliodanes and Sakurai-type organosilanes with the carbonated fragment of an aryl, propargyl or allyl silane being transferred to the arene in a very regioselective manner. These reactions lead to a series of attractive regioselective C-H functionalizations of arenes - both in close and remote positions. Within the organosilane partner diversity, we will also discuss the usage of geminally disposed polimetalloid reagents bearing a boron / silicon, or boron / tin group pairs, which provide access to di- and triaryl methane compounds as an avenue to access molecules with a high degree of sphericity [3].

Besides, and always fascinated by main-group elements such as boron, we have been working on the construction new boron-nitrogen modified skeletons presenting novel structural features. A series of these transformations will be illustrated from a synthetic and mechanistic point of view.

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Chemical biology for drug discovery

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The Tate lab develops novel chemical biology approaches to enable drug discovery against post-translational modification (PTM) pathways and intractable drug targets, including chemical proteomic target identification, screening technologies, and chemical probe discovery for protein-protein interactions and enzymes modulating PTMs. Recent highlights include the first cell-active activity-based probes (ABPs) for deubiquitinases (DUBs), new tools for analysis and discovery of pathogenic secreted protease activities, and the first comprehensive maps of specific classes of protein lipidation PTM through chemical proteomics. We are also interested in new modalities including antibody-PROTAC conjugates, and translation of drug candidates. Representative examples of our recent research are referenced below.

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Asymmetric autocatalysis and its implications for symmetry breaking and homochirality

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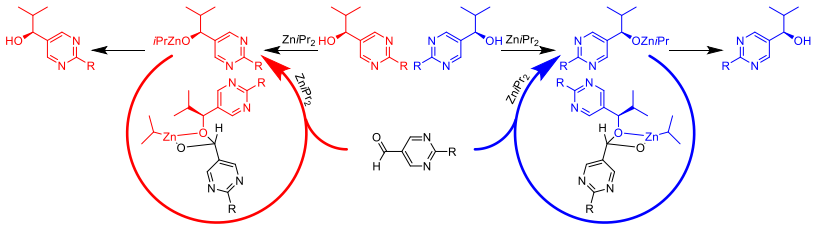
Chemical reactions leading to a spontaneous symmetry breaking or amplification of the enantiomeric excess are of fundamental interest in explaining the formation of a homochiral world. An outstanding example is Soai's asymmetric autocatalysis [1], in which small enantiomeric excesses of the added product alcohol are amplified in the reaction of diisopropylzinc and pyrimidine-5-carbaldehydes.

Here the elucidation of the reaction mechanism by detailed kinetic analyses, the *in situ* high-resolution mass spectrometric identification of the transient intermediates, and doping experiments by in situ reacting reaction mixtures is presented [2]. Key of the reaction is the formation of transient supramolecular hemiacetalate complexes, which can establish an autocatalytic cycle (Scheme).

Comprehensive kinetic data analysis of the hemiacetal formation and the Soai reaction allow the precise prediction of the reaction progress, the enantiomeric excess as well as the enantiomeric excess dependent time shift in the induction period [3]. Experimental structural data give insights into the privileged properties of the pyrimidyl units and the formation of diastereomeric structures leading to an efficient amplification of even minimal enantiomeric excesses, respectively.

These findings open the avenue for a directed synthetic design of (asymmetric) autocatalytic reactions [4].



Scheme

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Structure based identification of novel albumin binders for half-life extensions of proteins and peptides

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Prolonged in-vivo half-life of biomolecules is a desirable property for many injectable therapeutics, in order to increase patient compliance and satisfaction by reducing the burden of frequent injections. The principle of albumin protraction has been successfully applied for the in-vivo half-life extension of several now marketed insulins and peptides. At Sanofi, using a structure-based approach, novel albumin binders were identified and further modified for conjugation with peptides and insulins, leading to compounds with extended plasma half-life comparable to other publicly know acylating residues. Several aspects of the discovery and optimization strategy will be discussed in this presentation.

Development of new catalytic systems. Applications in asymmetric catalysis

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In our research group, we focus on the rational design of reagents, ligands, or catalysts with modulated steric and electronic properties, as well as the development of new activation modes to be implemented in (enantio)selective organic synthesis.

Over the years, we have exploited the nucleophilic character of hydrazones (masked acyl anion equivalents) in asymmetric synthesis. Specifically, the use of formaldehyde N-*tert*-butylhydrazone in combination with bifunctional H-bonding organocatalysts has facilitated efficient enantioselective functionalization of neutral electrophiles, predominantly carbonyl compounds [1]. Building upon this knowledge, we have recently devised an intriguing strategy of anion-binding catalysis. This strategy is based on the simultaneous chloride recognition by H-bonding organocatalysts and N-tert-butyl hydrazones, providing a tool for the asymmetric dearomatization of isoquinolines with high stereocontrol [2].

Concurrently, we have developed a direct approach to key building blocks for the synthesis of dihydro- and tetrahydrophthalazines, phthalazones, and piperazic acid homologues through enantioselective dearomatization of phthalazines. This process involves anion-binding catalysis and silyl ketene acetals as nucleophiles [3].

Furthermore, in line with our interest in Gold chemistry, we will discuss recent results on Au(I)-catalyzed alkynylation reactions [4].

Lastly, we will present results on silver-free gold-catalyzed heterocyclizations through intermolecular H-bonding activation. This involves the use of modulable monosulfonyl squaramides as an example of synergistic gold(I) and anion-binding catalysis [5].

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Biologically active xanthone and chromone-type compounds and their aza-analogues

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Natural products often play important roles in drug discovery and development processes. Xanthones, chromones, chromenes and their aza-analogues are important examples, presenting a wide range of biological activities.

In the last decades, our research group have been involved in synthesising and transforming several libraries of these types of compounds. The main goal is to establish new synthetic methods, the synthesis of novel derivatives and their biological assessment. In the present communication, we will present, among others:

i) an efficient and general methodology for synthesizing *C*-glycosylated phenolic compounds based on the Heck coupling of halogenated phenolic derivatives and sugar alkenes. The protocol was applied to prepare previously unreported *C*-glycosylated 2-styrylchromones and xanthones of potential biological relevance. In both cases, the *C*-glycosylated derivatives were isolated in high (*E*)-stereoselectivity [1];

ii) the design, synthesis, and biological evaluation of a family of chromeno[3,4-*b*]xanthones as well as their (*E*)-2-[2-(propargyloxy)styryl]chromone precursors, as first-in-class acetylcholinesterase (AChE) and β-amyloid (Aβ) aggregation dual-inhibitors [2];

iii) the two-step regioselective synthesis of a series of pyran-fused cholestane derivatives, chromone-type compounds. The initial aldol reaction step of cholestan-3-one with benzaldehydes was regioselective towards C-2. The second step involved the microwave (MW)-assisted cyclization reaction of the formed α,β-unsaturated carbonyl derivatives with malononitrile. In the presence of a high excess of malononitrile, there is the formation of 2-aminoisophthalonitrile fused to C2-C3 of the cholestane A-ring. This is a competing side reaction when higher amounts of malononitrile are input into the reaction [3];

iv) the design and synthesis of a family of steroid-quinoline hybrid compounds that inhibited Aβ1−42 self-aggregation *in vitro*. Our results show that the new cholesterol-quinoline hybrids possess wide and marked disaggregation capacities and are promising templates for the development of new drugs to deal with conformational disorders [4];

v) the synthesis several 1,2,3,4-tetrahydroacridine derivatives and evaluation of their activity against *Leishmania infantum* promastigotes and a structure–activity relationship (SAR) study. Even though the majority of the 1,2,3,4-tetrahydroacridines evaluated presented high levels of toxicity, the structural information gathered in this work allowed its application with another scaffold (quinoline), leading to the obtention of *N1*,*N12*-bis(7-chloroquinolin-4-yl)dodecane-1,12-diamine as a promising novel antileishmanial agent. This work was built on computational studies focusing on a specific enzyme of the parasite, *S*-adenosylmethionine decarboxylase (AdoMet DC), and the 1,2,3,4-tetrahydroacridines emerged as potential inhibitors, evidencing this scaffold as a promising building block for novel antileishmanial pharmaceuticals [5];

vi) the use of 3-formylchromones as Michael acceptors, which upon the use of nitromethane as Michael donor allowed for the one-pot formation of three new C—C bonds, leading to 3,5-disubstituted nitrobenzenes over very mild reaction conditions [6].

Acknowledgements: 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 UIDB/50006/2020 and Portuguese NMR Network.

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Keynote Lectures

Design, synthesis and *in vitro* evaluation of a series of endoperoxide hybrids designed to tackle latent tuberculosis

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Mycobacterium tuberculosis (*Mtb*) is the world's second leading cause of death from infectious diseases (after COVID-19).[1] The ability of *Mtb* to enter the nonreplicating persistence (NRP) and then transition to latent TB contributes to *Mtb*'s drug tolerance and treatment failure in chronically infected individuals.[2] Therefore, improvements in tuberculosis (TB) treatment require molecules with faster action capable of overcoming latency.

The DosRST two-component regulatory system regulates the *Mtb* physiology to promote NRP, in which peroxides such as the natural antimalarial drug artemisinin and synthetic 1,2,4-trioxolanes have been demonstrated to inhibit this system and re-sensitize *Mtb*.[3-5] This inhibition is attributed to the presence of a peroxide bond in the 1,2,4-trioxane structure of ART, interacting with the heme group in DosS and DosT, leading to their inactivation.[3,4]

The search for new molecules with dual action, capable of interrupting DosRST signalling and simultaneously inhibiting a known *Mtb* target protein, appears to be a valid treatment strategy to tackle latent TB. Hence, we proposed hybridizing two separate anti-TB classes by combining the 1,2,4-trioxane-containing moieties with the indole-2-carboxamide scaffold (MmpL3 inhibitors) and the benzothiazinone scaffold (DprE1 inhibitors), to establish a dual mode of action, by increasing *Mtb*'s sensitivity to the active anti-TB pharmacophore while also targeting the DosRST signalling (Figure 1). These hybrid compounds were evaluated for their *in vitro* antitubercular activity, and their pharmacokinetic and metabolism parameters (DMPK) were also assessed.

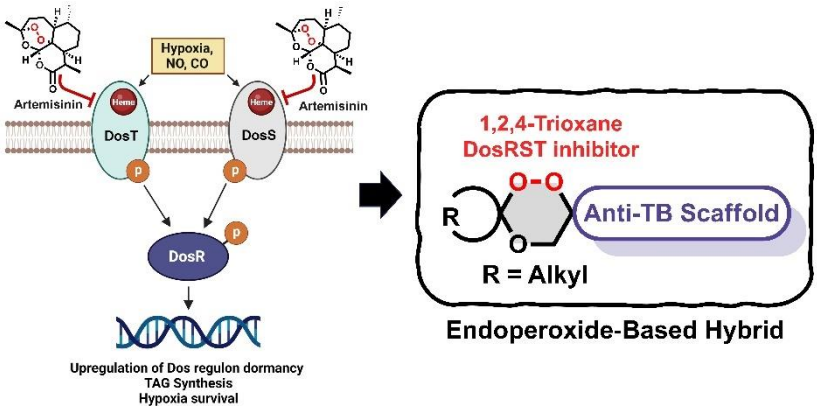

Figure 1: Endoperoxide-based hybrid approach

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Designing bioconjugates and nanomaterials for enhanced photodynamic therapy

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Porphyrins (Pors) and related chromophores are well-known light-induced dyes that have been largely explored on light-based sciences and technologies, including on photomedicine. In this area, photodynamic therapy (PDT), which combines cellular oxygen, light and a photoactive drug that, when together, are able to generate in situ cytotoxic reactive oxygen species (ROS), have been used as an alternative to the conventional cancer treatments. Despite several already approved photosensitisers (PSs), novel photoactive bioconjugates and nanomaterials, both based on Por and phthalocyanines (Pcs), have been developed and studied on molecular-targeted photodynamic therapy (^{t}PDT) as enhanced photoactive drugs and formulations. Actually, we have been involved in the preparation of different photoactive glycoconjugates, immunoconjugates and silica (nano)formulations with improved cancer PDT abilities [1-4]. These novel third generation PSs combine different properties which allow high selectivity for cancer cells and consequently high PDT efficacy. Considering the above, our most recent contributions on bioconjugated PSs and nanomaterials will be shown, detailing their synthetic design and preparation, and highlighting their photobiological properties on cancer tPDT.

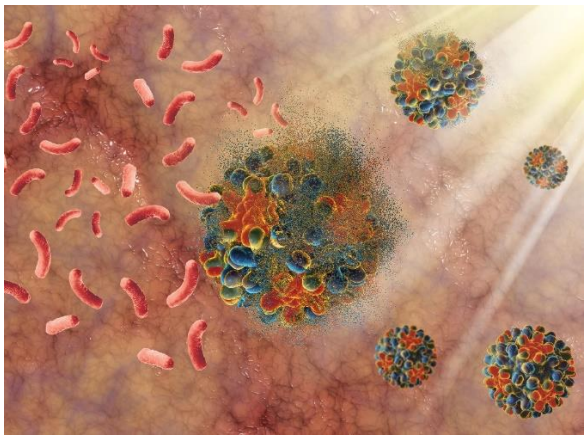

Figure 1: PS-SiO_2 nanorods for bladder cancer PDT

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Mechanochemistry: in search of sustainable methods for the synthesis of heterocycles

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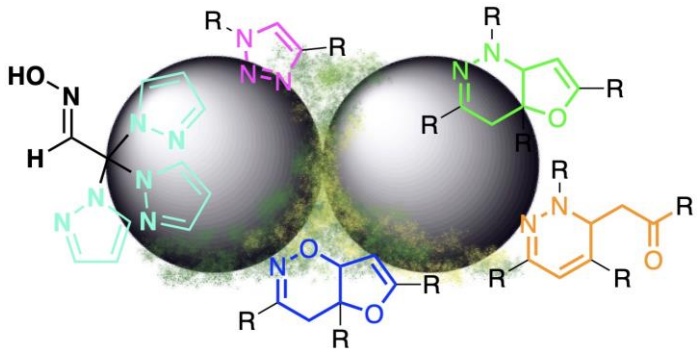
Mechanochemistry, which relies on mechanical force to drive chemical transformations, aligns with the principles of green chemistry in several ways. Therefore, mechanochemistry has emerged as a green and sustainable approach to the synthesis of organic compounds [1]. The most obvious advantage is the elimination of the reaction solvent, by performing reactions in the solid state or with minimal amounts of solvent, which significantly reduces the environmental impact associated with traditional solution-phase reactions, reduces the use of hazardous substances, and can also contribute to eliminate the need for time-consuming and energy-intensive purification processes.

Heterocyclic organic compounds are of paramount importance in several scientific fields, namely, medicinal chemistry, materials science or catalysis [2], where heterocycles play a crucial role as ligands. Using a bottom-up approach, mechanochemistry can promote sustainability by improving the synthetic processes for the synthesis of the heterocycles that are at the core of the application. In essence, mechanochemistry acts as a catalyst for positive change, promoting sustainability and efficiency in science and industry.

This presentation will highlight the role of mechanochemistry in the sustainable synthesis of heterocycles. Specific examples including the application of mechanochemistry to the synthesis of tris(pyrazol-1-yl)methanes, triazoles and furane derivatives will be examined. In addition, the improvement in sustainability will be evaluated through the analysis of green chemistry metrics.



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Pyrimido[5,4-*d*]pyrimidines as new tools to tackle old problems: vector-borne parasitic diseases

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Malaria, leishmaniasis and sleeping sickness are vector-borne parasitic diseases threatening more than 260 million people, mainly in tropical and subtropical regions of the world, affecting mostly low-income populations in poor and developing countries. Globally, they are responsible for more than 630,000 deaths in 2021[1]. Nowadays, drugs used for treating these diseases present limited therapeutic application due to several aspects, such as the highest incidence of diseases is present in marginal areas where drug access is limited, high treatment cost, severe adverse events, the emergence of parasitic resistance to treatments, variability in efficacy and high toxicity [2,3]. All these constraints encourage the search for novel therapeutic agents.

Recently, in our research group, pyrimido[5,4-*d*]pyrimidines were identified as a new class of compounds with promising *in vitro* activity against *P. falciparum*, *L. infantum* and *T. brucei* [4,5]. These compounds presented IC_{50} for *P. falciparum* and *T. brucei* in the nanomolar range and IC_{50} against *L. infantum* in the submicromolar range. Among these novel compounds, some also showed excellent selectivity indexes. In conclusion, pyrimido[5,4-*d*] pyrimidine derivatives constitute a class of compounds deserving further development as new agents to treat malaria, visceral leishmaniasis and sleeping sickness. The synthetic approaches to generate these target compounds [6] and the biological results will be presented.

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When less is more: downsizing peptide-ionic liquid conjugates delivers new candidates for topical treatment of skin infections

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Skin permeation is of undeniable significance in both healthcare and cosmetics, to facilitate the action of active pharmaceutical ingredients (API) and cosmeceuticals, respectively. Amongst the latest investigational chemical permeation enhancers, ionic liquids (IL) have been under the spotlight for dermal and transdermal delivery of either small drugs or larger bioactive peptides and proteins [1]. In view of this and building on our long-term research in antimicrobial peptides, we have produced peptide-ionic liquid conjugates (PILC) by solid-phase assembly and modification of peptides *via* click chemistry and investigated their potential as a new type of API for topical treatment of skin infections [2-4]. Results obtained so far, through a combination of microbiological, biophysical, and *in vivo* studies, will be communicated.

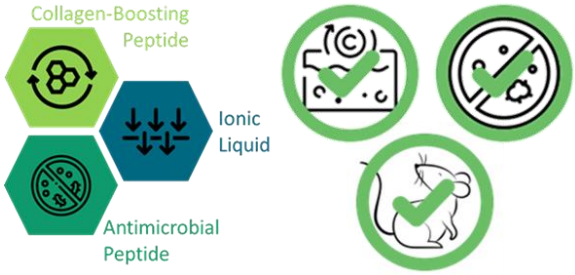

Figure 1: Peptide-ionic liquid conjugates with dual wound healing and antimicrobial properties.

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β-Modifications of *meso*-arylporphyrins: a roadmap to targeted applications

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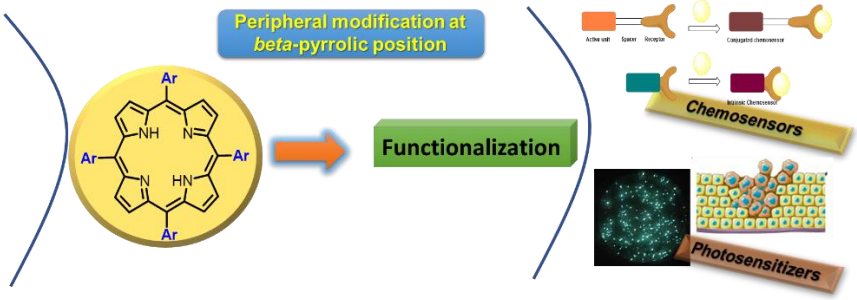
Tetrapyrrolic macrocycles, such as porphyrins and chlorins represent a prevalent class of compounds in nature, with established roles in crucial biological functions like respiration, electron transfer, or photosynthesis [1].

In recent years, natural and synthetic tetrapyrrolic macrocycles have become the focal point of numerous investigations, due to their physicochemical properties, which can be finely tuned through structural modifications of the tetrapyrrolic core. The distinctive properties exhibited by these macrocycles make them highly attractive and valuable compounds, finding utility across various application fields, including catalysis, water remediation, supramolecular chemistry, medicine, and (chemo)sensors [2,3].

The significance of synthetic porphyrins, namely of *meso*-tetraarylporphyrins goes beyond their distinctive stability, and photophysical and photochemical properties, conformational flexibility, and chemical versatility together with their biological relevance, which can be finely adjusted by incorporating suitable functionalities either at the inner core of the macrocycle or at its periphery. It is widely recognized that appropriate functionalization at both *meso*- and β-pyrrolic positions plays a pivotal role in influencing the optical and redox characteristics, thereby impacting the preconized applications. Given these properties, the synthesis of properly functionalized *meso*-tetraarylporphyrins has been extensively explored opening avenues for tailored applications in different areas [4].

In this communication, it will be discussed the synthetic strategies developed by Aveiro group, providing access to β-functionalized porphyrins bearing diverse units. Additionally, the potential applications for the obtained porphyrin derivatives will be explored [5].



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Oxindole-small-molecule hybrids in complex diseases

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Drug discovery is a costly and extensive process, but crucial to identify and recognize new molecular entities with potential to treat diseases and upset medical needs. Focused on uncurable and mortal complex diseases (like cancer and Alzheimer's disease), we strongly believe that development and design of new targeting drugs is an advantage in improving therapeutic efficacy, safety and even resistance profiles. Fortunately, in the last few decades, significant advances have been noticed in scientific research and technological innovation in drug discovery's process.[1]

Oxindole, a privileged heterocyclic unit, is common in many commercial drugs. It is a quite modular structure, and can be easily tuned to improve pharmacological, pharmacokinetic, toxicological, and other important drug properties.[2]

In the last ten years we have been active in the synthesis of new libraries of privileged oxindole scaffolds as inhibitors of some targeted enzymes (Figure 1), using isatin as biomass. Determined to develop new API's, special effort have been made considering the synthetic processes. The use of more sustainable and economically friendly processes is critical.

In this presentation we would like to reveal our latest findings about the synthesis and biological profile of such privileged frameworks.

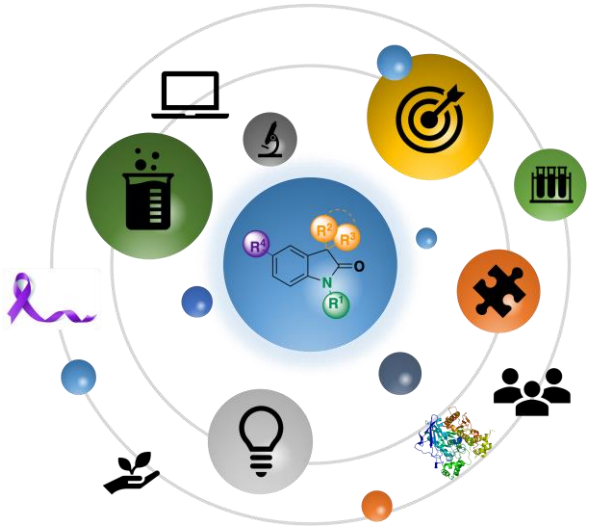

Figure 1: Oxindole-type hybrids as potent inhibitors of some targeted enzymes.

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New dual-color photoinitiators derived from photochromic naphthopyrans for 3D printing

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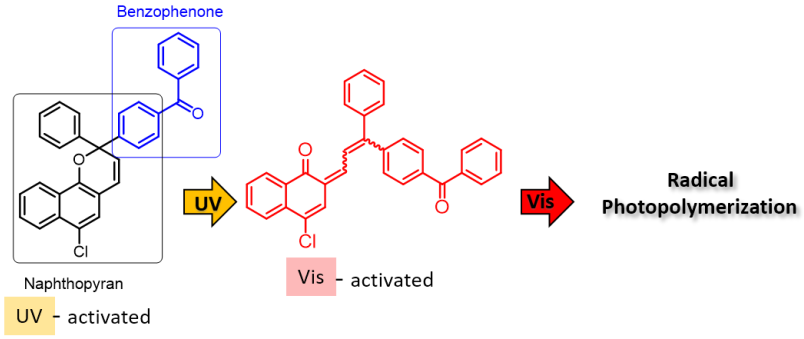
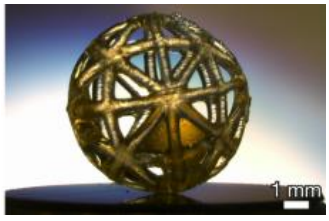
The room temperature polymerization of monomers using UV light is an excellent method for polymer production, requiring minimal expenditure beyond the chemical reactants. Typically, the formulation comprises a monomer (usually a polyacrylate) and a photoinitiator that, upon exposure to light, efficiently generates radicals which, in turn, promote a chain reaction, resulting in the creation of the polymer.

We have synthesized new polyaromatic molecules that joins photochromic naphthopyran units to a benzophenone nucleus. These colourless photoswitches are activated by UV light leading to a coloured species that showed the ability to induce radical formation when exposed to Vis light in the presence of an amine co-initiator [1]. This unique property enables the confinement of the photopolymerization to the volume where the two UV and Vis light beams intersect offering a straightforward method to control polymerization using only light.



These type of dual-colour photoinitiators are the core of the new 3D printing technique Xolography. This method uses two perpendicular laser beams (UV and Vis) to construct 3D objects inside a monomer solution, achieving high resolution without the need for any support structures [2].



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The BASHY dye platform as theranostic tool – from bioimaging to photodynamic therapy

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The quest for tailored dye architectures, that satisfy the requirements for applications in functional fluorescent materials, bioimaging or as light-activatable photosensitizers, is a topic that joins organic chemists and spectroscopists. Tetracoordinate organoboron dyes have been in the limelight since the introduction of boron dipyrromethene (BODIPY) dyes [1]. In this presentation I will discuss the photophysics and theranostic applications of an alternative structurally and electronically highly flexible organoboron platform, that is conveniently engineered in a multicomponent reaction of boronic acids and salicylidenehydrazone ligands (BASHY dyes) [2–4]. The resulting solvatofluorochromic dyes are strong light absorbers (ε ca. 60000 $M^{-1}cm^{-1}$; >450 nm) and show emission in the green-to-red spectral range with quantum yields that may reach up to 0.7. The spectral properties can be fine-tuned based on a particular mechanistic continuum of intramolecular charge transfer and cyanine-like behaviour (see Figure 1) [3, 4, 7]. BASHY dyes have been used as markers for lipid droplets [2], the imaging of myelin debris in Multiple Sclerosis [5], or for monitoring cell apoptosis [6]. Moreover, by drawing on the balance of the implicated photomechanistic features, the design of the dyes can be guided toward efficient singlet-oxygen photosensitizers. This opens the possibility for their application in photodynamic therapy of cancer-related pathologies [7].

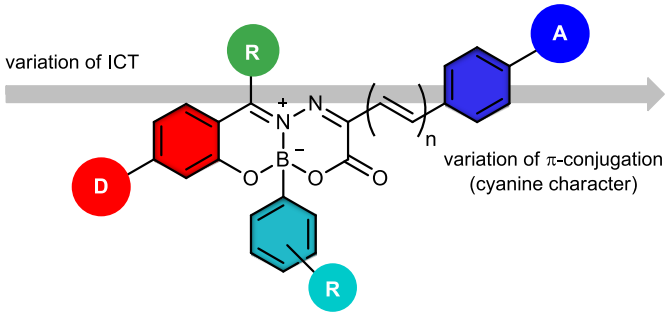

Figure 1: General structure of the BASHY dye platform, positions of electronic and structural diversification, and photomechanistic implications.

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(Thio)barbiturates combined with fatty acids with potential interest against prostate cancer

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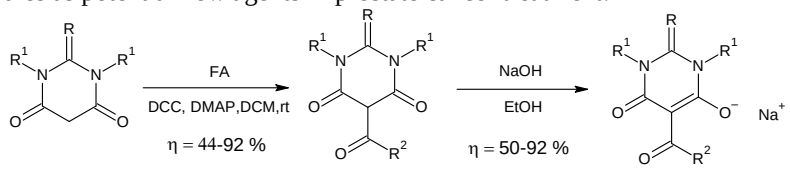
Currently, prostate cancer is the third most predominant cancer in men, which motivates intense research on new therapeutic drugs for this pathology. The deregulation of fatty acid (FA) metabolism has been recognized as a hallmark of carcinogenesis. The major contributor to cell FA uptake is the cluster of differentiation 36 (CD36), which was found overexpressed in several cancers. Therefore, this protein has been considered a potential target in cancer treatment [1]. Since both (thio)barbiturates and FA are recognized as two pharmacophoric groups with great versatility as antitumor agents [2], their hybridization has been explored by our research group aiming to develop new agents with potential interest in prostate cancer treatment. Two series of barbiturates were prepared through two different reactions of condensation, followed by a sodium enolate conversion, in good to excellent yields (Scheme 1). Thereafter, *in vitro* evaluation of their antiproliferative effects, caspase-3 activity, and FA uptake inhibition in 3 prostatic cell lines were performed. Moreover, an *in-silico* study involving molecular docking on CD36 and pharmacokinetics profile prediction was also accomplished. Of the compounds prepared, the hybrids 1,3-dimethylbarbituric acid and stearic acid, 1,3-dimethylthiobarbituric acid and stearic acid and 1,3-dimethylbarbituric acid and arachidonic acid were the most potent and selective, with half maximal inhibitory concentrations (IC_{50}) ranging from 1.43 to 43.43 μM in LNCaP and 11.69 to 43.43 μM in PC3 prostate cancer cells. In addition, an increase in caspase-3 activity was found especially relevant for the second hybrid pair referred. Taking in mind a possible relation between the antiproliferative activity and the inhibition of FA influx effects, the evaluation of FA uptake by the cells was also carried out. This last study revealed that four hybrids had higher inhibitory activity than sulfo-*N*-succinimidyl oleate, a very well-known CD36 inhibitor, used as a reference [3]. In fact, IC_{50} values from 4.96 to 17.00 μM were found to 1,3-dimethylbarbituric acid and 11-undecenoic acid, 1,3-dimethylbarbituric acid and palmitoleic acid and 1,3-dimethythiobarbituric acid and stearic acid. Interestingly, these last results were in accordance with the molecular docking predictions. Regardless of the apparent independence between antiproliferative and FA inhibition effects, these (thio)barbiturates and FA hybrids were revealed to be very promising candidates for further studies as potential new agents in prostate cancer treatment.



R = S or O; R^1= H, Me, Et or Ph; R^2 = FACC

Scheme 1: General synthetic route and structures for hybridization of (thio) barbiturates with FA in study. DCC - dicyclohexylcarbodiimide; DMAP - 4-Dimethylaminopyridine; DCM-dichloromethane, FA – Fatty acid; FACC – Fatty acid carbon chain; rt – Room temperature.

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C-N and S-N bond formation via hypervalent iodine reagents: the missing link

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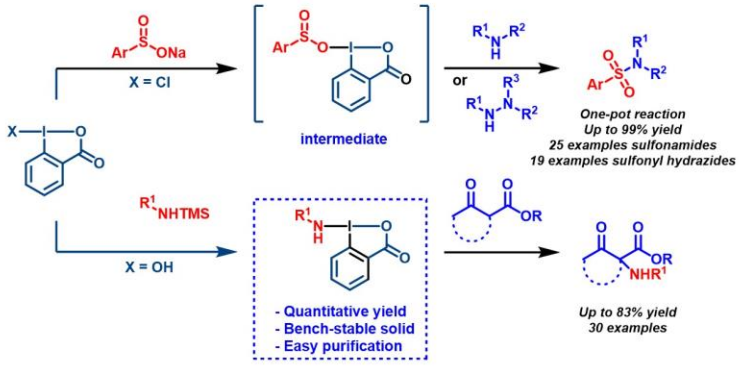
Nitrogen is ubiquitously found in important pharmaceutical agents, and a crucial element to induce unique biological activity as well as physical/chemical properties. The amine group is inherently nucleophilic, and most commonly utilized methods for construction of the C–N and S–N bonds involve nucleophilic nitrogen sources. This can present problems in the synthesis of complex molecules, often avoided by use of protecting groups. These problems have been addressed by developing umpoled strategies that utilize electrophilic nitrogen sources, offering the ability to functionalize typically unreactive bonds [1]. In this context, cyclic hypervalent iodine reagents have shown great promise due to their stability and high reactivity, enabling new disconnections, leading to a greater diversity and synthetic efficiency.

Remarkable progress has been made in this field, and these reagents have emerged as powerful tools in electrophilic amination reactions [2].

Our group has been investigating new benziodoxolone-derived reagents (Scheme 1). We have disclosed new transfer reactions for the sulfonylation of amines and hydrazines and oxidative amination of β-keto esters. We have combined hypervalent iodine chemistry with sulfinate salts to deliver a clean and mild transfer of sulfonyl groups to amines, anilines and hydrazines [3,4]. Furthermore, hypervalent iodine reagents have been prepared and applied as transfer reagents of primary amines to deliver an oxidative amination reaction [5]. These methodologies were applied in the preparation of key functional groups in medicinal chemistry, such as sulfonamides, α-amino carboxylic acids, aromatic amines and will be presented herein.



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

Acknowledgements: We thank FC&T for project funding (2022.04623.PTDC). This work was supported by the Associate 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).

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The Évora-Coimbra rearrangement: Tales from two (cities) labs

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The isatin unit is a common motif in a variety of natural products and medicinal compounds, it is considered a privileged structure and a useful pharmacophore. It is present in an overwhelming list of biologically active compounds. During the past 10 years, we have investigated various new reactions using the isatin-frame work as a starting point to afford a plethora of medicinally important compounds (Figure) [1-4].

In this communication, some the work in this field ranging across two labs will be discussed.

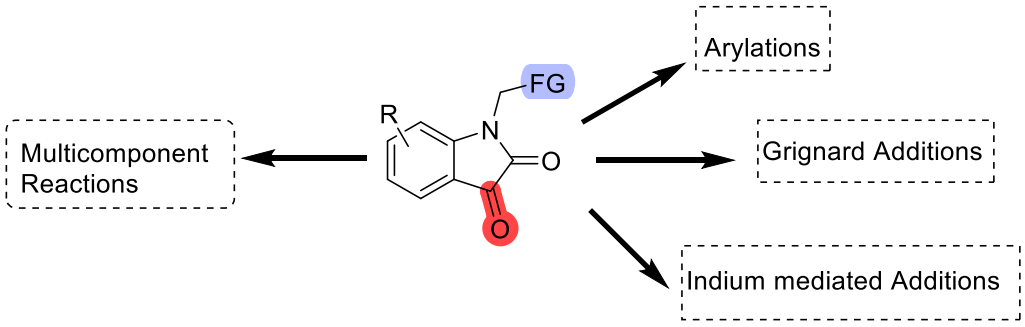

Figure: Isatin a privelaged structure in medicinal chemistry.

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Development of synthetic methodologies to obtain dicarboxymethyl cellulose with differentiated structure and properties

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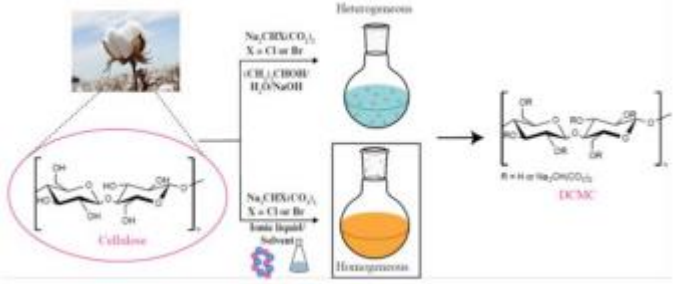
Cellulose, the main constituent of plants' fibres is a naturally occurring polymer and one of Earth's most available materials[1], its low solubility in common solvents, which is attributed to its extensive network of hydrogen bonds and hydrophobic interactions,[2] presents a challenge to its use. To address this issue, one solution involves chemically modifying cellulose, thereby interrupting the inter-unit and chain interactions to enhance solubility[3]. Dicarboxymethyl cellulose (DCMC) is a polyelectrolyte cellulose ether developed by us and usually synthesized via the heterogeneous reaction of cellulose with a halogenated malonate compound [4]. Our team recently developed and explored this compound which has a tuneable water solubility and double the number of ionizable groups compared to the well-known polymer carboxymethylcellulose (CMC) with the same degree of substitution (DS). As a result, DCMC exhibits a higher charge density over a wide range of pH values. However, achieving precise control over this etherification reaction is a non-trivial task. The resulting products may display an unpredictable DS and variable selectivity of the cellulose hydroxyl groups. To address this issue, we have focused on promoting the dissolution of cellulose in inert solvents that do not interfere with the etherification reagents.

Here we used several methodologies to investigate the production of DCMC under homogeneous and heterogeneous condition. The use of ionic liquids (ILs) and binary mixtures of ILs/molecular solvents as molecular solvents allowed the cellulose modification cellulose modification to achieve the tunability of DCMC properties like that observed for CMC, which also has distinct properties based on its degree of substitution and backbone selectivity [5].



Scheme 1: Routes for DCMC preparation from microcrystalline cellulose using heterogeneous or homogeneous conditions.

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Uncovering novel chemotypes targeting the mycobacterial energy metabolism as a strategy to control tuberculosis

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Mycobacterial infections, caused by bacteria of the genus "mycobacterium" such as *Mycobacterium tuberculosis* (Mtb) and non-tuberculous mycobacteria (NTM), are among the most widespread causes of infectious disease morbidity and mortality globally. Tuberculosis (TB) is one of the top 10 causes of death worldwide and one of the leading causes from a single infectious agent [1].

The energy metabolism has received attention as a target for TB therapy after the discovery of the ATP synthase inhibitor bedaquiline [2]. Mycobacterium tuberculosis (Mtb) relies on oxidative phosphorylation to produce ATP, crucial for growth and survival. In both aerobic and anaerobic conditions, the flow of electrons across the respiratory electron transport chain (ETC), to the terminal cytochrome oxidases cyt bc1-aa3 and cyt bd, generates a proton motive force necessary for ATP synthesis by ATP synthase. We now report the development of innovative hybrid compounds with the potential of dual targeting mycobacterial ETC, as the next generation tools to prevent the emergence of resistance and target the latent infection. The rationale behind the design involved the combination of a cytochrome c oxidase (cyt bc1-aa3) inhibitor with a nitroheteroaryl structural motif capable of releasing nitric oxide, a well-known ligand of respiratory terminal oxidases. The compounds were screened against Mtb H37Rv wild type and Mtb cyt-bd knockout strains. This mutant is hypersusceptible to compounds that target the QcrB subunit of cyt bc1-aa3, enabling a rapid identification of cyt bc1-aa3 inhibitors [3]. Evaluation of the antimycobacterial activity revealed novel anti-Mtb agents that share a 5-nitrofuran scaffold and display activity (MIC90 < 1 μM) against H37Rv and cytochrome bd knockout cydKO Mtb strains. As the Mtb cydKO strain does not express cyt bd, the inhibition of cyt bc1-aa3 in this mutant strain results in an effective disruption of the ETC. In addition, these compounds showed to be non-cytotoxic. These results strongly suggest that these hybrid compounds target both terminal oxidases cyt bc1-aa3 and cyt bd. The novelty of this chemotype in the toolbox of antimycobacterial agents, show it is possible to use a dual-targeting approach to disrupt the mycobacterial energy metabolism.

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Perspectives on catalytic continuous flow process in fine chemical industry

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Continuous flow manufacturing stands at the forefront of innovation in the fine chemical industry, namely fragrances and pharmaceuticals presenting a transformative technology platform that is rapidly gaining traction. This cutting-edge approach offers a multitude of advantages, positioning it as a game-changer in the field. [1-2]

These continuous processes facilitate faster and safer reactions when compared to traditional batch processes. Beyond the efficiency gains, this method boasts environmental friendliness, a smaller footprint, and the production of higher-quality products. While substantial global efforts have been invested in enhancing the flexibility and robustness of continuous flow processes for industrial fine chemical production, a pivotal challenge persists regarding its application in catalytic processes. [2]

In this communication we present and discuss relevant and tangible examples achieved by *Catalysis & Fine Chemistry* Coimbra Laboratory on the development of active and reusable catalysts for successful applications of flow technology in sequential hydroformylation, aminocarbonylation, epoxidation and CO_2 activation [3]. The large-scale preparation of potential fragrances, drugs and photosensitizers (porphyrins, BODIPYs…) will be presented.

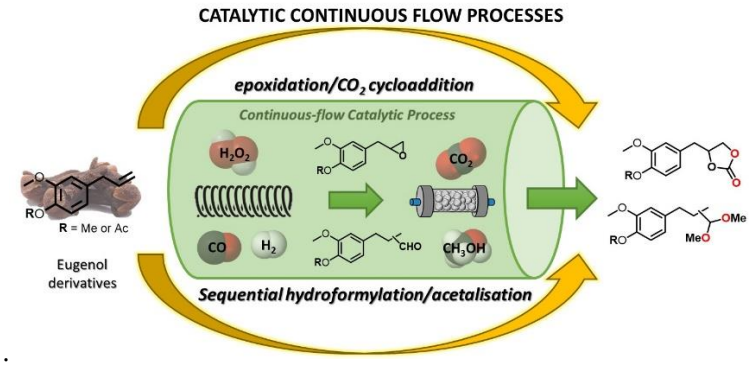

Figure 1: Examples of Continuous Flow Catalytic Processes for Fine Chemical Preparation.[3]

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A novel functional assay for the discovery of new drug targets in mycobacteria

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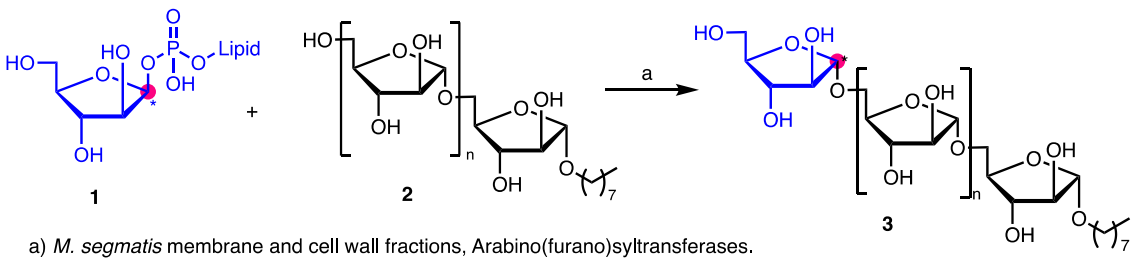
Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, remains one of the primary causes of human death worldwide. The survival and pathogenicity of mycobacteria depends on the integrity of the cell wall, which contains two main polysaccharides, arabinogalactan (AG) and lipoarabinomannan (LAM). D-arabinofuranose (D-Araf) is present in these polysaccharides but not found in mammals, thus compounds that inhibit the enzymes essential for the building of these polysaccharides are potential antimycobacterial drugs [1]. Arabinofuranosyltransferases (AraT) use decaprenylphosphoryl-D-arabinofuranose (DPA) to donate an arabinofuranose residue to a saccharide acceptor and are essential for *M. tuberculosis* growth [2].

In this work, a multidisciplinary approach was used for the development of novel and efficient enzymatic assays for the characterisation of AraTs. Several linear and branched (oligo)arabinofuranoside acceptors were synthesised and their binding affinity with AraT was screened using differential scanning fluorimetry (nanoDSF) to select the best synthetic glycosyl acceptors. The total synthesis of [1]-^{13}C-labelled DPA analogues **1** (Scheme 1) was optimised achieving an overall yield of 38% and an excellent anomeric ratio of 31:1 (β:α). The total syntheses of several linear and branched arabinosyl acceptors for the enzymatic reactions were also efficiently accomplished. In order to study the protein conversions of the synthesised labelled donor with the acceptors a flexible NMR protocol was designed and implemented.



a) *M. segmatis* membrane and cell wall fractions, Arabino(furano)syltransferases.

Scheme 1: ^{13}C NMR AraTs functional assay

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Electroorganic oxidation of biorenewable resources into functionalized products

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Research into novel energy conversion and storage technologies has surged in response to the increasing awareness of the potential devastation caused by current energy usage schemes, predominantly dependent on fossil fuels. In the field of chemical synthesis, electroorganic methodologies have gained popularity as an attractive and eco-friendly alternative to potentially hazardous redox reagents used in traditional organic synthesis for the functionalization of organic molecules. Advances in electroorganic synthesis have dramatically changed the course of modern organic synthesis, enabling a significant number of chemical transformations.[1]

In this communication, we will provide an overview of our recent research on the use of electroorganic synthetic methods for the functionalization of bisquinolizidine alkaloids and abietane diterpene acids (Figure 1). Specifically, electrochemical amine oxidation using batch and flow electrolysis allows for the selective functionalization (e.g., cyanation) of sparteine and lupanine.[2] Electrochemical benzylic and vinylic oxidations enable the oxyfunctionalization of abietic acid and derivatives.[3]

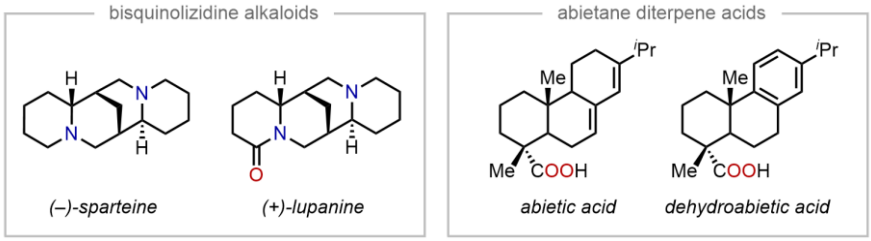

Figure 1: Bisquinolizidine alkaloids and abietane diterpene acids of interest.

Funding: We thank Fundação para a Ciência e a Tecnologia (FCT, UIDB/04138/2020, UIDP/04138/2020, UIDB/00100/2020, UIDP/00100/2020, LA/P/0056/2020 and PTDC/QUI-QOR/1786/2021) for financial support. J.A.S.C. thanks FCT for Scientific Employment Stimulus 2020/02383/CEECIND. The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951996.

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The Elsevier's Chemistry Ecosystem

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- Embiology and Embase [5], two biomedical databases that can be used to monitor adverse reactions to specific compounds or gain insights into potential implications on biological pathways and protein regulation.

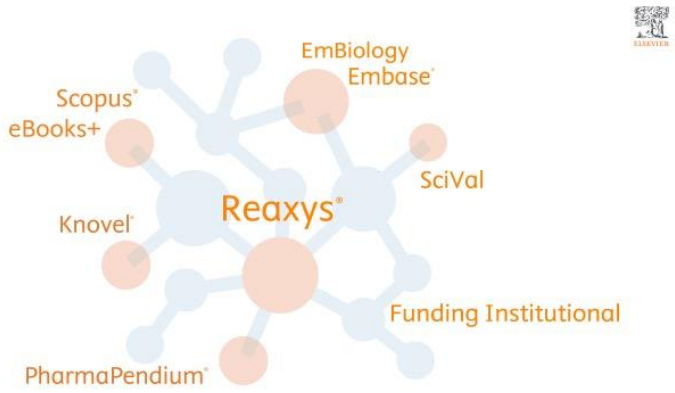

Figure 1: The Elsevier's Chemistry Ecosystem

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[5]. https://www.elsevier.com/solutions/embase-biomedical-research

Oral Communications

Plastic depolymerization using commercially available Mo, Zn, Mn catalysts

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Modern society has also become critically dependent on high-performance/low-cost plastics that support our lifestyles. A plastic-free world is presently utopistic and the increasing production and overuse of plastic packaging materials have caused severe environmental pollution problems.

Plastic pollution represents not only a global environmental crisis but also a loss of valuable resources. A key strategy to overcome this problem, is regarding plastic waste as a potentially cheap source for the production of value-added products or raw materials for the industry. The reductive depolymerization has emerged as an excellent methodology for the valorization of plastic waste into a variety of valuable products[1]. Methanolysis is another important strategy for the depolymerization of plastic waste into valuable compounds.

Catalysts play a key role in the reductive depolymerization and methanolysis of plastic waste. They should be highly active, inexpensive, stable to air, moisture and, if possible, commercially available. In this context, the search for non-toxic and inexpensive catalysts is very important for the sustainability of depolymerization process.

In continuation of our work[2-4], in this communication we describe the reductive depolymerization and methanolysis of polyester and polycarbonate plastic waste catalyzed by several commercially available molybdenum, zinc and manganese catalysts with excellent yields (Fig. 1) [5-7].

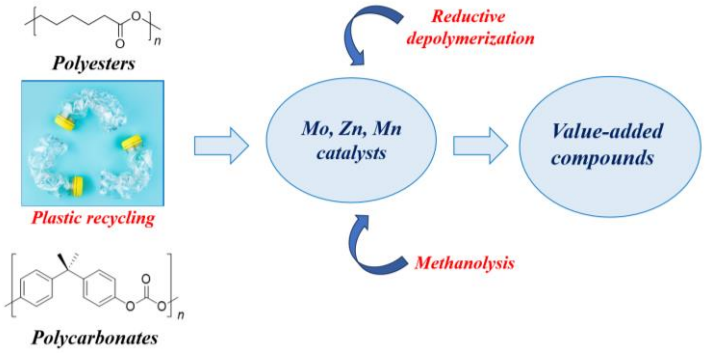

Figure 1: Plastic recycling using commercially available catalysts.

***Acknowledgements*:** This research was supported by Fundação para a Ciência e Tecnologia (FCT) through projects PTDC/QUI-QOR/0490/2020, UIDB/00100/2020, UIDP/00100/2020 and LA/P/0056/2020. DLL thanks to FCT for the grant (2022.11513.BD).

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Active polymeric filtration membranes with siderophore for iron(III) removal from aqueous systems

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The excess of iron(III) in industrial effluents and in the blood is an issue. Not only the iron catalyzes the oxidation of organic compounds from living beings but also forms highly insoluble precipitates of iron(III) oxyhydroxides [1]. Then, that solid's deposits interfere with the fluidic systems' normal flow.

One way to solve this problem is to dop filtration membranes with active agents such as siderophores to enable the chemisorption of the iron(III) present in the samples during filtration. It was chosen compounds of the hydroxamic acid family, with long alkyl chains for that purpose. They are known to have very high complex formation constants [2]. The addition of an alkyl chain to the hydroxamic acid was the strategy found to improve the lipophilicity of the siderophore, avoiding its leaching from the polymeric membrane structure during the nonsolvent-induced phase inversion process.

Those membranes, with the siderophore included, were prepared by spin-coating. They were then characterized with respect to their siderophore contents, porosities, and maxima water flow. Their specific iron(III) absorptions were analyzed in static and dynamic conditions.

The results suggest an excellent inclusion of the siderophore in the membrane structure. Under batch conditions, the iron(III) absorption was superior to the 1:1 iron/ligand proportion.

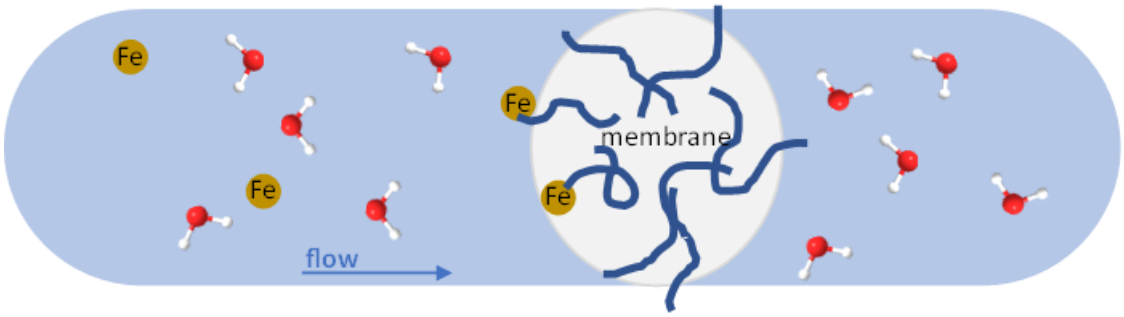

Figure 1: Graphical Abstract – the iron(III) capture by the hydroxamic acid functional groups included in the membrane.

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Pd-Catalyzed cycloaddition of bicyclic aziridines with isocyanates for imidazolidinone synthesis

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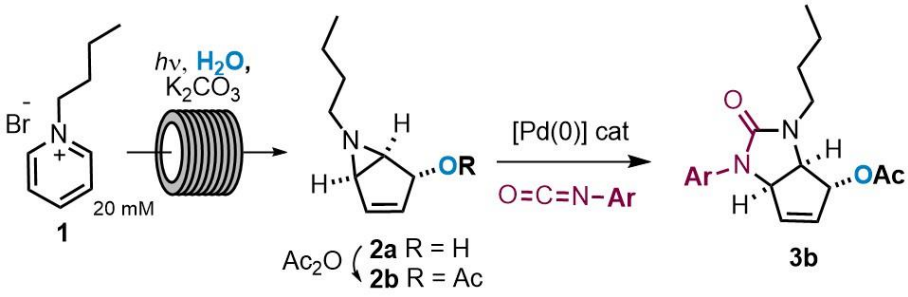
Nitrogen-containing heterocycles can have several applications in the pharmaceutical industry since they contain a wide spectrum of biological activities. Imidazolidinones have shown activity against leukemia, lung cancer and metabolic disorders [1]. These cyclic urea frameworks can be obtained through transition-metal-catalyzed intermolecular cycloaddition using an aziridine moiety as starting material. These reactions often provide effective one-step procedures that result in heterocyclic derivatives, that are challenging to access through conventional approaches [2,3].

We have previously described the photoreaction of pyridinium salt **1** into the corresponding bicyclic aziridine **2a** under continuous-flow [4,5]. Additionally, we reported that palladium-catalyzed ring opening of bicyclic aziridine **2a-b** with active methylenes presented a new S_N2' selectivity [6]. In this study, the reaction between bicyclic aziridine **2b** and several isocyanates, in the presence of Pd(0)-catalyst is presented (Scheme 1). The reactions proceed through ring opening of the aziridine moiety, with the formation of the π-allylpalladium complex, followed by cyclization via nucleophilic addition of nitrogen to the isocyanate, affording regioselectively imidazolidinones **3b**.



Scheme 1: Pd-catalyzed reaction of bicyclic aziridine **2b** with isocyanates.

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The chemistry of malvidin 3-*O*-glucoside and malvidin 3,5-*O*-diglucoside networks from acidic and basic paradigms. The irreversible reactions.

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While in acidic medium the chemistry of anthocyanins is well known, their behavior in basic medium remains scarcely studied. In the present work malvidin mono and di glucoside were selected to perform a holistic approach by extending the anthocyanins studies to the basic medium [1]. There is no continuity in the chemical reactivity of anthocyanins between the acidic and basic paradigms. They are separated by a pH range (transition pHs), that includes the physiological pH (7.4), where irreversible reactions are faster than hydration and OH^- nucleophilic addition. In acidic medium, the kinetics of the flavylium cation (at pH≤1) toward the reversible equilibrium at higher pH values, exhibits for both compounds, three kinetic steps well separated in time: proton transfer (sub-microseconds), hydration followed by tautomerization (seconds to minutes), and cis-trans isomerization (hours). All these processes are much faster than the degradation rates. In basic medium, after the formation of the respective anionic quinoidal bases (sub-microseconds), the rate-controlling step toward the reversible equilibrium for both compounds is the OH^- nucleophilic addition, for the monoglucoside with a rate 0.045[OH-] s^{-1}. However, in the case of the diglucoside, the anionic quinoidal base equilibrates in a few seconds with a kinetic product B_4^{2-} (kinetic reservoir) detected by its kinetic signature in stopped-flow measurements and identified by ^{1}H NMR. The observed rate constant toward the equilibrium is thus the product of the mole fraction of the respective anionic quinoidal base (A^-) available from the equilibrium with B_4^{2-} (pK_{obs}=10.7) multiplied by 4.5[OH-] s^{-1}. In the transition pHs of the monoglucoside only quinoidal bases are observed, their degradation rates are faster than hydration and OH^- nucleophilic addition, preventing the system from reaching the equilibrium. Besides the loss of glucose to give the more unstable aglycone (a minor degradation route), there is experimental evidence based on HPLC-DAD-MS and NMR, for degradation products resulting from the initial formation of colored malvidin-3-*O*-glucoside dimers that yield subsequent oligomers (**Figure 1**). In the case of the diglucoside, the transition pHs region is narrower than the one of the monoglucoside. In this pH interval, the kinetics toward the equilibrium goes together with the degradation processes and is affected by the equilibrium established with B_4^{2-}. No evidence for colored product formation was achieved.

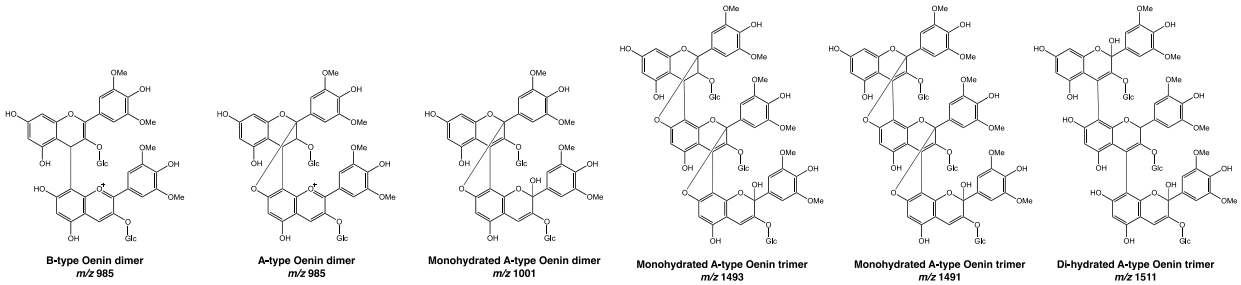

Figure 1: Putative structures for degradation products of M3G based on LC-MS/MS data.

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Lewis base-catalyzed reactions of chromans and allenoates: Access to structurally diverse chroman frameworks

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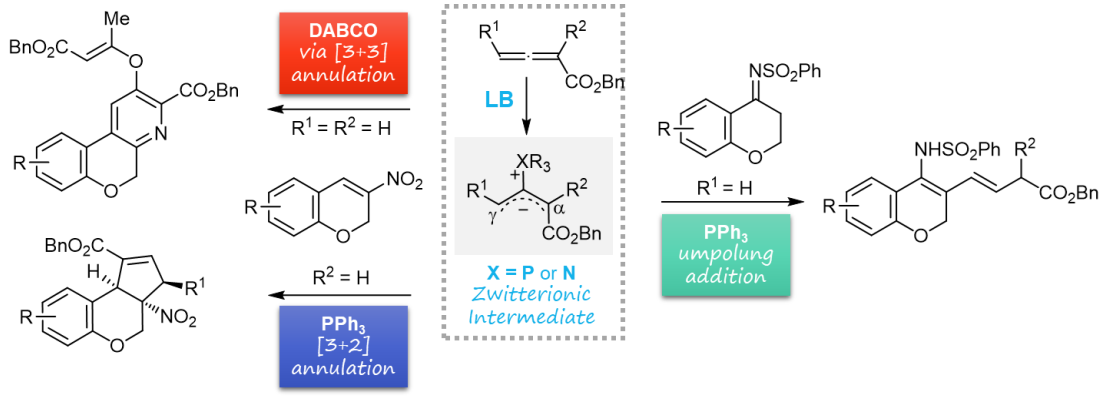
Allenic esters (allenoates) are attractive building blocks, as their chemical behavior can be modulated by selection of the appropriate Lewis base (LB) catalyst. The zwitterionic intermediate generated by the addition of a LB to the β-carbon of an allenoate can react differently with electrophiles such as activated alkenes and imines, depending on the nature of the catalyst [1]. Under phosphine catalysis [3+2] annulation products are obtained, whereas in the presence of tertiary amines, conjugate additions are observed. On the other hand, allenoates react with nucleophiles to give Michael-type adducts. However, in the presence of a catalytic amount of a phosphine, umpolung addition is observed, giving γ-adducts. Our group has been interested in the LB-catalyzed reactions of allenoates and chroman-based substrates as an approach to the construction of structurally diverse chroman scaffolds, systems that can be found at the core of a wide variety of natural products and synthetic analogues with remarkable biological activities [2]. Fused-chroman systems were obtained via phosphine-catalyzed [3+2] or DABCO-catalyzed [3+3] annulation reactions of allenoates and 3-nitro-2*H*-chromenes [3,4], while substituted 2*H*-chromenes were obtained by phosphine-catalyzed umpolung γ-addition of chroman-4-imines to allenoates (Scheme 1). In this communication, our latest studies on the LB-catalyzed reactions of allenoates and chroman substrates bearing activated alkene or imine functionalities will be presented.



Scheme 1: LB-catalyzed reactions of 3-nitro-2*H*-chromenes and chroman-4-imines with allenoates.

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Easy access to functionalized sparteine via electrochemical cyanation in batch and in flow of quinolizidine alkaloids

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Quinolizidine alkaloids (QA) are largely abundant in the Leguminosae family, especially in the genera Lupinus [1]. Maulide and Afonso's groups developed a process for the extraction of lupanine from *Lupinus albus* seeds wastewater and the preparation of (+)- and (-)- sparteine [2]. These natural products are known for their pharmacological activities, which includes antimicrobial, antihypertensive, antimuscarinic and antidiabetic, as hyperglycemia agents, effects on the central nervous system and uses 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 in asymmetric synthesis and, due to the continuous flow advantages, herein we present a new methodology for the cyanation of lupanine (Figure 1) under batch and flow conditions.

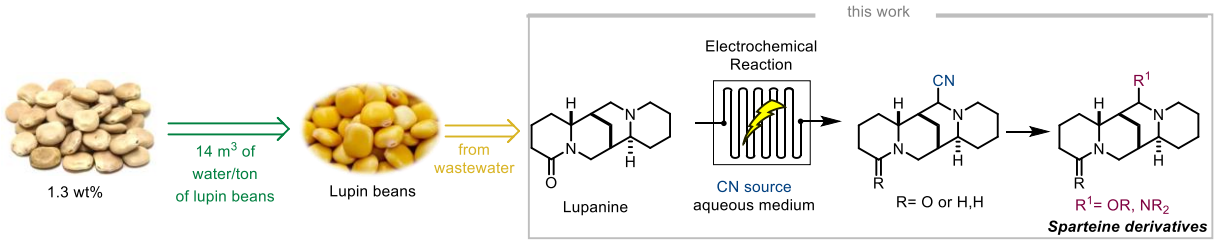

Figure 1: Electrochemical functionalization of quinolizidine alkaloids.

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Synthesis of new conjugated elongated tryptanthrin derivatives for optoelectronic devices

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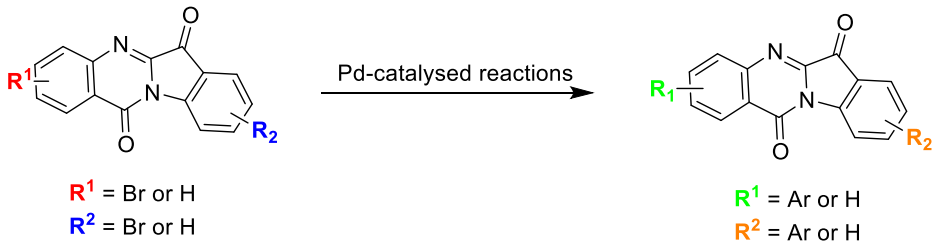
Tryptanthrins are a class of golden yellow compounds formed by quinazoline ring fused to an indole moiety with carbonyl groups in the 6- and 12-positions.[1,2] Many tryptanthrin derivatives, both natural and synthetic, have been reported.[1,3]

The possibility of introducing different functional groups in their core makes these compounds versatile building blocks for various applications. In this work, we demonstrate the possibility of π-expansion of the tryptanthrin core through Pd-catalyzed reactions (Scheme 1) to evaluate their photophysical properties for optoelectronic devices.



Scheme 1: Synthetic route for new Tryptanthrins derivatives

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Wild-type p53 modification by a tryptophanol-derived oxazoloisoindolinone

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The protein p53 is responsible for the genome integrity of cells. In human cancers, its tumor suppressor function is inactivated, either due to mutations in the *TP53* gene or due to inhibition by negative regulators.[1] So, there is a high interest to reactivate the tumor suppressor functions of p53. Currently, there are only ten inhibitors of MDM2 (negative regulator of p53), one dual inhibitor of MDM2 and MDM4 and two reactivators of the R175H mutant p53 in clinical trials, but no small molecule is available for clinical use.[1] On the other hand, modifying proteins is of great significance because it allows us to modulate their functions, stability and even their drugability.[2] In the last years, our research group has been involved on the development of tryptophanol-derived oxazoloisoindolinones to target wild-type (wt-) p53.[3,4] Following a hit-to-lead optimization process, we identified a lead six-fold more active than the hit molecule in HCT116 cells. Moreover, the lead as increased selectivity for HCT116 $p53^{+/+}$ cells over HCT116 $p53^{-/-}$ cells and has low toxicity in normal cells.[3]

In this communication, we will disclose our latest results on the optimization of the developed tryptophanol-derived oxazoloisoindolinone scaffold and study of the mechanism of action of the lead compound (Figure 1). The tryptophanol-derived oxazoloisoindolinones were obtained in their enantiopure form in good yield (68-84%) starting from (*S*)- or (*R*)-tryptophanol with oxo-acids in toluene under reflux using a Dean-Stark apparatus. The lead compound was tested against wt-p53 using a differential scanning fluorimetry (DSF) assay, and the covalent modification of multiple cysteine residues of wt-p53 was confirmed by high resolution mass spectrometry (HRMS). The optimization processes of expression/purification of the hexa-histidyl (6xHis)-p53 fusion protein and cleavage of the N-terminal 6xHis-tag to obtain the wt-p53 will be addressed. Finally, prospects for testing this compound with mutant forms of p53 will also be discussed.

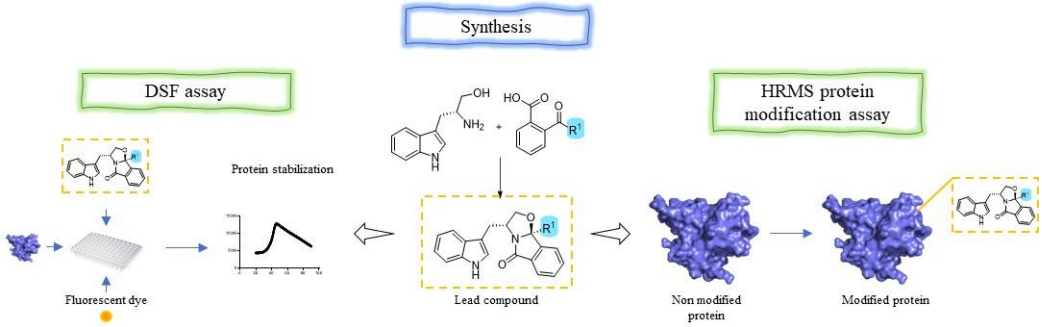

Figure 1: Overview of the assays

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Sphaerococcenol A: Extraction, analogue synthesis, and antitumor assays

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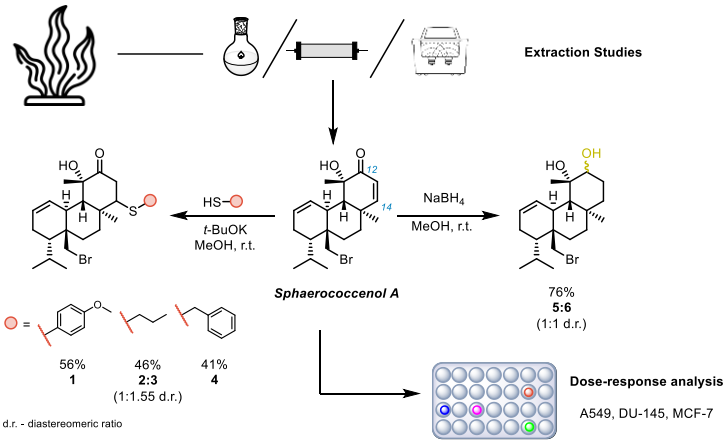
The drug discovery road is entailed with high failure rates, despite substantial investments of time and funds. Natural Products (NP) are known for their structural complexity, and the inspiration they pose for scientists to develop new scaffolds with bioactive relevance. Moreover, Marine Natural Products (MNP) are a source of approved drugs with growing interest, but still underexplored mainly due to access challenges [1].

Sphaerococcenol A is a MNP found in the red alga *Sphaerococcus coronopifolius*, first isolated by Fenical and co-workers in 1976 [2]. Since its discovery, it has been explored as an antitumor, antimicrobial, and antimalarial compound [3]. Despite the demonstrated medicinal potential, no attempts for synthesis of analogues were attempt since Cafieri in 1978 [4].

Herein, we detail the studies for more efficient isolation of Sphaerococcenol A from *Sphaerococcus coronopifolius*, spanning for different solvents and methodologies (batch, flow and sonics), and the synthesis of derivatives of Sphaerococcenol A. This was achieved through thiol-Michael additions, resulting in the creation of four new analogues (Scheme 1, **1-4**), and through enone reduction, yielding two new additional analogues (Scheme 1, **5-6**), all with moderate yields. These analogues were submitted to a dose-response analysis on A549, DU-145 and MCF-7 cell-lines in order to evaluate their cytotoxic effects.



Scheme 1: Sphaerococcenol A extraction studies, analogues synthesis and dose-response analysis on A549, DU-145 and MCF-7 cell lines.

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Study of the action of a tryptophan metabolite, 8-hydroxyquinoline-2-carboxylic acid, and its Ga(III) complex on microbiota exposed to ionizing radiation

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Cancer patients submitted to radiotherapy often suffer from severe side effects, which can also arise from imbalance of the normal metabolic pathways. Tryptophan (Trp) is an essential amino acid, with the three major Trp metabolism pathways leading to serotonin, kynurenine, and indole derivatives being under the direct or indirect control of the microbiota. A few gut microbes have been shown to produce kynurenine derivatives and a recent work showed that kynurenic acid provided long-term radioprotection *in vivo* [1]. Furthermore, there is evidence that changes in the plasma metabolome and microbial metabolite levels can be associated with disease progression and severity [2]. This study aims to the understanding of the ability of 8-hydroxyquinoline-2-carboxylic acid (8-HQA, an end product of kynurenic Trp metabolic pathway), and the corresponding 2:1 ligand-to-metal Ga(III) complex $[Ga(8\text{-}HQA)_2]^-$ in the protection of different human microbiome bacteria against ionizing γ-radiation. The bacterial isolates included *Actinomyces viscosus*, *Streptococcus mutans*, *Streptococcus sobrinus*, *Pseudomonas putida*, *Pseudomonas fluorescens*, and *Escherichia coli*. An assessment of the susceptibility of each microbe to the compounds was initially accomplished by the disk diffusion method. The microbial inactivation kinetics by gamma radiation was assessed by the irradiation of suspensions of the bacteria in the absence or in the presence of the compounds at a Co-60 experimental irradiation chamber. Preliminary results indicated that both ligand and complex can have a protective effect on the tested strains against ionizing γ-radiation, with an increase in the D_{10}-values (dose required for 90 % inactivation of the initial population). Also, the anti-inflammatory activity of the compounds was determined using the RAW264.7 cells (murine monocytes macrophage) to generate the pro-inflammatory molecule nitric oxide (NO), which can affect the inflammatory stimuli and immune disorders in the cancer patient. The preliminary results of this study will be presented and discussed, hopping to provide further insights on the safer application of radio- and chemo- therapeutics to fight cancer.

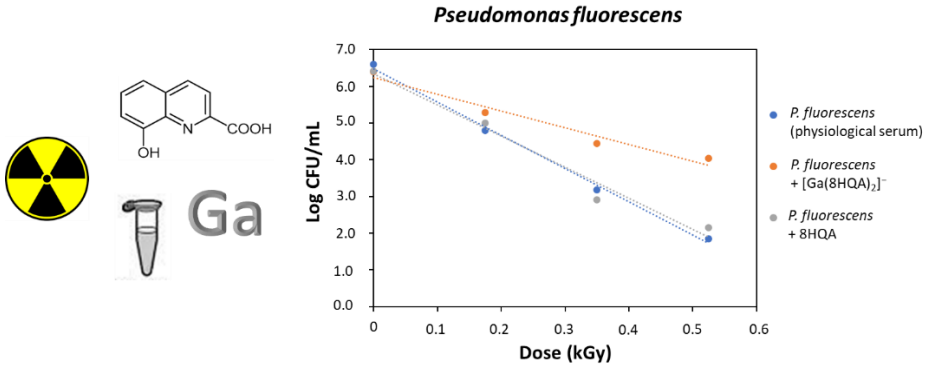

Figure 1: Inactivation kinetics of *Pseudomonas fluorescens* by gamma radiation in physiological serum and in the presence of the compounds, 8HQA and $[Ga(8HQA)_2]^-$.

Funding: This work is supported by FCT through project 1801.P.00979.1.01-UIDB/04349/2020 and the National Science Centre (NCN), Poland, under the scope of the research project number 2020/39/B/ST4/03060.

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Incorporation of unnatural alpha,alpha-dialkylglycines in polymyxins: synthesis and characterization

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Lower respiratory infections caused by Gram-negative pathogens classified by the WHO as priority targets (e.g. *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*) pose a great concern as they are often mediated by recalcitrant polymicrobial biofilms and multidrug resistant (MDR) strains. Current antibiotics, and antibacterial agents in clinical development, remain ineffective against these bacteria and do not even address the biofilm problematic [1,2]. Polymyxins (PMs) have recently been rehabilitated as last-resort drugs against MDR Gram-negative bacteria but their high efficacy is counteracted by serious side effects such as nephro- and neurotoxicity. Unfortunately, resistance to PMs has already emerged in response to their increased use, rendering some infections untreatable [3]. These issues have raised the interest in developing new PM derivatives to improve activity, including against biofilms, reduce side effects, and better understand their structure-activity relationships.

Bearing this in mind, polymyxins B (PMB) and E (PME), which are the two PMs in clinical use, were chosen as starting point for the design, synthesis, and characterization of novel analogues with tuned core scaffolds by incorporation of unnatural alpha,alpha- dialkylglycines at selected positions of the cyclic heptapeptide in the PM structure, directed by *in silico* studies. We now report the synthesis of alpha,alpha-diisobutylglycine (Dibg) and alpha,alpha-dibenzylglycine (Dbng), by an Ugi multicomponent reaction [4], the preparation of six PMB and PME analogues (Figure 1) by microwave-assisted solid phase peptide synthesis, and their characterization by the usual spectroscopical characterization techniques.

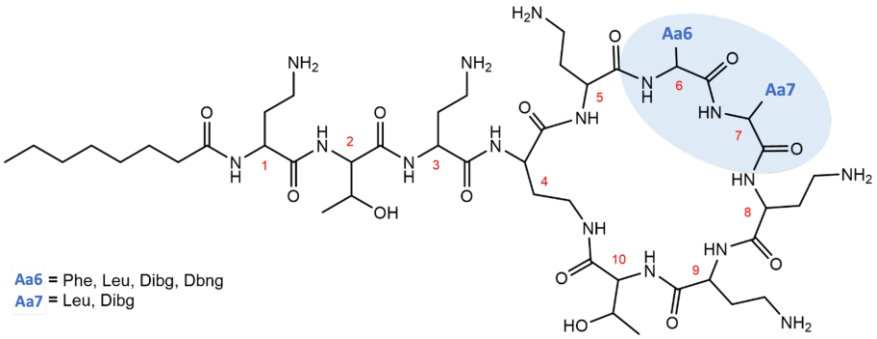

Figure 1: PMB and PME structural modification at positions 6 and 7 (in blue).

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Searching novel therapeutic targets against MRSA: a mass spectrometry multi-omics approach

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of nosocomial infections, with high mortality due to drug resistance. The limited availability of effective MRSA treatments demands innovative drugs, so understanding resistance mechanisms is critical [1]. A multi-omics mass spectrometry (MS)-based approach was employed to assess the impact of ampicillin, chloramphenicol, ciprofloxacin, methicillin, and vancomycin on MRSA's lipidome, proteome, and metabolome, affording a comprehensive insight into MRSA's drug resistance. Post-translational modifications (PTMs) were also investigated to gain insight into the underlying mechanisms of resistance.

Results show that MRSA's protein expression is robust, with small changes in response to these drugs, impacting DNA replication and peptidoglycan biosynthesis at both endo- and exoproteome levels. Quorum sensing dysregulations were also observed for ampicillin, ciprofloxacin, and vancomycin. Endoproteome alterations in DNA repair and glycerophospholipid metabolism, accompanied by the up-regulation of ABC transporters. Noteworthy, increased codY expression was observed as an adaptative antibiotic response.

Under vancomycin exposure, several PTMs alterations were observed, including deamidation, oxidation, acetylation, phosphorylation, and succinylation in specific proteins of MRSA. Notably, there was a decrease in deamidation PTM in a putative cell wall hydrolase, possibly indicating an inhibition of peptidoglycan hydrolysis. Simultaneously, the observed up-regulation of acetylation PTM in the large ribosomal subunit protein could indicate a compensatory response to stress. These changes suggest adaptations affecting cell wall integrity and stress response pathways.

Both drug-specific and common metabolomic changes were observed. All antibiotics interfere with the glycan and peptidoglycan pathways and have a wide effect on energy and nucleos(t)ide pathways. Interestingly, all drugs except ciprofloxacin dysregulate molybdopterin and folate biosynthesis, as well as the acetyl-CoA related pantothenate and mevalonate pathways. The pantothenate and mevalonate pathways, crucial for cell wall biosynthesis and energy metabolism, are also altered at the exometabolome level. Additionally, ampicillin, methicillin and vancomycin specifically induce changes in the biosynthesis of peptidoglycan, underscoring their role in cell wall biosynthesis. Lipidomics revealed drug-dependent alterations in lipid profiles, at the menaquinone biosynthesis level, indicating an impact on the electron transfer chain.

In summary, this combined MS-omics approach provides a comprehensive analysis of MRSA's resistance against diverse antibiotics (Figure 1). These alterations not only contribute to understanding resistance pathways but also to identifying novel targets to overcome MRSA resistance by exploiting the cellular pathways part of the system-wide MRSA response to current drugs.

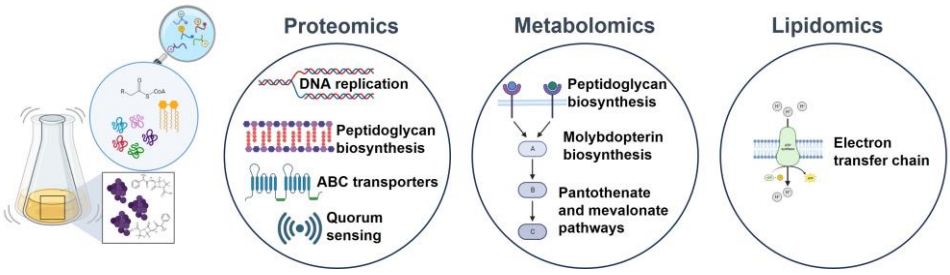

Figure 1: Multi-omics mass spectrometry reveals MRSA resistance mechanisms and potential drug targets.

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Layer-by-layer supramolecular assembly of alginate/pyranoflavylium-modified chitosan acidochromic biomembranes

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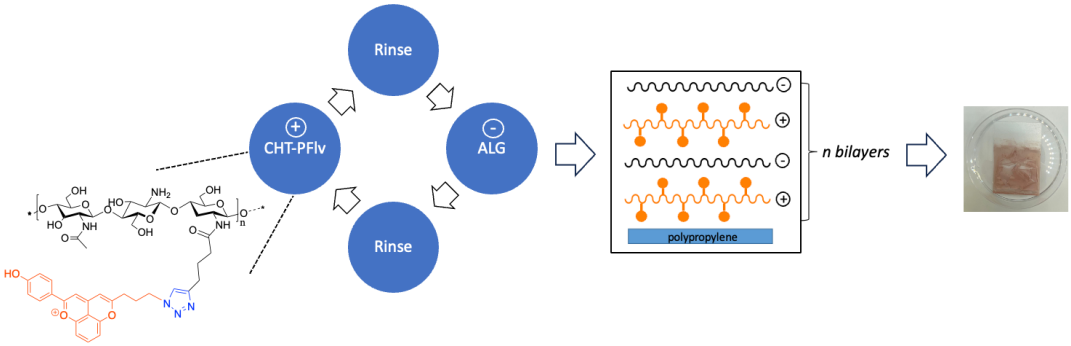
Food waste reduction as well as food safety increase have been increasingly concerning consumers worldwide.

To that end, the development of active and smart packaging technologies to provide both food shelf-life extension and real-time monitoring of their freshness states has been investigated. Biopolymers incorporating pH-sensitive dyes have been extensively studied to develop pH-freshness labels or membranes, since pH variation could be directly correlated with the formation of food metabolites (e.g., organic acids, biogenic amines) during the spoilage event [1-3].

In this work, the fabrication of sustainable, acidochromic and free-standing multilayered membranes using pyranoflavylium-based pH-sensitive dyes and marine-origin biopolymers for sensing food spoilage was pursued. To this purpose, an azide-containing pyranoflavylium-type dye was rationally synthesized and further used for the functionalization of alkyne-modified chitosan through copper-catalyzed azide-alkyne cycloaddition (CuAAC). Afterwards, the positively charged pyranoflavylium-chitosan conjugate (CHT-PFlv) was combined with negatively charged alginate (ALG) to fabricate multilayer membranes through electrostatic interactions using Layer-by-Layer (LbL) supramolecular assembly methodology (Scheme 1). The interaction behavior and deposition process was firstly monitored by quartz crystal microbalance with dissipation (QCM-D) equipped with gold substrates, and then the biomembranes were built up using a home-made dip coating robot. The films were submitted to physical-chemical characterization, while pH-responsive chromatic studies in simulated metabolite-rich solutions and in real food samples are ongoing.



Scheme 1: Fabrication of multi-layered ALG/CHT-PFlv biomembranes through LbL technology.

Funding: This work was supported by the Associate Laboratory for Sustainable Chemistry, Clean Processes and Technologies LAQV and financed by national funds from UIDB/50006/2020.

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Pharmaceutical ionic (nano)systems: a sustainable approach for infection diseases

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Infectious diseases are considered the second major cause of death worldwide and the antibiotic treatment sometimes fails due to drug resistant strains or to inadequate concentration of antibiotics at the site of infection. Currently, it is important to discover sustainable and efficient solutions for the associated problems of different pharmaceutical drugs such as polymorphism, drug resistance and reduced bioavailability. The combination between APIs and biocompatible counter-ions seems a very attractive research topic to be explored [1]. In last years, our research team already reported examples of pharmaceutical ionic systems (ionic liquids & organic salts; API-OSILs) based on anti-inflammatory, antibiotics, anti-tumoral and anti-tuberculostatic with significant advantages comparing with original APIs [2-5]. Although these recent developments, API-OSILs seem to be a suitable drug delivery system for APIs by improving bioavailability (solubility, permeability) and eliminate polymorphism. Herein, we will present our latest developments in the field of API-OSILs including the synthesis and characterization of novel Silica Nanoparticles combined with pharmaceutical ionic systems as very promising nanomaterials to treat bacterial infections [6]. The present methodology can be extended to engulf a broader range of antibiotics, together with different combinations of ionic liquid precursors, which makes the current protocol a very attractive alternative to the production of novel pharmaceutical ingredients immobilized on nanoparticles, with high emphasis on the fight against bacterial resistance.

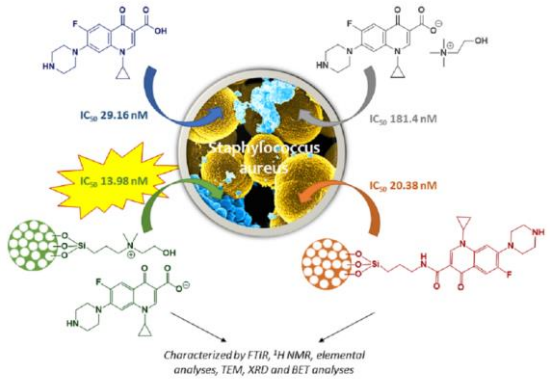

Figure 1: General approach for Pharmaceutical Ionic (Nano)Systems

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Radicals at very low temperatures: Monitoring reactions and interactions through IR spectroscopy

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Radicals are intermediates in a wide range of chemical reactions. With at least one unpaired electron, these chemical species, and their complexes with small solvent molecules are often difficult to detect and characterise due to their short lifetimes. Nowadays, these typically short-lived species can be studied immediately after their generation, in general in short time frames, or alternatively, be trapped under special environmental conditions of temperature that allow further insight into their structures using spectroscopic tools [1-3]. Experimental methods such as low-temperature matrix isolation coupled with infrared spectroscopy, afford advantageous conditions for the direct detection and characterisation of reactive intermediates in general, including radicals, and has provided many contributions to the field of mechanistic chemistry.

In this talk, we report the investigation of several photo-induced reactions that proceed by mechanisms involving elusive radical intermediates, and we highlight non-covalent interactions between radicals and small solvent molecules, which were monitored at low temperatures by infrared spectroscopy and quantum chemical calculations. Moreover, the spectral predicting power of several quantum chemical methods and their ability to tackle the open-shell electronic structure are also highlighted in this talk.

Figure 1: Schematic representation of a matrix-isolated radical in an inert environment.

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Revealing the potential of phthaloperinones as key optoelectronic components for electronic devices

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Since the electronics revolution in the 20th century, the search and development for new and more efficient electronic devices have been one of the major focuses of our society. These technological advancements have been crucial to improve our quality of life, bringing comfort and pleasure [1] .

Recently, among a plethora of potential compounds, phthaloperinones emerged as promising materials for application in organic electronics due to their unique molecular structure and exceptional electrochemical properties. Additionally, their inherent stability under natural conditions and responsiveness to light make them an attractive alternative for organic based optoelectronic devices [2,3].

In this communication, we present the synthesis of optoelectronic active phthaloperinone derivatives. Electro-, photochemical and computational studies were performed revealing the promising optoelectronic properties of these compounds. These small molecules were used to fabricate electronic device structures, including OLEDs and heterojunctions (Figure 1). The electrical characterization of these devices was used to measure basic material parameters such as charge carrier mobility.

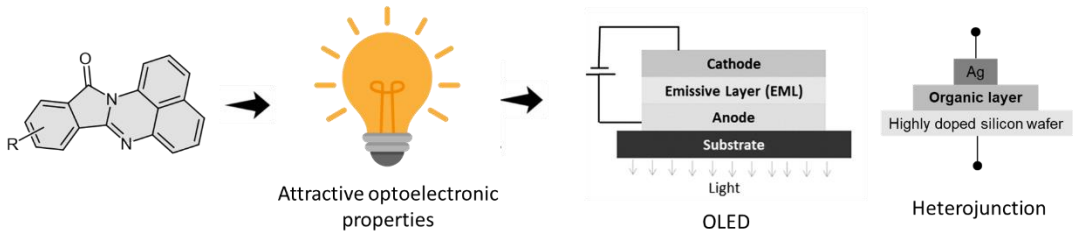

Figure 1: Application of phthaloperinones in OLEDs and heterojunctions.

Funding: This work is financed by national funds through FCT, within the scope of the project ConChiMOL- New Structurally Contorted and Chiral Molecules for Optoelectronic Applications, (2022.01391.PTDC).

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Synthesis of *C*-glycosyl quinolones, acridones and related compounds: Classical *versus* ohmic heating conditions

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4-Quinolones and acridones, also known as quinolin-4(1*H*)-ones and acridin-9(10*H*)-ones, respectively, have a remarkable ability to target type IIA topoisomerases, as DNA gyrase and topoisomerase IV, enzymes involved in DNA replication and repair, being regarded as promising anticancer compounds. Some studies have shown their ability to induce cell cycle arrest, inhibit cell proliferation, and promote apoptosis in cancer cells [1]. In turn, the attachment of a carbohydrate to a compound, can enhance its biological properties, including anticancer activity, by improving solubility, bioavailability, and targeted delivery to cancer cells [2]. The anticancer effects of glycosylated quinolines have been studied, *in vitro* and *in vivo*, and improved selectivity towards cancer cells, sparing normal healthy cells to some extent, was observed [3]. Although quinolones are compounds closely related to quinolines, as far as we know, there are no studies about the evaluation of the anticancer activity of glycosyl quinolones.

In this context, we have been interested in the synthesis of novel *C*-glycosyl quinolones **1** and **2,** *C*-glycosyl acridones **3** and related compounds **4** (Figure 1), for further evaluation of their potential as anticancer drugs. *C*-glycosyl quinolones **1** and **2** were synthetized by a palladium(Pd)-catalyzed Heck reaction of a 3-iodoquinolone with a vinylsugar derivative. Depending on the reaction conditions, in the synthesis of **2** different compounds **2** and/or **3** can be obtained. In our group, we have been using ohmic heating to promote Pd-catalyzed reactions with success [4]. However, the effects of ohmic heating parameters in this kind of reactions remain unexplored. In this work, the effects of frequency and waveform on the heating profile, yield and selectivity of the Heck reaction were studied and we compared the best ohmic heating conditions with classical heating conditions. Furthermore, *C*-glycosyl quinolones **1** were used as building blocks for the synthesis of acridone related compounds **4** by an ohmic heating assisted Diels-Alder reaction with different maleimides, in aqueous medium. More details about the developed methods for the synthesis of these compounds will be presented and discussed in this communication.

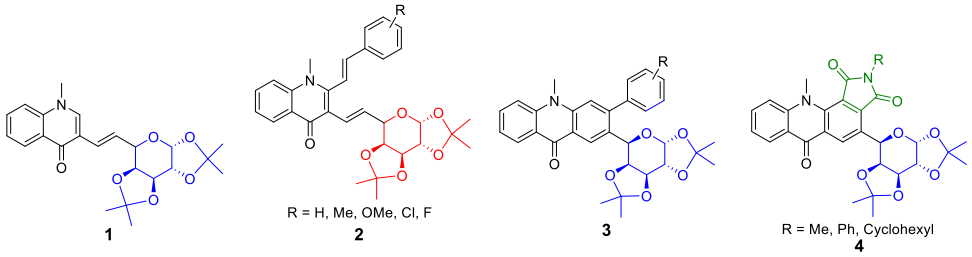

Figure 1: Structures of *C*-glycosyl quinolones **1** and **2**, *C*-glycosyl acridones **3** and related compounds **4**.

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Efficient visible-light-driven imines synthesis using carbon nitride photocatalyst

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Imines are essential intermediates in synthesizing biological *N*-containing compounds, valuable chemicals for several industrial processes. Because of their wide application, the synthesis of imines has been gaining tremendous attention in recent years. The conventional method of synthesizing imines involves the condensation of amines with reactive carbonyl compounds, which often requires Lewis's acid catalysts, expensive dehydrating agents, and additional heating, leading to the generation of considerable undesirable chemical wastes. New routes for green synthesis of imines leading to more sustainable strategies start to gain importance in the new chemical industry paradigm.

Metal-free carbon nitride (g-C_3N_4) based photocatalysts exhibit advantages like low preparation costs, easy availability of necessary raw materials, wide spectral response ranges, high physiochemical stability and flexible functionalization possibilities. The g-C_3N_4 synthesis process has a reduced environmental impact compared with the conventional metal oxide catalysts because it does not involve harsh chemicals or severe temperature and pressure conditions.

In the present work, we describe the use of exfoliated carbon nitride (GCN-T) photocatalyst prepared by a facile and cost-effective method as a visible-light catalyst for the photocatalytic oxidative coupling of amines to prepare imines with high selectivity. To increase the catalyst activity toward imine synthesis, the reaction conditions, such as the solvent, the atmosphere and the wavelength emission of the irradiation source, were optimized. After 30 minutes of reaction, a maximum output of *N*-benzylidenebenzylamine (0.45 mM) was obtained with 99% selectivity using acetonitrile as solvent under visible LED (λ_{max} = 417 nm) irradiation. To clarify the photocatalytic mechanism, the main active species in the reaction process were determined by quenching experiments (Figure 1). In addition, a series of Electronic Paramagnetic Resonance (EPR) experiments acutely explored the nature of the photocatalytic reaction. Based on the EPR studies, it was found that the main photogenerated species formed during the production of the imine were superoxide radicals, singlet oxygen, and other radicals, which corroborate the results reported in the literature. The by-products generated in the process were also identified, and a complete reaction pathway was proposed [1].

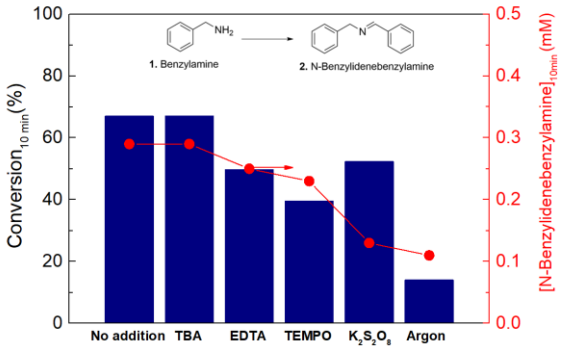

Figure 1: Conversion of benzylamine and *N*-benzylidenebenzylamine concentration after 10 minutes of visible light irradiation in the presence of different scavengers and argon instead of air.

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Furan-based asymmetric diketopyrrolepyrrole dyes: Optimization of acceptor unit for Dye-Sensitized Solar Cells

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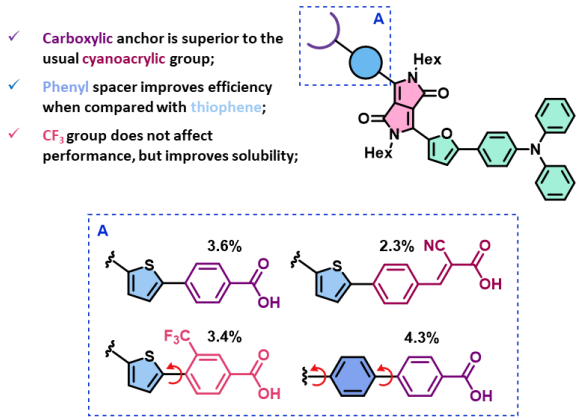
Diketopyrrolopyrroles (DPPs) are a recent class of pigments that have garnered much attention as of late, owing to their excellent stability, light-harvesting ability, and charge-carrier mobility. Additionally, their great synthetic versatility[1] has granted access to thousands of derivatives employed in a wide variety of applications, with the fields of photovoltaics and organic semiconductors being standouts[2].

All the above make DPP dyes particularly appealing for use in Dye-Sensitized Solar Cells, a promising solar technology that excels in indoor and flexible applications. In fact, several high performing dyes have been reported in the literature, with efficiencies of up to 10%[3]. A clear trend among these is the superior performance of DPPs with asymmetric aromatic substituents, given their improved charge separation. Since five-membered heteroaromatic groups significantly red-shift the absorption and increase the molar absorptivity, we devised new sensitizers possessing a furan ring as a substituent, which is comparatively scarce in the literature.

As shown in **Scheme 1**, we set out to investigate the effect of several modifications on the acceptor and anchoring units, such as the use of a simple carboxylic group in place of the often employed cyanoacryllic anchor. Finally, we replaced the thiophene with a phenyl group in one example and introduced a trifluoromethyl substituent ortho to the thiophene in another, with the goal of twisting the geometry of the acceptor/anchor and hopefully supress recombination of the injected electrons with the oxidized dye. The photovoltaic performance of the dyes was evaluated/compared using two different electrolytes and rationalized based on their respective photophysical and electrochemical properties, as well as DFT optimized geometries.



Scheme 1: General architecture, acceptor structures and respective efficiencies of the four prepared DPP dyes

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Mechanosynthesis of chiral oligosulfides by inverse vulcanization

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The valorisation of industrial waste by-products is of enormous importance since impacts on both sustainability and circular economy. From this perspective, the development of new products from residues, especially with high added value, is not only challenging but economically attractive. Sulphur has been known since Antiquity and is an unwanted by-product of the petrochemical industry, with a worldwide production estimated in 78 million tonnes in 2020 [1]. Similarly, limonene is a well-known cyclic monoterpene that is obtained as a by-product from the citrus juice industry, by cold pressing or distillation from orange and lemon fruit peel, reaching a production around 60 thousand tonnes/year [2]. The preparation of polysulfides by inverse vulcanization, a process where elemental sulphur (S_8) is a comonomer and reaction medium, has been explored in the last decades [3]. Mechanosynthesis is an emergent green technology that can be applied under solventless or vestigial solvent conditions. Major advantages lie in waste reduction and lower energy consumption, without compromising or enhancing reaction conversion [4].

An iron-free mechanochemical-assisted limonene inverse vulcanization is reported. The process makes use of only limonene and sulphur, under mild conditions and short time using a zirconium oxide reactor and a planetary ball mil. The obtained high value products are light yellow solids, readily soluble in chloroform, optically active oligosulfides (Figure 1), which are different from polysulfides reported under conventional conditions (*ca.* 185 ºC), as confirmed by NMR spectroscopy and mass spectrometry. A general reaction mechanism is proposed, initiated by homolytic sulphur ring opening triggered by mechanical stress, and involving thiirane intermediates, via an addition-elimination reaction of sulphur to the limonene double bonds.

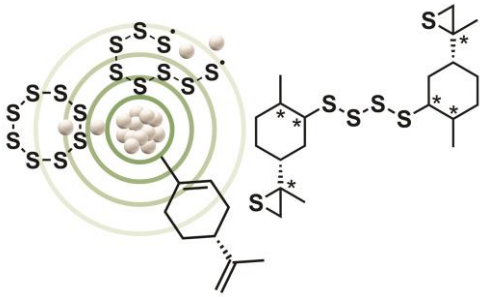

Figure 1: Example of a chiral oligosulfide obtained via mechanically assisted limonene inverse vulcanization.

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Photocatalytic oxidation of bio-based heterocyclic compounds

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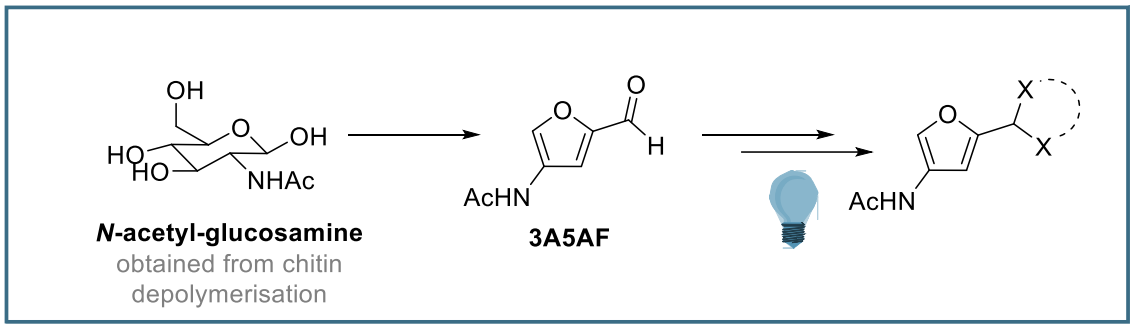
The demand for novel biomass-derived fine and commodity chemicals has driven the exploration of innovative methodologies and synthetic building blocks based N-heterocyclic compounds have proven to be highly versatile, finding applications in various fields such as natural compound production and coordination chemistry. In this context, the photochemical oxidation of heterocycles emerges as a versatile and valuable approach for accessing a wide range of oxidized derivatives. By utilizing light energy and a photocatalyst, this process selectively oxidizes organic compounds that contain heteroatoms within ring structures. Excited states of the heterocyclic compound engage in electron transfer with the photocatalyst, leading to the generation of radicals. These radicals actively participate in oxidation reactions with molecular oxygen or other oxidizing agents, ultimately yielding a variety of oxidized products. Notably, recent advances have introduced visible light-active, porous organic, and metal-free materials as photocatalysts in various photoredox applications [1]. These advancements enhance the versatility and efficiency of the photochemical oxidation process.

Chitin, an abundant waste byproduct, is a biopolymer composed of N-acetyl-glucosamine (NAG) units, which serve as a valuable source of bio-renewable nitrogen. In this study, we developed a novel photocatalytic oxidation route for heterocycles derived from 3-acetamido-5-acetyl furan (3A5AF), a fascinating N-rich furan obtained from chitin biomass [2]. Through our photocatalytic approach, we have successfully harnessed the potential of 3A5AF and its nitrogen-rich composition. By utilizing appropriate photocatalysts and leveraging light energy, we achieved the selective oxidation of heterocycles derived from 3A5AF [Scheme 1].



Scheme 1: Photocatalytic oxidation route for heterocycles derived from Chitin Depolymerisation

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Degradation products of plastic polymers as markers of microplastics

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Plastics are widely used inexpensive, light, and durable materials. These properties, together with a large and increasing production and improper management and disposal practices, generate a large amount of waste that accumulates in natural environments. The degradation of plastics proceeds at very slow rates in environmental conditions. However, the large surface of plastics exposed to environmental degradation processes releases considerable amounts microplastics, nanoplastics and organic compounds, which impact ecosystems and human health. Chemical transformation and sunlight-induced photodegradation are major degradation pathways of these materials.

We have been investigating the analysis and degradation of microplastics on natural surfaces [1], namely the release of organic compounds after chemical and photochemical reaction of plastics and microplastics on sand surfaces to evaluate the potential environmental contamination by these compounds. Chemical reactions have been studied applying 100 ºC and 250 ºC thermal treatments while the photoreaction studies have been made using a xenon arc lamp. Analyses have been conducted by SPME-GC-MS and LC-HRMS and using metabolomics tools.

Both, volatile and non-volatile compounds are released from polyethylene (PE) and polystyrene (PS) microplastics on silica and sand surfaces. Most released molecules are oxygen containing compounds indicating chemical and photochemical oxidation is taking place. Volatile compounds include aliphatic acids, aldehydes and ketones from PE and styrene and benzaldehyde from PS, among other. Non-volatile compounds include aliphatic dicarboxylic acids from PE and dibenzoylmethane and 3-phenyl propiophenone from PS, among other. As expected, the photochemical oxidation of PE is very slow due to the very weak absorbance by this polymer material.

Having identified compounds uniquely related with PE and PS polymers, we evaluated both, their presence in natural sand samples and their use as markers of the presence of PE and PS microplastics on sand natural surfaces. Analysis of samples revealed the presence PE and PS degradation products. Furthermore, the thermal treatment of natural samples releases markers of both polymers indicating the procedure can be used to detect microplastics in environmental samples.

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Bioorthogonal pretargeting for anchoring photoactive BODIPY on the plasma membrane of HER2$^+$ gastric tumours

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The early diagnosis of gastric cancer, the second most prevalent cause of cancer-related fatalities, will allow an increase in the survival rate. Until now, the most common diagnostic methods have been endoscopic ultrasound combined with immunohistochemistry and fluorodeoxyglucose (FDG) positron emission tomography–computed tomography (PET-CT). However, these techniques only give static information and are limited to certain types of gastric cancer [1,2]. Optical imaging using fluorescent probes as BODIPYs conjugated with monoclonal antibodies (mAbs) can be considered a complementary technique because it can increase the tumour contrast and selectivity [2]. Preparing fluorescently labelled immunoconjugates usually involves directly modifying the lysine residues, resulting in a complex mixture with a possible loss of affinity to the corresponding receptor [3]. The use of a bioorthogonal approach with inverse-electron-demand Diels–Alder (iEDDA) reactions between tetrazine (Tz) and mAbs modified with *trans*-cyclooctene (TCO) has already been explored *in vivo*, showing great selectivity and fast kinetics. This approach offers the opportunity to develop imaging agents directly within the living system, eliminating the need for prior mAbs modification. BODIPYs are highly stable fluorescent molecules and are already used for cell imaging [4]. The overexpression of human epidermal growth factor receptor 2 (HER2) in gastric cancer allowed it to be used as a tumour biomarker and therapeutic target. This study used a BODIPY bearing a tetrazine group (Figure 1) and the HER2-targeting antibody trastuzumab as pretargeting imaging agents to target HER2 receptors in gastric tumours. We also present preclinical findings testing the potential of a click approach for delivering a fluorescent probe to target HER2$^+$ gastric tumours *in vitro* and *in vivo*.

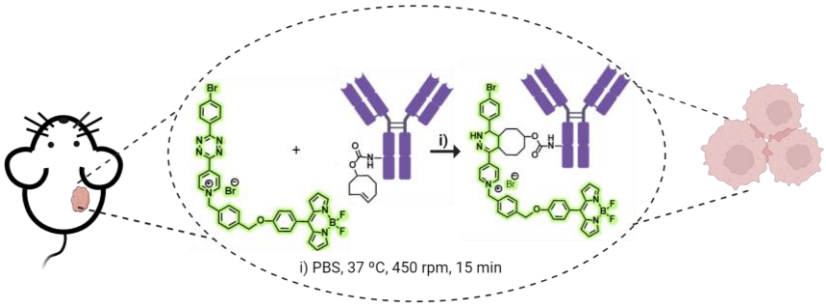

Figure 1: *In vivo* and *in vitro* bioorthogonal approach with BODIPY-tetrazine.

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Graphitic carbon nitride: new support for glucose oxidase immobilisation towards cancer therapy

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The enzyme glucose oxidase (GOx) has attracted increased interest in cancer therapy due to its unique catalytic properties against glucose. GOx catalyses glucose oxidation into gluconic acid and hydrogen peroxide (H_2O_2). On the one side, by cutting off glucose (an energy supply used for tumour growth), GOx can effectively starve the tumour cells to death. Conversely, the production of gluconic acid, H_2O_2, and the reduction of oxygen levels promote increased acidity, oxidative stress, and hypoxia, respectively, in the tumour microenvironment, all of which combined can have a synergic impact on cancer treatment. However, these GOx-based therapies are still restricted by the enzyme's low stability and poor blood circulation, which limits its application. The immobilisation of GOx onto nanoparticle catalysts is a viable and promising method to address these issues. That allows an increase in the enzyme's stability and kinetics and a targeted release of the enzyme in tumour areas, potentially improving treatment efficacy and minimising adverse effects [1].

This work aims to use thermally exfoliated graphitic carbon nitride (GCN-T) for the first time as support for GOx immobilisation for cancer therapy (Figure 1). Synthesised by earth-abundant elements (i.e., C, N, and H), GCN-T has outstanding biocompatibility, stability, photocatalytic activity, and tunable functionalisation, all of which provide a unique set of interesting properties for its use in various fields [2]. Different immobilisation conditions were optimised, such as GCN-T/GOx ratio, contact time between the enzyme and the nanomaterial, and pH. The results demonstrate the excellent performance of the GCN-T as support of GOx with immobilisation yields of 90%. The bioconjugate also showed outstanding reusability, retaining 80% activity after 12 cycles, and increased thermal stability against higher temperatures than the free enzyme. After obtaining the optimal system, the bioconjugate´s capacity for glucose degradation and H_2O_2 production was investigated in a reactor with controlled parameters (glucose concentration, dissolved oxygen, and pH) to mimic physiological conditions.

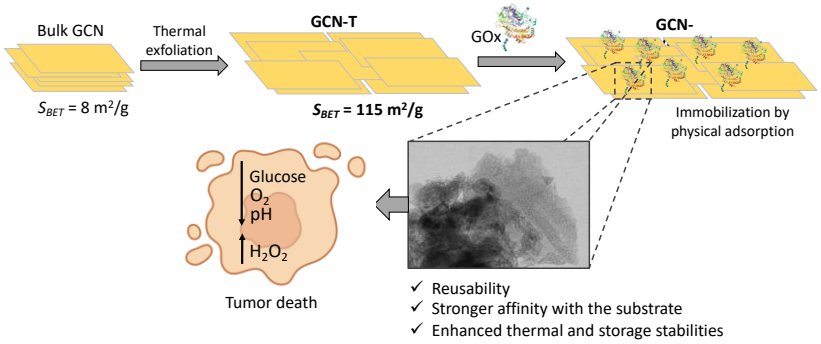

Figure 1: Schematic representation of the immobilisation of GOx onto GCN-T and its application for cancer therapy.

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Blocking replication of tumour cells with G-quadruplex DNA stabilizing ligands

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Telomeres are structures localized at each end of chromosomes that act as "sealants", stabilizing the linear strands and that contribute to chromosomal and genomic stability by protecting the end of chromosomes from enzymatic degradation. During cell division, shortening of telomeres undergoes and, when telomeres become too short, cell cycle arrest or programmed cell death processes were activated. Telomerase is a reverse transcriptase enzyme able to protect telomeres from that shortening process by introducing repetitive and specific DNA sequences to the 3′ telomere end of chromosomes. Nearly 85% of human malignancies were shown to overexpress this enzyme, and telomerase has been identified as a target for the development of novel antitumor drugs. The abnormal expression of oncogenes, also closely associated with proliferation of tumour cells, justifies the focus on this type of structures as other potential target for antitumor drug design [1].

The discovery that telomeres and oncogene promotor DNA sequences are rich in the purine base guanine that can fold into G-quadruplexes (G4) structures motivated researchers to search for G4 stabilizing ligands that may interfere with cancer cell growth. This stabilization can allow the inhibition of the telomerase function and/or the regulation of oncogene expression, the key players on replication, transcription and translation processes.

With the aim of interrupting the uncontrolled proliferation of cancer cells, new molecules with promising structural characteristics have been developed by our group and tested in the stabilization of G-quadruplexes [2]. We report here the ability of a group of ligands, including (metallo)porphyrins, zinc phthalocyanines and pyrrolopyrroles to stabilize sequences able to form G4. The affinity and selectivity of the selected ligands for G4 structures will be presented and discussed based on the data obtained using different biophysical and biochemical experiments (Figure 1).

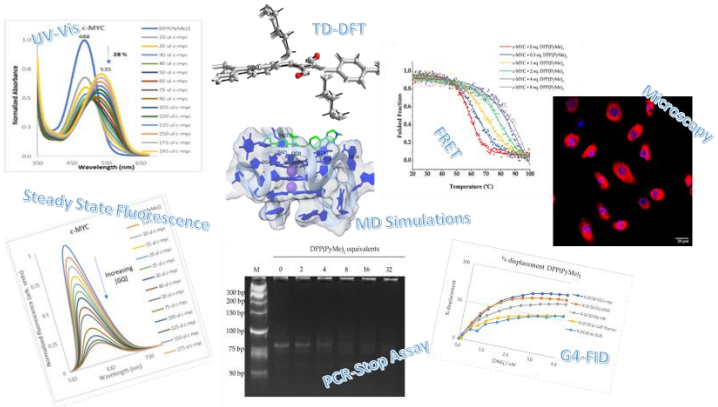

Figure 1: Different complementary biophysical and biochemical techniques to evaluate G4 stabilization by ligands

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Exploring the cytotoxic diterpenoid 7α-acetoxy-6β-hydroxyroyleanone from *Plectranthus* spp. as a PKC-α activator for breast cancer therapy

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Breast cancer is the most prevalent cancer worldwide, requiring the development of novel therapeutic strategies [1]. Protein kinase C-α (PKC-α), a member of the serine/threonine kinase family has been associated with breast cancer pathogenesis [2]. *Plectranthus* spp. (Lamiaceae) are recognized for their extensive ethnobotanical applications and by the presence of bioactive compounds, such as abietane diterpenoids. Specifically, the diterpenoid 7α-acetoxy-6β-hydroxyroyleanone (Roy **1**), the major constituent of *P. grandidentatus* acetonic extract, displayed notable cytotoxic activity against several cancer cell lines [3]. In a recent study, Roy **1** proved to be a potential lead molecule for the interaction with PKC isoforms and revealed promising activity in some breast cancer cell lines [2].

The key point of this work was to functionalize the structure of compound **1** thorough esterification, aiming to enhance its cytotoxic potential focus on breast cancer therapy. A previous study showed that esterification or royleanones afforded stable and bioactive derivatives compared to the original compound [4].

In this context, thirty new analogues (**2** to **31**) were prepared by hemi-synthesis of compound **1**. The aqueous stability of Roy **1** and standard derivatives **2** and **20** was evaluated. Results indicate that **1**, **2** and **20** were completely stable in aqueous medium (0.1 mM, pH 7.4, and 37°C, for 10 days). On the other, hand Roy **1** and its derivatives displayed low-water solubility and the preparation of a new nanosystem was explored aiming to overcome this limitation. Roy **1** was successfully conjugated with gold NPs (Roy-NPs). The synthesized Roy-NPs showed promising size, poly dispersion index and zeta potential and antiproliferative effect against the aggressive breast cancer cell line MDA-MB-231. Additionally, the cytotoxic activity of all compounds (**1** to **31**) was evaluated in breast cancer cell lines (MCF-7, MDBA-MB-231 and MDBA-MB-468) and nontumorigenic fibroblast cell line (HFF-1). Most of the derivatives exhibit cytotoxic effect against all cell lines. Some of the compounds showed selectivity towards cancer cells and low IC_{50} concentrations. Among them, compounds **6**, **7**, **18** and **21** were selected for evaluation as PKC-α activators in a yeast-based assay. Analogue **7** exhibit the most promising PKC-α activation potential and was further evaluated in a PKC-α activation enzymatic assay. In this assay, compound **7** exhibit PKC-α activation potential higher than the positive control (PMA). Considering these promising results, there is a growing interest in further studying this hit derivative as antitumoral agent focus on breast cancer therapy. These findings are a step forward in our ongoing efforts to developed new antitumoral compounds from natural sources.

Funding: This research was funded by Foundation for Science and Technology (FCT, Portugal) through the projects UIDB/04539/2020 and UIDP/04539/2020 and the PhD grant (SFRH/BD/137671/2018).

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Inhibition of G4-helicase interactions: A promising approach for cancer targeting therapy

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Guanine-rich segments in nucleic acids have the ability to form G-quadruplexes (G4s), which are non-canonical four-stranded structures formed by four guanine moieties linked via hoogsteen hydrogen bonding [1]. The prevalence of G4s within the promoter and telomere of major oncogenes indicates their vital role in genome stability and regulation in cancer cells [2]. For instance, G4s in the promoter of c-MYC are associated with the stalling of DNA replication and transcription in cancer cells. Thus, helicase, DHX36, is recruited by cancer cells to unwind G4s and maintain cell proliferation. This interaction has been highlighted as a promising strategy for targeted cancer therapy [2,3].

In our project, we designed indoloisoquinoline derivatives (IDiQs) capable of binding to the G4 in the c-MYC promoter, thereby blocking the interaction with DHX36 (FIG 1.). In the early stage, we docked a library of 1104 compounds with the crystal structure of c-MYC G4 and selected the most promising candidates with high affinity to c-MYC G4. In the second step, we focused on the chemical synthesis of the selected IDiQs and optimized the synthesis conditions. The binding affinity of the synthesized compounds to c-MYC G4 was assessed by fluorescence titration. These compounds showed to be good /very good c-MYC G4 ligands with Ka values in the 106 -107 M-1 range. In addition, preliminary studies indicate that inhibition of helicase DHX36 unwind activity by the indoloisoquinoline derivatives correlates with binding affinity to the G4, corroborating the approach being used in this project.

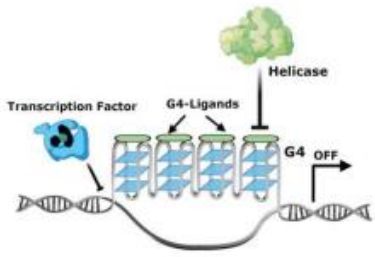
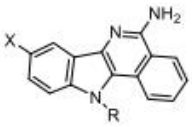


FIG 1. Indoloisoquinoline derivatives designed to act as G4 ligands that inhibit the helicase resolving of G4 structures in the c-MYC promoter region.



Compound	1	2	10	11	12	13	14
x	H/Cl	H/Cl	H/Cl	Cl	Cl	Cl	Cl
R	COOEt	H					

FIG 1. Compounds for Fluorescence Titration

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High“light”ing dansylpiperazino-functionalized squaraine dyes for enhanced anticancer photodynamic purposes

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Photodynamic therapy (PDT) is a minimally invasive therapeutic approach that exploits the interaction between a photosensitizing molecule, molecular oxygen, and an appropriate light source. This strategy is designed to selectively destroy target tissues or cells by harnessing the combined toxicity of these three elements, while minimizing the impact on healthy cells [1]. Numerous photosensitizing compounds, dyes, and pigments - natural, synthetic, or hemi-synthetics - have been identified. Among them, porphyrins have been extensively studied, but their limitations, such as low absorption in the red and near-infrared regions and higher absorption in the less transparent blue and green regions, have led to a quest for alternatives to enhance their efficacy [2,3].

This communication details the synthesis of six dansylpiperazino-functionalized *N*-ethyl and -hexyl-based benzothiazole-, indolenine-, and benz[*e*]indole-derived squaraine dyes. After full structural characterization, the squaraines’ light stability and capacity to generate singlet oxygen were assessed. Half-maximal inhibitory concentration (IC_{50}) values of squaraine dyes were determined against four cell lines: Caco-2 colorectal adenocarcinoma cells, HeLa cervical carcinoma cells, PC-3 prostate adenocarcinoma cells and normal human dermal fibroblasts cell line. Subsequently, the dyes exhibiting the most noteworthy *in vitro* therapeutic potential underwent a comprehensive mechanistic study, including assessments of preferential organelle accumulation, reactive oxygen species involvement, cell cycle arrest, and activation of caspase-3 and -7 – key proteins in apoptosis cell death mechanism.

The results underscore the promising phototherapeutic application of squaraine dyes, with one derivative, particularly the *N*-ethyl bearing benzothiazole derivative, unexpectedly demonstrating superior features. Among them, this dye exhibited high apoptosis-mediated phototoxicity and tumor selectivity ratios, aligning with several photophysicochemical and photobiological properties characteristic of an ideal photosensitizer.

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Shining Against Resistance: Photodecontaminant Materials for inactivation of Bacteria

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The global rise of antibiotic-resistant bacteria is a critical public health concern, causing 1.27 million deaths annually [1]. Infection transmission via contaminated surfaces, especially in hospitals, is alarming. One promising approach to tackle this issue is the development of photodecontaminant materials, where a photosensitizer (PS) is incorporated into a polymeric matrix, forming a material that can inactivate microorganisms when irradiated, through photodynamic inactivation (PDI) [2,3].

Herein, we present our recent studies on the synthesis and incorporation of curcumin and curcumin derivates in a polymeric matrix of poly(vinyl)chloride (PVC), aiming their potential use as photodecontaminant materials (Figure 1). Through solvent casting, thin PVC-photosensitizer films were prepared containing up to 30% photosensitizer load and characterized using thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), UV-Vis spectroscopy and stress-strain evaluation. The photoinactivation efficiency of the PVC-photosensitizer films was evaluated in planktonic cultures of Gram-positive (*Staphylococcus aureus*) bacteria. After light irradiation (blue LED), the films displayed 6 log CFU reduction at 23.5 J/cm2 light dose, concomitantly with no cytotoxicity against human fibroblast cells. These results, combined with their great mechanical properties and photostability, showcase the potential of PVC-photosensitizer materials in controlling spread of microorganisms through the creation of next-generation photodecontaminant materials.

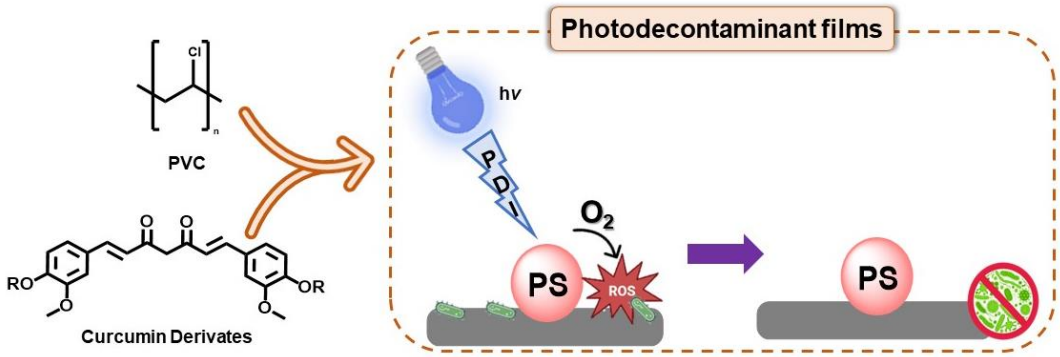

Figure 1: Photodecontaminant PVC-photosensitizer films for the inactivation of bacteria.

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On the development of novel cellulose derivatives for microplastic flocculation

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Many studies delve into the potential of cellulose as a substitute for common synthetic polymers prevalent in the industrial landscape [1]. Cellulose, being a polymeric material, exhibits several favourable attributes. However, it also poses challenges, such as poor solubility in common solvents and a lack of thermoplasticity. Addressing these limitations requires strategic chemical modifications to enhance cellulose reactivity and permit further adaptations. In our research, we employed controlled modification strategies, specifically cationic and hydrophobic modifications, to achieve derivatives with varying degrees of substitution, molecular weight, and hydrophobicity, aiming at their use as flocculation agents for microplastic removal from wastewaters. The cationization process involved a dual step: initial oxidation with periodate followed by a reaction with a cationic agent (Girard T reagent). Simultaneously, hydrophobic modification of cellulose was pursued, adhering to the principles of green chemistry, utilizing renewable feedstocks (i.e., plant oils). Fatty acids were extracted from vegetable oils, and cellulose was esterified in methanol. The ecotoxicity of cationic-modified and hydrophobically-modified cellulose derivatives, each with varying substitution degrees (i.e., DS +0.3, +1, +1.8, and DS -1H), was evaluated in four representative species from different freshwater trophic levels. The obtained derivatives were also evaluated regarding their flocculation performance in effluents contaminated with microplastics by laser diffraction spectroscopy (LDS), optical and scanning electron microscopy. The biofloculants developed in this study were found to successfully aggregate and remove model microplastics from aqueous media. Overall, this work demonstrates that "greener" approaches based on biobased flocculants can be promising solutions for removing microplastics from aqueous media thus contributing to minimize their potential negative effects on aquatic environments.

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Recent insights on the multifunctional scaffold of chromeno[3,4-*b*]xanthone derivatives against Alzheimer's disease

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Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder, which affects an estimated 50 million people worldwide, number that is expected to rise up to 150 million by 2050 [1]. Alongside the demographic challenge of the growing number of AD patients around the world is the low success rate in the development of new disease-modifying therapies. In fact, since 2003 only a few drugs were approved, including the monoclonal antibodies Aducanumab and Lecanemab [2,3]. Despite the controversial approval of Food and Drug Administration (FDA), both monoclonal antibodies were a landmark in the AD drug development and in the resurgence of a critical hypothesis related to its onset. However, due to the high cost associated to this type of therapy, many experts believe that the number of people that will be able to get it will be extremely limited, particularly countries with under-resourced public health systems [4]. For this reason, there has been a worldwide effort to develop a more effective and affordable therapy for AD focused on small molecules. To address this issue, in 2021 we disclosed a novel class of dual-targeting chromeno[3,4-*b*]xanthone derivatives [5]. Herein, we describe the lead optimization of these compounds *in vitro*, including the design, synthesis, anticholinesterase (AChE and BChE) and antiaggregating properties (Aβ and tau), docking studies, cytotoxicity in human neuroblastoma cell lines (SH-SY5Y), blood–brain barrier (BBB) permeability and application in cell models of AD.

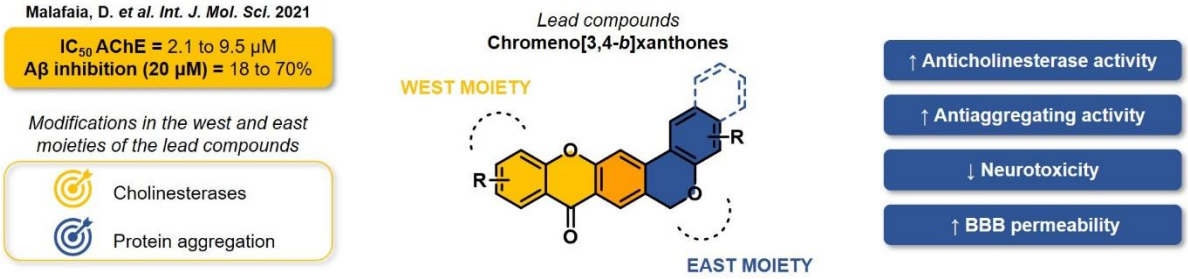

Figure 1: Design and *in vitro* profiling of chromeno[3,4-*b*]xanthones as multifunctional compounds for AD.

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Synthesis of 3-(arylamino)thieno[3,2-*b*]pyridines and evaluation of their neuroprotective activity on transgenic *C. elegans* for Machado-Joseph disease

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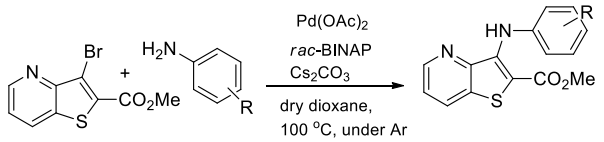
Neurodegenerative diseases such as Machado-Joseph disease (MJD) are progressive clinical pathologies and only drugs that attenuate the symptoms are known but do not prevent their onset or modify the progression of the disease [1]. MJD or Spinocerebellar Ataxia type 3 (SCA3) is the most common dominant inherited ataxia in the world and the second most common polyglutamine (polyQ) disease, after Huntington's disease. The genetic base of the MJD is the expansion of a polyQ tract within the protein ataxin-3 (ATXN3) [2].

Based on the antioxidant activity of di(hetero)arylamines derivatives of thieno[3,2-*b*]pyridines [3], it was decided to prepare novel methyl 3-(arylamino)thieno[3,2-*b*]pyridine-2-carboxylates, by palladium-catalyzed C-N cross-coupling (Scheme 1) and evaluate their therapeutic potential for the neurodegenerative MJD.



R = H; *o*-F; *m*-F; *p*-F; *o*-OMe; *m*-OMe; *p*-OMe; *m*, *p*-diOMe and *o*, *p*-diOMe

Scheme 1: Nine di(hetero)arylamines prepared by Pd-catalyzed C-N cross-coupling

The neuroprotective activity of the nine di(heteroarylamines prepared were studied *in vivo* using the transgenic nematode *Caenorhabditis elegans* (*C. elegans*) as a model for MJD (AT3q130) in which mutant ATXN3 proteins expressed in the neurons cause aggregation and motility defects [4]. None of the di(hetero)arylamines were toxic to *C. elegans* wild type (WT) at the concentrations tested using the food (*E. coli*) clearance assay, but only the compounds bearing one OMe group in *ortho* or *para* and two OMe groups in *ortho* and *para* positions relative to the N-H improved the neuronal dysfunction caused by the expression of the mutant protein. The three compounds exhibit similar effect on ameliorating the animals motor behavior using motility assays [4], which will be presented, however the dimethoxylated compound acts at the lowest concentration [5]. The results suggest that the methoxylated di(hetero)arylamines in the thieno[3,2-*b*]pyridine series are promising therapeutic drugs for the treatment of MJD and possibly for other neurodegenerative diseases.

Acknowledgements: *Foundation for Science and Technology - Portugal.*

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[5]. Manuscript in preparation.

Electrochemical oxidation of abietanes using continuous-flow

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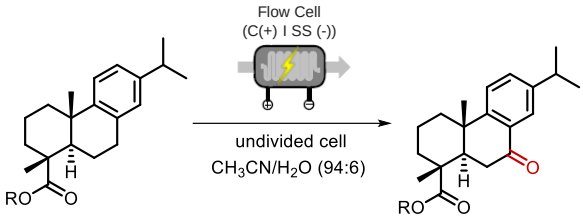
Rosin or Colophony is a natural resin that is extracted from pine trees. Besides having multiple industrial applications, it is also constituted by a group of diterpenes known as abietanes, which, along with its derivatives, has been found to have a wide variety of interesting biological activities, including antimicrobial, antiviral, antitumoral, and anti-inflammatory [1].

The benzylic oxidation of dehydroabietic acid, and its methyl ester derivative has been previously reported using various oxidative protocols, such as Swern oxidation [2] or chromium trioxide in either stoichiometric [3] or catalytic quantities [4]. However, these protocols fail in the context of sustainability for several reasons, such as the use of toxic reagents and stoichiometric amounts.

Herein we present a more sustainable protocol for the oxidation of both dehydroabietic acid and abietic acid, and their methyl ester derivatives. We used modern electrochemical methods to achieve good yields of the ketone for both abietanes. Furthermore, we report the development of an electrochemical flow process towards increase its productivity [5]. Finally, we extended this strategy to colophony and report its successful application both in batch and in flow [6].



Scheme 1: Continuous flow electrochemical oxidation of dehydroabietic acid (DHA) and its methyl ester derivative (MDHA).

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Uncovering the origins of supramolecular similarity in a series of benzimidazole structures

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Research on supramolecular similarity in crystalline structures is of the utmost importance to the pharmaceutical industry and the development of new materials, since crystal structures with supramolecular similarity may have similar properties[1]. Hence, searching for tools that can help shed more light on the isostructurality in crystals and how to modulate structures to obtain the desired properties is pivotal. These supramolecular tools can allow one to assess the similarity between complete crystalline structures, although additional insights on the occurrence of differences in the crystallization process of each structure that affect the consequent similarity are also relevant. In this sense, this study pursued to propose the origins of the supramolecular similarity between a series of five benzimidazole derivatives structures (**1**-**5**)[2]. The benzimidazole scaffold was chosen as it is present in molecules of major interest due to its wide range of biological/pharmacological activities. Our findings indicated that the similarity occurs due to the approximation of the initially formed one-dimensional nuclei during crystallization. To achieve these insights, supramolecular comparisons were carried out by calculating the quantitative similarity indices I^X (X = D, C, or G) based on geometric (I^D), contact area (I^C), and stabilization energy (I^G) parameters[3]. The similarity indices were successfully used as tools to quantify and classify the different regions of supramolecular similarity between the crystal structures. The multiparameter index I^{DCG} demonstrated distinct similarity regions in the supramolecular comparisons. All structures with substituents (**2**–**5**) presented a high similarity when compared amongst each other; the unsubstituted compound **1** was the only with a low similarity after being compared to the rest of the series. To understand how supramolecular similarity arises and how the crystals were formed in this series of compounds, crystallization mechanisms were proposed using a retrocrystallization process, which indicates how the crystallization occurred from the energy hierarchies of the formed crystal[4]. The crystallization mechanisms proposed for all structures presented two main stages. In the first stage, one-dimensional nuclei formation occurs, which is assisted by hydrogen bond interactions combined with π···π interactions, showing the dominance stabilization energy parameter. After the first stage, the one-dimensional nuclei present a pattern of approximation (interaction) similar to compounds **2**–**5**; this led to crystal lattices with high supramolecular similarity. Nevertheless, given the absence of a substituent, compound **1** favored a distinct complementarity between the one-dimensional nuclei, giving rise to a crystal lattice distinct from compounds **2**–**5**. It was possible to uncover the origins of the supramolecular similarity between **2**–**5** (and the dissimilarity with compound **1**) using the similarity indices I^X and crystallization mechanism proposals. From this, we reinforce that isostructurality must be seen as a broad concept and consider a supramolecular perspective using distinct quantitative and comparable parameters to classify regions of similarity. In the way we see it, we need to discuss more *Supramolecular Similarity* instead of only *Isostructurality* because the supramolecular environment is pivotal in understanding this phenomenon.

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Synthesis of amphiphilic di-cationic imidazolyl porphyrins for photoinactivation of bacteria

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The increasing emergence of multidrug-resistant bacteria has led to a growing need to develop new drugs combined with therapeutic alternatives, such as antimicrobial photodynamic therapy (aPDT). aPDT is based on the administration of a photosensitizer (PS) capable to absorb light and transfer it to oxygen, yielding oxidative stress that triggers multiple cell death mechanisms. Cationic imidazolyl porphyrin-based PSs have shown promising results in the photoinactivation of planktonic bacteria and biofilms [1, 2]. The easy structural modulation of these type of PSs enables structure-activity studies, which are highly necessary in the development of molecules with ideal properties for aPDT [3].

This work incorporates the synthesis of di-cationic imidazolyl porphyrins-based PSs, whose amphiphilicity was modulated in attempt to develop molecules with optimized structures and properties for the inactivation of Gram-negative bacteria (*Escherichia coli*). The developed family of cationic porphyrins was obtained with good yields and the photophysical and photochemical characterization of the synthesized compounds was performed, as well as biological studies in planktonic *E. coli*. The most promising results were observed for the photosensitizer bearing an alkyl chain with OH groups at the end of the chain (Figure 1). These findings suggest that porphyrin structural modulation is a key issue in the design of ideal PSs aimed at inactivation of clinically relevant topical infections.

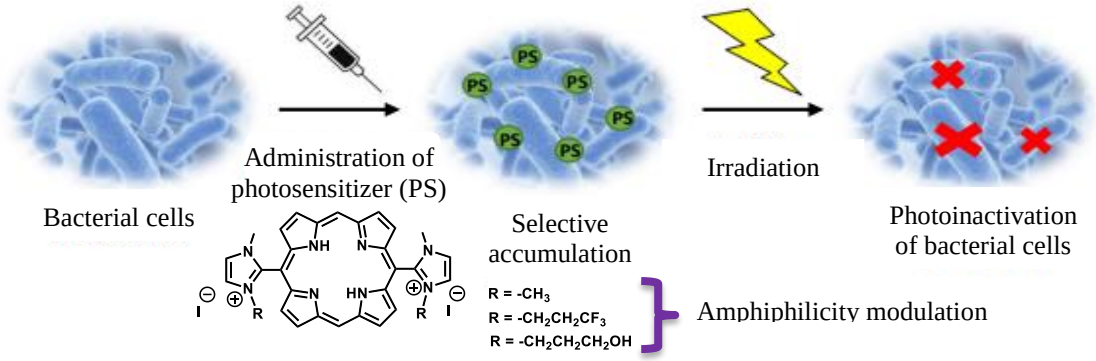

Figure 1: Schematic representation of antibacterial photodynamic inactivation (aPDT) using the synthesized amphiphilic *meso*-imidazolyl porphyrins as photosensitizers

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Nitrogen rich biomass furanics – synthesis and applications

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The demand for new biomass-derived fine and commodity chemicals propels the discovery of new methodologies and synthons. Amongst the several examples, furanic platforms obtained from lignocellulosic biomass have emerged as a cornerstone for the sustainable development of new valuable chemicals, as a replacement for oil-based products, and as a starting material for the preparation of "drop-in" chemicals. In fact, furfural is currently being produced in over 250 kTonne/year with over 80 synthons being prepared from it[1]. Despite this, a major limitation of these furans is the lack of nitrogen (Figure 1A). Often introducing external nitrogen requires non-sustainable sources, the most common being ammonia. Knowing that circa 1.5% of the total world energy consumption is used to produce ammonia, which is then introduced in fine and commodity chemicals, several academia and industry-based groups have turned their attention to nitrogen-rich biomass sources[2,3]. Besides lignocellulosic biomass, chitin is one of the most abundant waste byproduct. Whereas furfural and 5-hydroxymethylfurfural are cornerstones of sustainable chemistry, 3-acetamido-5-acetyl furan (3A5AF), an N-rich furan obtained from chitin biomass, remains unexplored, due to the poor reactivity of the acetyl group relative to previous furanic aldehydes. Here we developed a reactive 3-acetamido-5-furfuryl aldehyde (3A5F) and demonstrated the utility of this synthon as well as 3A5AF as a source of bio-derived nitrogen-rich heteroaromatics, carbocycles, and as a bioconjugation reagent (Figure 1B) [4].

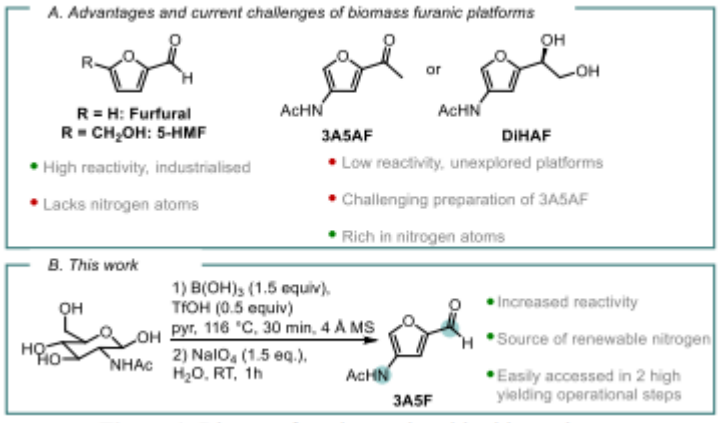

Figure 1: Biomass furanics explored in this work

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Chan-Lam reaction of arylvinyl boron reagents with (hetero)aromatic amines: application in the synthesis of *N*-heterocycles

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The non-toxicity, stability and the different applications of organoboron compounds has reinforced the importance of these substrates in the modern organic chemistry [1]. Furthermore, besides being commercially available, their synthesis from alkynes is also quite simple. Organoborane compounds are widely used in reactions such as Suzuki coupling or Chan-Evans-Lam coupling. In the latter, an organoborane substrate reacts with a nucleophile usually leading to a C–N or C–O bond formation. The most commonly used boron-based reagents in this type of reaction are arylboronic acids, while arylvinyl boron-based reagents have been scarcely explored [2]. In this work, we investigated the reactivity of anilines and aminopyridines in the formation of a C–N bond through a Chan-Evans-Lam reaction using arylvinyl boron-based reagents. The products obtained have been applied in the synthesis of N-heterocycles via sequential Heck reaction. (Figure 1) [3,4]. The results obtained will be presented herein.

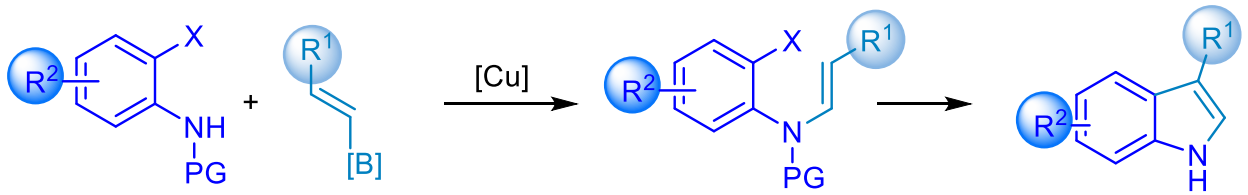

Figure 1: Chan-Lam reaction of (hetero)aromatic amines with arylvinyl boron reagents and its application on the synthesis of indole derivatives.

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Total synthesis of marine natural product (-)-agelastatin A: Biological evaluation of N3-alkylation.

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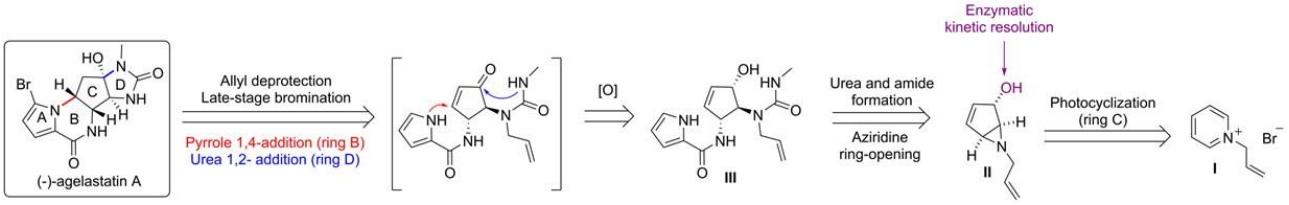
Agelastatin alkaloids have attracted scientific interest since the isolation of (-)-agelastatin A (AglA) from the sponge *Agelas dendromorpha* by Pietra *et al.* in 1993.[1] AglA showed remarkable cytotoxicity against a variety of tumour cells[2] and strong inhibition of osteopontin-mediated neoplastic transformation and metastasis.[3] Additionally, it displays high brine shrimp toxicity and insecticidal properties.[4] The SAR of AglA is very strict and virtually every modification results in abrupt loss of activity. However, until now, the effect of N3-substitution was not investigated, likely due to difficulties in the synthesis of analogues. Since large quantities of AglA are unreasonable to obtain via natural sources, its total synthesis is highly desirable, and some have been developed.[5] Asymmetric synthesis is very challenging and requires laborious steps and protecting groups to construct the four contiguous nitrogen-bound stereocenters of the cyclopentane C-ring. We have developed a strategy (Scheme 1) that involves the early-stage photochemical transformation of pyridinium salts to bicyclic vinyl aziridines that originate, in one step, the AglA's C-ring with the desired functionality and relative configuration. The presence of a secondary alcohol on the cyclic core allowed enzymatic kinetic resolution in high ee (>98%). Both mentioned transformations were performed under flow conditions to increase the efficiency and scale of the processes. Then, a sequence of nitrogen-carbon bond forming reactions culminated in the total synthesis of (-)-agelastatin A in only 12 steps with 4% overall yield, with the use of a single protective group.[6] This novel synthetic methodology allowed to evaluate for the first time the effect of N3-substituition in the natural product. It was observed that alkylation of N3 greatly diminishes the cytotoxicity of AglA against a series of human cancer cell lines.



Scheme 1: Retrosynthetic analysis of (-)-agelastatin A.

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The neurotoxic effects of emerging synthetic cathinones and its metabolites: the role of metabolism

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The emergence of the new psychoactive substances (NPS), into the recreational drug market, present serious dangers to public health due to their potential toxicity and poses difficulties for their detection in forensic and clinical contexts [1]. These challenges are emphasized by the metabolic fate NPS, highlighting the need for cooperation between research, forensic and clinical institutions[2].

Synthetic cathinones represent the first largest group of NPS seized in Europe and the second largest group reported to EMCDDA in terms of the number of substances [3]. These compounds undergo extensive metabolic transformations. Frequently, metabolites can serve as consumption biomarkers, thereby extending the detection window beyond what the parent cathinone allows. Furthermore, the profile of these metabolites can provide insights into toxicity mechanisms, guiding the development of effective therapies for managing non-fatal intoxication cases and understanding the molecular basis of neurotoxicity events of other drugs.

With the ultimate goal of contributing for a proactive response to the forensic and health problems associated to NPS, we report herein the synthesis and characterization of the standards of ten emerging cathinones, and their corresponding reduced metabolites. Their neurotoxicity of was subsequently evaluated in SH-SY5Y cell line. The results revealed that almost all metabolites show a higher toxicity when compared with the parent cathinone. These results suggest that metabolism can have a key role in the onset of the adverse effects induced by this class of NPS.

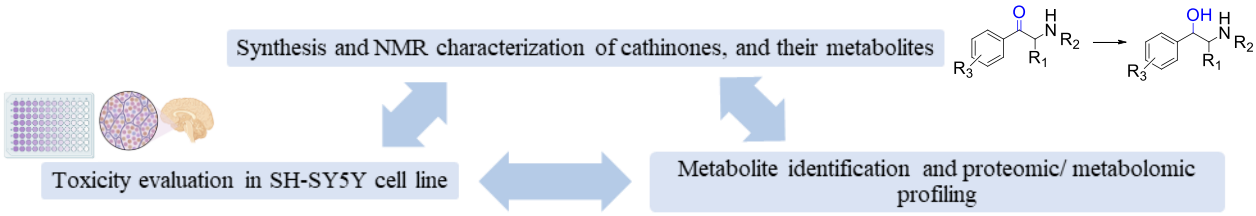

Figure 1: Metabolic profiling and toxicity evaluation of synthetic cathinones standards, and of their reduced metabolites.

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Towards therapeutical applications of camphorimine Ag(I) and Au(I) complexes

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Aiming at the design of coordination compounds with biological properties, in particular with combined antimicrobial and anticancer activity, we synthesized several silver based – $[\{Ag(NO_3)\}_xL_n]$, $[\{Ag(OH)\}_xL_n]$, $[\{AgL\}_2(\mu\text{-}O)]$ – and gold based – $K_x[\{Au(CN)_2\}_xL_n]$, $[\{Au(CN)\}_xL_n]$ – compounds, using as ligands camphorimine derivatives, with distinct electronic and steric properties.

The properties of coordination compounds can be tuned by choice of the metal and the ligands, prompting the design of a wide variety of molecules. In coordination compounds, the presence of the metal prompts mechanisms distinct from those of the organic molecules in pharmacological use. Cisplatin and silver diamine fluoride are among the coordination compounds actually in use as anticancer or antimicrobial agents.[1]

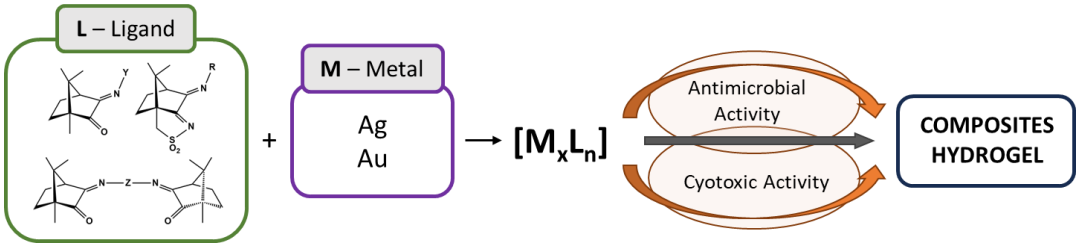

Figure 1: Synthesis of different camphorimine ligands and biologically active complexes for biological applications.

The antimicrobial properties of the synthesized camphorimine complexes were evaluated through the determination of the Minimum Inhibitory Concentration (MIC) towards Gram-positive *(Staphylococcus aureus*) and Gram-negative (*Burkholderia contaminans*, *Escherichia coli*, *Pseudomonas aeruginosa*) bacteria. The assessment of the anticancer properties was based on the determination of the Inhibitory Concentration that killed 50% (IC_{50}) of the cancer cells (A2780, A2780cisR, OVCAR3, HOS, A375) and non-tumoral cells (V79, HEK 293, HDF) exposed to the complexes. The results showed that the Ag(I) and the Au(I) camphorimine complexes have high antimicrobial and anticancer activities.[2-5] Fostering their use in orthopaedic or wound dressing applications, silver complexes were incorporated in calcium phosphate-based materials and hydrogels, respectively.

In the first case, a set of silver complexes were selected, and several hydroxyapatite (HAp) composites were prepared and their biological properties were assessed showing that the composites essentially maintained the anticancer and antimicrobial activities of the complexes. In the second case, a silver complex with high-anticancer activity against the melanoma cell line A375 and high antibacterial activity against *B. contaminans*, *E. coli* and *P. aeruginosa* was selected for incorporation in HEMA (2-hydroxyethyl methacrylate) based hydrogel, aiming at the treatment of wounds or scars in oncologic patients. Preliminary results obtained show that the complex retains the activity when incorporated in the gel. As an overall the camphorimine Ag(I) and Au(I) complexes are quite promising for the applications under study.

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Antimicrobial evaluation of water-soluble pyrazole-pyridinium zinc(II) phthalocyanines: A promising approach for microorganism eradication

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Infectious diseases continue to be one of the major global causes of death [1]. In recent decades, the growing emergence of drug-resistant bacterial and viral strains has raised concerns within the scientific community [1,2]. Photodynamic inactivation (PDI) approach has emerged as a viable alternative for neutralizing microorganisms, including bacteria and viruses [3–5]. The efficacy of phthalocyanine (Pc) derivatives as photosensitizers (PS) in PDI has already been demonstrated against various microorganisms [3,4]. In this study, we synthesized and characterized new tetra- and octa-β-substituted quaternised PSs with pyridinium-pyrazolyl units [4]. We analysed their photophysical and photochemical properties and conducted *in vitro* investigations using bacterial planktonic forms (e.g., *Escherichia coli*) and/or an RNA-virus model to evaluate their potential as PDI agents.

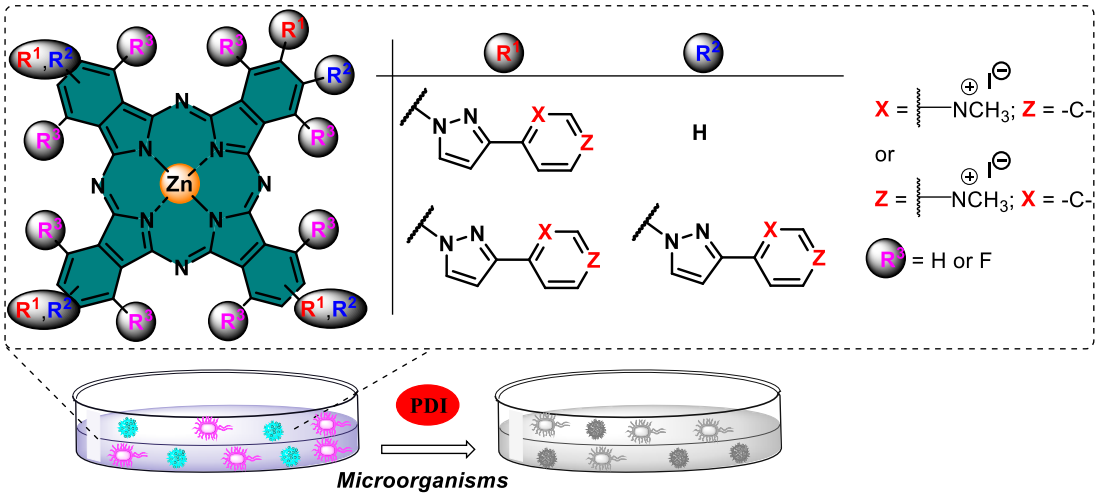

Figure 1: Pyrazole-pyridinium zinc(II) phthalocyanine dyes for microbial inactivation.

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Bacterial siderophores – iron thievery weapons in environmental research

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Iron is an essential trace metal for most living organisms due to its role in vital cellular processes. However, certain organisms, particularly bacteria, face a big challenge to obtain iron, since the ferrous ion [Fe(II)] is easily oxidized to its ferric state [Fe(III)] which is insoluble at physiological pH [1]. Consequently, microorganisms and plants have developed the ability to produce siderophores under iron-deprived conditions as a strategy for iron uptake. Siderophores are small molecules of organic nature secreted by these organisms to chelate and transport Fe(III) to the cytoplasm [2]. Beyond iron, siderophores can chelate with other metals, including the ones that are toxic to the environment, forming soluble metallophores (metal-siderophore complexes). Owing to that, these chelators have been widely investigated in several environmental applications [3].

In this study, the synthesis of a natural siderophore (**AG2**) and two siderophore mimetics (**AT2** and **APh2**) was accomplished through intermediates **AG1**, **AT1**, and **APh1** (Figure 1). These catecholate-type siderophores were evaluated for their chelating behaviour with metals, including Fe(III), Zn(II), Cu(II), Ga(III), and Cd(II) using an analytical reversed-phase high performance liquid chromatography (RP-HPLC) protocol. Additional studies to evaluate the impact of these compounds on the growth of an ESKAPE pathogen present in the environment, *Escherichia coli* ATCC 25922, capable of up-taking *in vivo* catecholate-type siderophores, were also performed using a modified time-kill assay.

Four siderophore mimetics were capable of complexing Fe(III) with a good affinity (> 30 % of complex formed) in comparison to the other metals studied. Surprisingly, **APh1** intermediate showed the best complexation results (47 % of the complex formed). Results on the antibacterial activity showed that this *E. coli* ATCC strain, when placed in a medium deprived of iron, tends to form a higher number of cells but with a smaller size (less biomass), and this may be an indication of the bacteria's stress. Briefly, compound **APh1** has shown to be effective in inhibiting the growth of this bacterium in an iron-deficiency medium. The other compounds only promoted the same stress effect on *E. coli* ATCC 25922, pointing to the possibility that these siderophore mimetics are further depriving this bacterium of iron by complexing it.

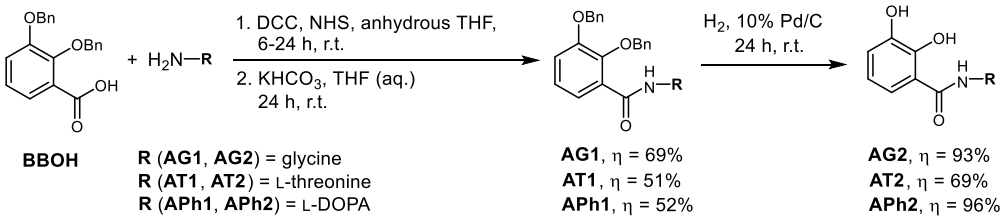

Figure 1: Synthesis of natural siderophore (**AG2**) and two siderophore mimetics (**AT2** and **APh2**).

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Promising antiviral small molecules: from *in silico* studies to effects on cellular infection and cytotoxicity

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One of the most significant threats to global public health was the recent coronavirus pandemic. Ongoing research on SARS-CoV-2 is of paramount importance to enhance our scientific comprehension, develop preventive and therapeutic approaches, monitor viral variants, and adequately prepare for potential future outbreaks. Research on inhibiting viral interaction with host receptors is fundamental to the design of antiviral therapies and prophylactic strategies. Angiotensin-converting enzyme (ACE2) was found to be the main host cellular receptor recognized by the spike protein of SARS-CoV-2 virus [1]. An increased ACE2–spike affinity is known to correlate with a higher infectivity of SARS-CoV-2 [2]. In this work, we aimed to identify, from our in-house library of synthetic compounds, potential inhibitors of SARS-CoV-2 infection by blocking the interaction of spike protein with the ACE2 host receptor [3].

Therefore, using AutoDock Vina, we performed a structure-based virtual screening of approximately 300 small molecules to identify the ones with the highest affinity for the targets spike (receptor binding domain of spike protein, PDB code 6M0J) and/or ACE2 (PDB code 6M17). Ten small molecules with the best docking scores were selected for functional studies. From these, six are xanthones with bulky substituents (four are GAG-like derivatives and two are aminated), three are xanthenes (two presenting bulky sulfonamides and one exhibiting symmetry), and another is an amide derivative of a bile acid. Symmetry and bulky substituents seem to be important features for inhibition of the ACE2–spike interaction. To understand how these compounds would affect infection inhibition and viability of infected cells, Vero-CCL81 cells were treated with the selected small molecules at different concentrations and then infected with the virus. Results, observed 48 hours after infection, showed that five small molecules inhibited cell infection without compromising cell viability at their viral IC_{50} (13 μM – 32 μM). These five promising small molecules (two symmetric glucosulfated xanthones, two sulfonamide xanthenes, and the bile acid derivative) were selected for further studies, in which it was observed that the two sulfonamide xanthenes and the bile acid derivative significantly reduced viral replication. Additionally, none of them interfered significantly with ACE2 expression, which is promising since a downregulation in ACE2 expression could lead to an aggravation of the disease. Moreover, cytotoxicity assays were performed in A549 human lung cells. It was possible to observe that one of the sulfonamide xanthenes did not present cytotoxicity up to 50 μM.

In conclusion, from a library of approximately 300 synthetic small molecules, *in-silico* studies allowed to select ten which were predicted to interact with ACE2 and/or spike protein. From these, one seemed to hold significant potential as an anti-SARS-CoV-2 agent, as it inhibited viral entry and replication, without exhibiting noteworthy cytotoxicity at their viral IC_{50} concentration, in human lung cells. These studies enabled the discovery of promising scaffolds for new molecular modification research. Future work will explore synthesis of novel compounds and their anti-SARS-CoV-2 activity, to establish structure-activity relationships.

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Unveiling the COVID impact on biochemical pathways through an integrated omics expedition towards preparedness

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While the COVID pandemic might be slowly turning into an endemic disease, exploring into the cellular response to SARS-CoV-2 infection becomes increasingly pertinent. Analysing these responses not only helps in identifying predictors of disease progression with clinical relevance but also serves as a crucial step toward enhancing pandemic preparedness. By unravelling the intricacies of the biochemical pathways through a comprehensive mass spectrometry (MS)-based omics exploration, coupled to a high-throughput FTIR spectroscopy approach, we aim to proactively shape strategies for a more resilient response to future challenges.

We analysed easily accessible serum samples of ICU-admitted COVID patients and focused on exploring the metabolome and proteome changes associated with the viral infection and with the diverse stages of disease progression.

Patients that required invasive mechanical ventilation (IMV) were found to exhibit widespread metabolomic changes, affecting amino acid, lipid and sugar metabolism, and that partially recapitulate the serum clinical changes associated with hypertension and cirrhosis. On the other hand, when analysing the metabolome of deceased vs. surviving patients, changes centred around the energy-producing pathways, as well as in anaplerotic pathways; in keeping with this, the metabolome-level COVID phenotype resembles that of several metabolic disorders, as well as that of asphyxia, anoxia, and respiratory chain disorders.

While the mass spectrometry metabolomic approach offers an unsurmountable level of detail, it is a time-consuming process when compared to a FTIR approach. We analysed the same samples by mid infra-red spectroscopy, and applied a multiple PCA-LDA model approach, and were partially able to offer a predictive model to discriminate between patients requiring IMV or not, and between deceased and surviving patients. This high-throughput approach could be implemented at point-of-care sites, generating meta-information to the clinicians for a faster decision when it comes to more invasive measures.

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Exploring the hyaluronidase inhibitory activity of phytosterol derivatives

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Hyaluronic acid (HA) degradation in the extracellular matrix (ECM) can compromise structural integrity, increasing tissue permeability and contributing to various biological processes such as skin aging, cancer progression, microbial pathogenesis, and allergic reactions. Inhibiting HA degradation through hyaluronidase inhibitors emerges as a critical strategy with potential applications in anti-aging, anti-inflammatory, antimicrobial, anticancer, anti-venom/toxin, and contraceptive therapies, as it regulates HA homeostasis and influences diverse bioactive processes within the ECM [1].

The anti-inflammatory activity of phytosterols, namely stigmasterol, has recently been associated with their high inhibitory activity of hyaluronidase [2], so this work aimed to synthesize a series of derivatives of β-sitosterol and stigmasterol to obtain compounds with increased potency against hyaluronidase.

The derivatives were obtained by esterification with substituted benzoic or cinnamic acids, scaffolds known for their antioxidant and enzyme inhibition properties [3]. The reaction yields varied from 72.7% to 5.2%, depending on the substituent groups, and the obtained derivatives were characterized through NMR and MS techniques.

The results from the inhibition assays showed that β-sitosterol (IC_{50} = 12.97 ± 0.03 µM) was about 2 times more active than sodium aurothiomalate, the positive control (IC_{50} = 26.93 ± 0.11 µM). In comparison, stigmasterol was inactive at the maximum concentration tested (100 µM). The best results were obtained for β-sitosterol 3-(2-methoxybenzoate) with an IC_{50} of 2.88 ± 0.71 µM followed by β-sitosterol 3-benzoate with 3.45 ± 0.42 µM, showing that the modifications highly increased the inhibitory activity (Figure 1).

Molecular docking studies were conducted for the best compounds to assess their interactions with the different types of human hyaluronidase. The results will be further discussed in the communication.

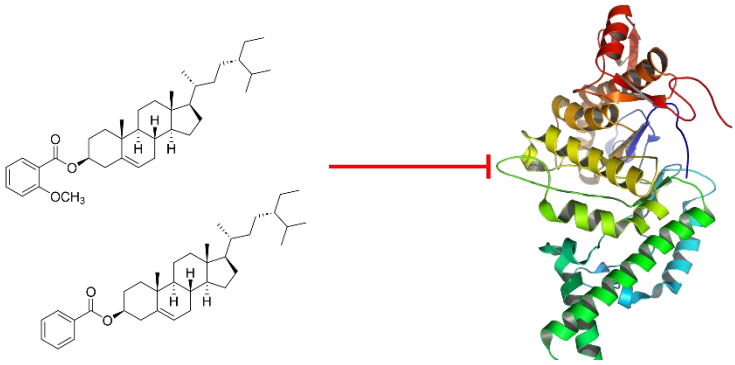

Figure 1: β-sitosterol derivatives with highest inhibitory activity of hyaluronidase

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Poster Communications

TIGIT/PD-L1 dual inhibition: finding small molecules to fight cancer

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Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment by harnessing the patient's immune system to target malignancies. Despite their promise, limitations such as low response rates and resistance to ICIs impose the exploration of combination therapies. Of those, targeting both PD-L1 and TIGIT has demonstrated potential in enhancing anti-tumor immunity, as evidenced in various preclinical and clinical studies. Currently, only antibodies targeting the PD-1/PD-L1 pathway have received FDA approval and only one small molecule inhibitor against TIGIT is in clinical trials. Drawbacks of antibodies, such as their short half-life and high production costs, highlight the urgency for developing small molecules. Thus, we aim at identifying a dual inhibitor that targets both PD-L1 and TIGIT, with an initial emphasis on TIGIT due to the scarcity of approved inhibitors for this checkpoint.

Focusing on TIGIT, we analyzed the α-carbon root mean square deviation (RMSD) across its PDB structures to assess structural changes post-alignment and superimposition for the identification of any conformational differences across the various structures. They revealed high structural consistency, with α-C RMSD values ranging from 0.361-1.15 Å. A homology model was then constructed using Modeller software, with all PDB structures serving as templates. This model was validated through a Ramachandran plot analysis, confirming that all residues fell within the allowed regions. To gain insight into the molecular interactions within the TIGIT binding pocket, we explored structures of TIGIT when bound to either antibodies or its receptors *in vivo* using PLIP software. THR55, GLN56, ASN70, ASP72, LEU73, THR112, TYR113, and PRO114 were identified as the key residues for effective TIGIT interaction. Using the insights from these interactions, we developed two pharmacophore models using the PHASE module: one based exclusively on TIGIT's structure (Figure 1), and the second model was derived from TIGIT complexes with the best docked small molecules retrieved from recent studies [1-4].

The outcomes from our study pave the way for the development of novel potential inhibitors targeting TIGIT. Our approach includes the creation of a homology model, developing pharmacophore, and pioneering the *de novo* generation of small molecules. Looking ahead, our goal is to refine this model further and potentially develop a new pharmacophore that could also target PD-L1. Such advancements would significantly contribute to the expanding realm of cancer immunotherapy, offering new avenues for therapeutic interventions.

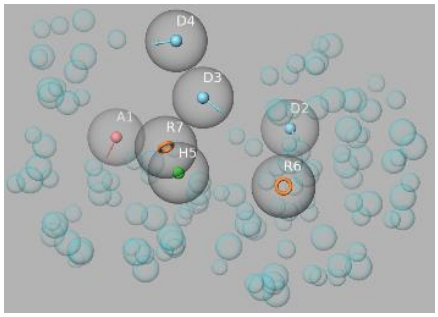

Figure 1: Pharmacophore model based on TIGIT's structure. Hydrogen bond donors (D), Hydrogen bond acceptors (A), Rings (R), Hydrophobic regions (H), and the excluded volume are displayed.

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Cinnamic acid-acridine hybrids as multi-stage antiplasmodial leads

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Malaria is still one of the deadliest infectious diseases in the world and this is due in part to (i) the complex *Plasmodium* parasite's life cycle and (ii) the fast selection and spread of parasite strains resistant to the antimalarial drugs [1]. In an effort to increase efficacy, while reducing the possibility of the emergence of resistant parasites, antimalarial drug discovery has been focused on developing multi-stage drugs that might simultaneously affect different phases of the *Plasmodium* parasite's life cycle [1].

Quinacrine (QN) was the first synthetic antimalarial drug, acting as a blood schizonticide, but chloroquine (CQ) quickly took its place because of its better safety, effectiveness, and bioavailability. However, the widespread of parasites resistant to CQ revived the interest in QN derivatives [2]. QN can be regarded as a fusion of CQ with the heterocyclic core of primaquine (PQ), another antimalarial active against both liver forms and gametocytes. This inspired us to develop two new families of QN derivatives, 4-aminoacridines and 4,9-diaminoacridines, which reflect the combination of PQ and CQ into one single scaffold, whose expected multi-stage activity was confirmed [3,4]. Encouraged by these findings and based on the "covalent bitherapy" concept first advanced by Meunier [5], we have now developed a second generation of those two families (Figure 1) through conjugation of first-generation ones to *trans*-cinnamic acids (CA) [6,7]. In this communication, we present the chemical synthesis of these new conjugates and their *in vitro* evaluation against (a) hepatic stages of *Plasmodium berghei*, as well as (b) erythrocytic forms and (c) early and mature gametocytes of *Plasmodium falciparum*. Results show that the introduction of the CA moiety has a positive impact on the overall antiplasmodial activity since the new compounds show improved in vitro activity against all three stages of the malaria parasite life cycle.

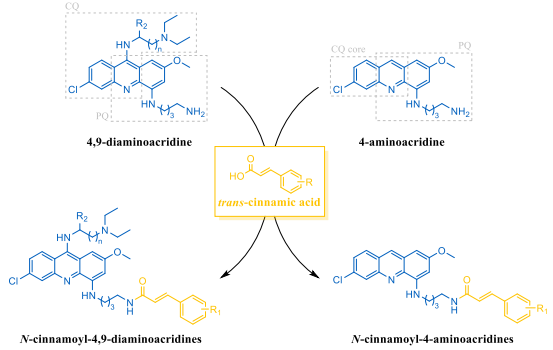

Figure 1: *N*-cinnamoyl-4-aminoacridines and *N*-cinnamoyl-4,9-diaminoacridines produced as multi-stage antiplasmodial leads.

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 project UIDB/50006/2020. ***Acknowledgements:*** Thanks are further due to FCT/MCTES for the doctoral grant SFRH/BD/147345/2019 to MF. MP further acknowledges the "la Caixa" Foundation for Grant HR21-848.

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Development of AI-2 chemical probes for the identification and characterisation of novel AI-2 receptors

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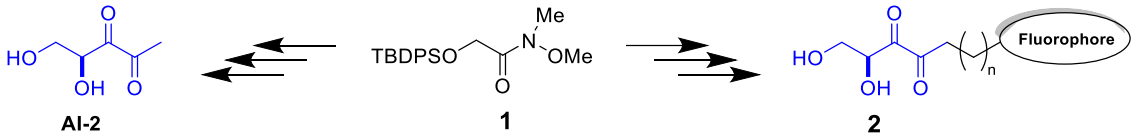
Communication between bacteria, known as *quorum sensing*, is enabled by the production of signalling molecules called autoinducers, whose presence in the environment modulates the behaviour of bacterial populations. Autoinducer-2 (AI-2) is unique within this group of molecules, as it is the only one to be recognised by different species of bacteria, regulating various biological functions, such as biofilm formation, motility or even susceptibility to antibiotics. Currently, two main families of AI-2 receptors have been studied over different species, LuxP and LsrB, but responses to AI-2 have been previously reported in species which do not possess these receptors, suggesting the existence of alternative receptors yet to be discovered. [1]

The group's previous discovery of a synthetic route to AI-2 [2] was an important contribution to the research of its sensing mechanism. Currently, a new strategy for the synthesis of AI-2 derivatives, which act as chemical probes that can aid in the identification of novel AI-2 receptors, is being developed.

Weinreb's amide **1**, a previous intermediate of our AI-2 synthesis, was alkylated using alkynes with linkers of various lengths and with suitable functional groups for coupling to fluorophores as represented by **2.**

These probes will be tested in both cell extracts and whole cells, with the goal of identifying other microbiota members that recognize AI-2.



Scheme 1: Compound **1** is the starting point for AI-2 as well as its fluorescent derivatives **2**.

These probes are an important tool to further understand quorum sensing mechanisms, which can lead to novel therapeutics based on the modulation of bacterial behaviour in a world where antibiotic resistance is a strong concern.

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Novel *trans*-A_2B_2 porphyrins: from oxime/hydrazone *α*-substituted dipyrromethanes to *meso*-substituted functionalized macrocycles

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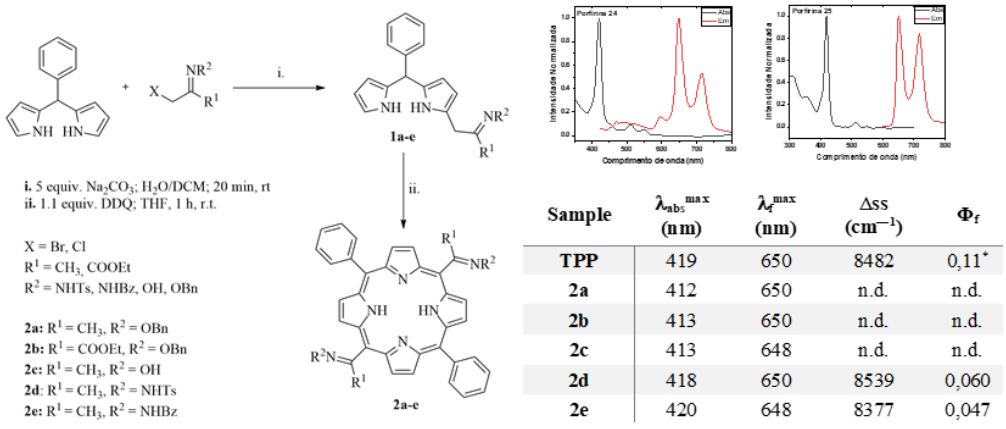
Porphyrins represent a category of highly conjugated heterocyclic compounds distinguished by photophysical attributes, such as high singlet oxygen sensitization yields, pertinent to their application as agents in photodynamic therapy (PDT) [1]. In this communication, we disclose the synthesis of novel *trans*-A_2B_2 porphyrins featuring oxime or hydrazone groups at the 5- and 15-*meso*-positions ('A' substituent) and phenyl groups at the 10- and 20-*meso*-positions ('B' substituent). Through the introduction of specific substituents into their core structure, we aimed to create derivatives with unique photosensitizing properties. Within our research group, we developed innovative methods for synthesizing and functionalizing dipyrromethanes using nitroso- and azoalkenes chemistry. The synthetic pathway shows that dipyrromethanes **1a-e** served as precursors for pioneering *trans*-A_2B_2 porphyrins **2a-2e** incorporating oxime or hydrazone groups (Figure 1) [2-5]. Preliminary tests with radical initiators suggest that porphyrin formation may occur via a radical mechanism, facilitating the dimerization of two dipyrromethane moieties leading to the corresponding porphyrinogen, which then undergoes oxidation to yield the functionalized porphyrin. The novel *trans*-A_2B_2 porphyrins synthesized display a unique substitution pattern showcasing promising photophysical properties.



Sample	λ_{abs}^{max} (nm)	λ_f^{max} (nm)	Δss (cm^{-1})	Φ_f
TPP	419	650	8482	0,11*
2a	412	650	n.d.	n.d.
2b	413	650	n.d.	n.d.
2c	413	648	n.d.	n.d.
2d	418	650	8539	0,060
2e	420	648	8377	0,047

Figure 1: a) Schematic route for *meso*-substituted *trans*-A_2B_2-porphyrins synthesis; b) absorption spectra (dotted line) of hydrazone *meso*-substituted *trans*-A_2B_2-porphyrins **2d-e**; c) $\lambda_{abs}^{max}/\lambda_F^{max}$, stokes shift, and fluorescence quantum yield for functionalized (**2a-e**) and non-functionalized (TPP) porphyrins (*Photochemcad database).

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Using the Passerini multicomponent reaction as a tool to access small-libraries of oxindole-type hybrids as promising anticancer agents

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Cancer is a major health problem worldwide, mainly attributed to the difficulty in developing target-specific drugs, drug resistance and is still linked to terrible side-effects for patients. Among the various drugs targeting specific proteins involved in tumorigenesis, the ones targeting tyrosine kinases are among the most reported, due to the important role and propensity for mutations of the tyrosine kinase protein.[1] However, they are hard to develop due to therapeutic target's structure and physiological role, and even more when sustainability, innovation, and economically favored processes are considered. In previous studies it was discovered that oxindole-type compounds have important structural features and have been considered promising as anticancer agents for targeted therapy and to overcome drug resistance.[2] Our work-plan is based on the synthesizes of new families of promising oxindole-type hybrids as anticancer agents and it is expected to reduce substantially the waste generation through prevention, reduction, and reuse during the synthetic process. In this presentation we would like to disclose our latest findings and preliminary outcomes regarding the use of the Passerini multicomponent reaction in the synthesis of a new family of 3-carbamoyl-2-oxoindolin-3-yl 2-halobenzoate derivatives, promising building blocks for Buchwald-Hartwig coupling reaction (Figure 1).

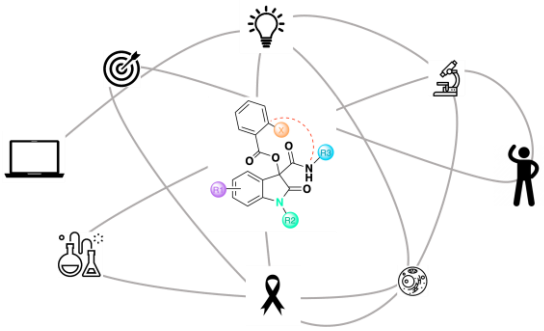

Figure 1: 3-Carbamoyl-2-oxoindolin-3-yl 2-halobenzoate hybrids as potential anticancer agents.

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Building novel amyloid probes featuring D-A-D architectures

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Early diagnosis of Alzheimer's disease (AD) is essential for a successful therapy [1]. Many near-infrared fluorescent (NIRF) probes targeting Aβ, and tau species have been developed over time [2]. Cyanines, BODIPYs, DANIRs, carbazoles, and derivatives of curcumin are a few examples [2]. Either donor-acceptor (D-A) or donor-acceptor-donor (D-A-D) architectures are used to build-up these probes [2]. However, the resolution and imaging depth of widely used NIRF-I probes in the 700-900 nm range are limited, which hinders their application in living organisms [3]. Furthermore, because of lower photon scattering and autofluorescence, fluorescence imaging in the second near-infrared window (NIR-II, 1000-1700 nm) offers unrealized potential since it enables deeper penetration and higher resolution [4]. As previously noted, chromone building blocks have the potential to be used to create aggregation-induced emission (AIE)-active probes for accurate Aβ plaque mapping [5]. When employed *in vivo* and with individuals suffering from AD, these probes faced challenges due to their emission of light in the NIR-I range [5].

Here, we report the synthesis and comprehensive 1D and 2D NMR characterization of completely organic chromone-based probes **4** with D-A-D architectures. The synthesis would begin with the Heck reaction between styrenes and halogenated 2-methylchromones **1**, proceeded by a Knoevenagel condensation with malononitrile, and finally, a reaction with cinnamaldehydes (Figure 1).

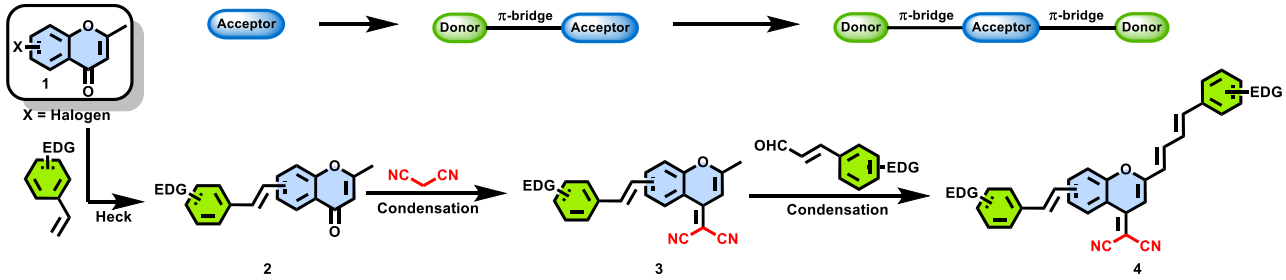

Figure 1: Synthesis of chromone-based probes **4** featuring D-A-D architectures.

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"Seasoning" antimalarial drugs action: chloroquine bile salts as novel triple-stage antiplasmodial hits

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Malaria is one of the "Big Three" global infectious diseases, having caused above two hundred million cases and over half a million deaths only in 2020 [1,2]. The continuous demand for new treatment options prioritizes the cost-effective development of new chemical entities with multi-stage antiplasmodial activity, for higher efficacy and lower propensity to elicit drug-resistant parasite strains [3]. Following up on our long-term research towards the rescue of classical antimalarial aminoquinolines like chloroquine (CQ) and primaquine (PQ) [4-9], we have developed new organic salts by acid-base pairing of those drugs with natural bile acids. These antimalarial drug-derived bile salts were screened *in vitro* against the hepatic, blood, and gametocyte stages of *Plasmodium* parasites, unveiling CQ-derived bile salts as unprecedented triple-stage antiplasmodial hits [10]. Owing to their amphiphilic nature, these salts are currently being investigated as potential surface-active ionic liquids (SAIL), which could have a positive impact on their self-promoted delivery *in vivo*. Overall, our findings pave a new pathway for cost-effective drug rescuing, far beyond antimalarial drugs.

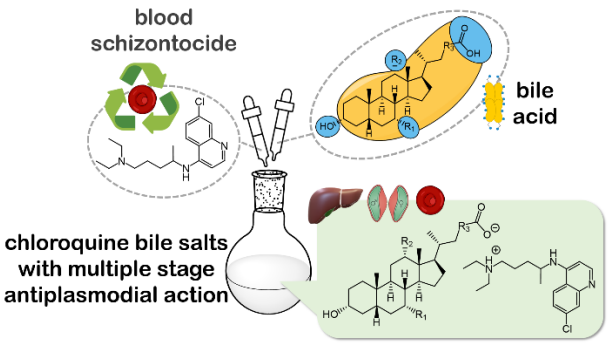

Figure 1: Straightforward production of chloroquine-derived bile salts as triple-stage antimalarial hits.

Acknowledgements: Thanks are due to Fundação para a Ciência e Tecnologia and Ministério da Ciência, Tecnologia e Ensino Superior (FCT/MCTES) for funding through projects UIDB/50006/2020 (LAQV-REQUIMTE), UIDB/00081/2020 (CIQ-UP), and UID/Multi/04413/2013 (GHTM). MP acknowledges the "la Caixa" Foundation for Grant HR21-848. Thanks are further due to FCT/MCTES and to Sociedade Portuguesa de Química (SPQ) for the doctoral grant SFRH/BD/150649/2020 to ATS.

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Quinic acid: A new framework for α-glucosidase inhibitors

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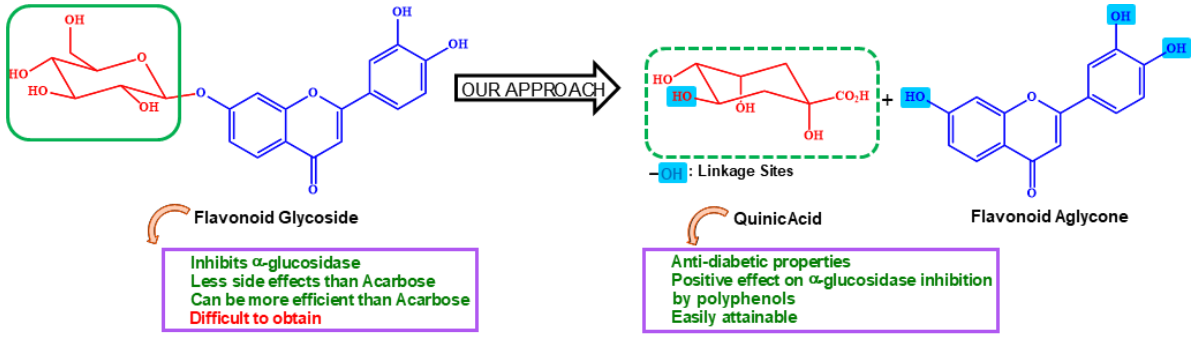
One approach to managing type 2 diabetes involves the inhibition of α-glucosidase, being acarbose the foremost inhibitor [1]. Yet, due to its side effects, finding new and potent compounds with fewer drawbacks poses a pertinent challenge.

Flavonoid glycosides exhibit promising inhibitory potential with reduced adverse reactions [2]. However, obtaining them naturally, through chemical synthesis, or via biotechnological means can be impractical due to environmental concerns, low yields, and high costs [3]. While synthesizing flavonoids is feasible [4], the stumbling block lies in their glycosylation. A potential solution involves functionalizing them with a derivative of quinic acid, easily sourced from coffee beans, fruits, and various plants [5], and also known for its antidiabetic properties [6] and positive impact on α-glucosidase inhibition with certain polyphenols [7].

This study aims to craft a viable alternative for creating α-glucosidase inhibitors by functionalizing flavonoids with a quinic acid derivative.



Scheme 1: Functionalization of flavonoids with quinic acid as a possible alternative to flavonoid glycosides

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Synthesis and functionalization of non-symmetrical *N*-alkyl diketopyrrolopyrroles

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Diketopyrrolopyrroles (DPP) are one of the latest synthetic organic pigments. These compounds show remarkable physical and photophysical properties and, thus, are being extensively studied for applications in various fields such as OLEDs, solar cells, or sensors [1][2]. This suggests the potential use of DPP as fluorophores, possibly with better performance than commonly used fluorophores that frequently display drawbacks such as low Stokes shift and are susceptible to photodegradation [3].

Alkylation is generally the first step when working with DPP leading to soluble derivatives, thus facilitating further modification. However, little attention has been given to the N-alkylation step, particularly with two different groups that can be further functionalized. Previously reported methods to non-symmetrical DPP derivatives involve a long synthetic route, leading to low yields [4].

In this work, we report the synthesis of a DPP derivative bearing two different alkyl groups using pigment red 254 as the starting material (Figure 1). After the alkylation steps, the nitro group was reduced and converted into a maleimide moity. The use of this compound as a fluorophore, as well as the optimization of the reaction conditions, are currently in progress.

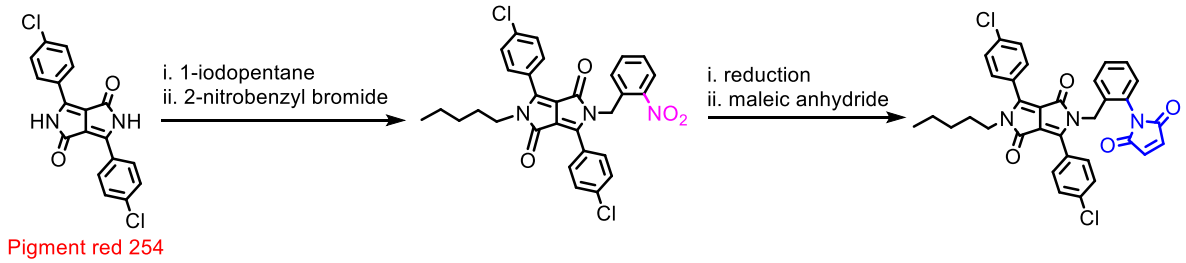

Figure 1: Strategy for the synthesis of a non-symmetrical DPP derivative bearing a maleimide moity.

Funding: This work received financial support from PT national funds (FCT/MCTES) through projects UIDB/50006/2020 and UIDP/50006/2020.

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Continuous flow phosphine-catalyzed [3+2] annulation of allenoates: Towards efficient synthesis of chiral spirocyclopentene-penicillanates

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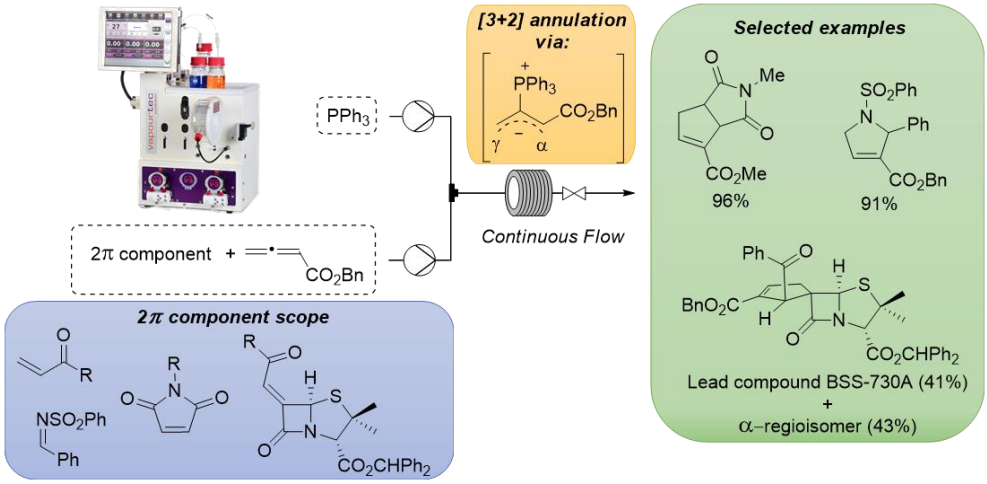
Studies on the synthesis and biological evaluation of spiro-β-lactams derived from 6-aminopenicillanic acid led to the discovery of lead compounds, exhibiting remarkable antiviral properties [1,2]. The successful use of the continuous flow technique stands out for allowing very short reaction times, and by its inherent characteristics that ensure easy scale-up processes. In this context, we describe the development of a continuous flow approach to chiral spirocyclopentene-penicillanates via phosphine-catalyzed [3+2] annulation of allenoates with 6-alkylidenepenicillanates.

Initially, model reactions were carried out using simple alkenes, such as methyl vinyl ketone and *N*-substituted maleimides, leading to the corresponding products in excellent yields (up to 96%). The [3+2] annulation reaction was subsequently extended to the reactivity of 6-alkylidenepenicillanates, a more complex 2π-component with an exocyclic carbon-carbon double bond, allowing the synthesis of spirocyclic compounds. Two regioisomeric chiral spirocyclopentene-β-lactams were obtained, including the bioactive derivatives, in moderate to good overall yields (31-84%). The continuous flow synthesis proved to be an efficient alternative to the conventional methodology [3,4], leading to the formation of the desired compounds in competitive yields and high productivity.



Scheme 1: Phosphine-catalyzed [3+2] annulation of allenoates under continuous flow chemistry.

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Acknowledgements: We acknowledge the UC-NMR facility for producing the NMR data (www.nmrccc.uc.pt).

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Novel semisynthetic A-ring-cleaved glycyrrhetinic acid derivatives as potential anticancer agents

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Introduction: Glycyrrhetinic acid (**1**) is a hydrolysed metabolite of glycyrrhizin, a major pentacyclic triterpenoid saponin sourced from the roots of Glycyrrhiza species, commonly known as liquorice [1,2]. Notably, **1** has demonstrated considerable antiproliferative properties against various types of cancers. However, its effectiveness and selectivity as an antitumor agent have limitations. **Methodology:** To explore novel potential antitumor agents, a series of innovative glycyrrhetinic acid (**1**) derivatives was synthesized through the cleavage of its A-ring and coupling with amino acids [3]. The antiproliferative activities of these novel semisynthetic derivatives were evaluated against a panel of nine human cancer cell lines. **Results:** Compound **17** was the most active compound, displaying a remarkable IC_{50} value of 6.1 μM against Jurkat cells, a type of acute T-cell leukaemia (Figure 1). This derivative was 17-fold more potent than the parent compound (**1**) against this cancer cell line. Additional studies showed that the anticancer activity of compound **17** was due to cell cycle arrest at the S phase and induction of apoptosis in Jurkat cells. **Discussion:** Considering the promising results obtained with derivative **17**, further biological studies were performed to gain a deeper understanding of the mechanisms underlying its anticancer activity. **Keywords:** pentacyclic triterpenoids; glycyrrhetinic acid; cancer.

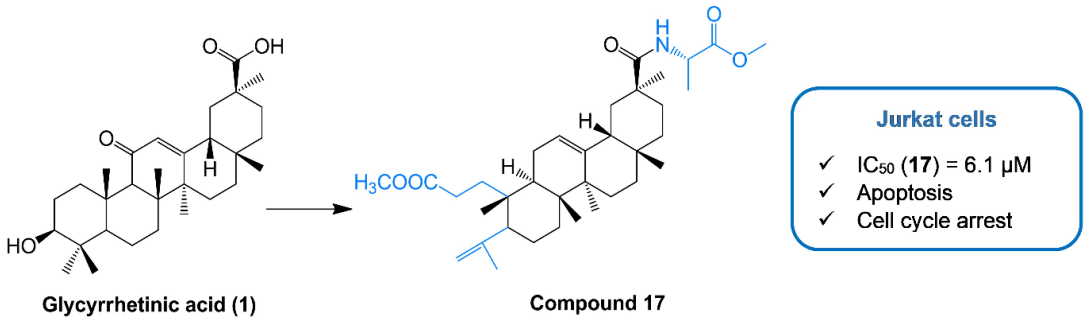

Figure 1: Structure of glycyrrhetinic acid (**1**) and its derivative **17** with potential anticancer activity.

Acknowledgements: Jorge Salvador gratefully acknowledges PT2020 (Programa Operacional do Centro 2020) and the financial support by FEDER (European Regional Development Fund) through the COMPETE 2020 Programme (Operational Programme for Competitiveness and Internationalisation), project CENTRO-01-0247-FEDER- 003269, drugs2CAD. Jorge Salvador also acknowledges financial support from the University of Coimbra. Daniela Alho and Pedro Sobral thanks Fundação para a Ciência e Tecnologia (FCT) for financial support with research grants SFRH/BD/66020/2009 and 2020.04950.BD, respectively. Marta Cascante and Silvia Marin thank MINECO-European Commission FEDER—Una manera de hacer Europa (SAF2017-89673-R) and Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR)—Generalitat de Catalunya (2017SGR1033).

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Towards the discovery of novel ubiquitin specific protease 7 (USP7) Inhibitors: an integrated protocol of pharmacophore modelling and virtual screening

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Ubiquitin-specific protease 7 (USP7) is a member of one of the most largely studied families of deubiquitylating enzymes. It plays a key role modulating the levels of multiple proteins, including tumor suppressors, transcription factors, epigenetic modulators, DNA repair proteins, and regulators of the immune response. The abnormal expression of USP7 is found in various malignant tumors and a high expression signature generally indicates poor tumor prognosis. This suggests USP7 as a promising prognostic and druggable target for cancer therapy. Wherefore, the main goal of this study was the identification of promising small molecules that could potentially inhibit USP7 enzymatic activity. The work was conducted according to an integrated molecular modelling protocol, including structure-based pharmacophore and molecular docking virtual screening. Such protocol disclosed new USP7 hit compounds, highlighting the utility of computer-aided drug discovery in the early drug discovery process, and paved the way for the identification of promising USP7 inhibitors that might represent a steppingstone for cancer treatment.

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Antituberculosis agents multitargeting the electron transport chain of *Mycobacterium tuberculosis*

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Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), stands as one of the world's most lethal infectious diseases [1]. TB remains an uncontained health challenge, primarily attributed to prolonged treatment regimens, low patient compliance, and the emergence and spread of multidrug-resistant and extensively drug-resistant TB [2,3]. Furthermore, most of the existing anti-TB drugs do not effectively target latent forms, which are prevalent in 90% of infected patients that can later evolve into a replicant form, leading to symptomatic and contagious disease. So, it is crucial to explore novel scaffolds and develop new drugs with potent activity against drug-resistant replicant and latent Mtb [3].

After the discovery of ATPsynthase inhibitor bedaquiline, the mycobacterial energetic metabolism has gained attention as a promising anti-TB therapeutic target, since Mtb's viability and pathogenicity depend on the energy produced by its respiratory chain. Combining compounds that target several components of the electron transport chain (ETC) has been contemplated as an innovative and potentially successful strategy to target TB and avoid the onset of resistance [4].

Our aim is to progress a set of pyrroloquinolones (PYQ), that arose from a screening against Mtb H37Rv strain, into promising lead candidates, developed to multitarget Mtb's ETC. These compounds tackle both active and latent Mtb forms, through the concurrent inhibition of cytochrome *bcc* and of cytochrome *bd*, by releasing nitric oxide.

Here we outline a small library of cytochrome *bcc* inhibitors and hybrid derivatives, featuring diverse linkers connecting the molecules' two pharmacophores (Figure 1). Compounds' solubility determination and biological evaluation against Mtb H37Rv and Mtb cyt-*bd* knockout mutant will also be presented. Additionally, a computational approach to perform a structure-based design of novel inhibitors, with improved activity and solubility is also included.

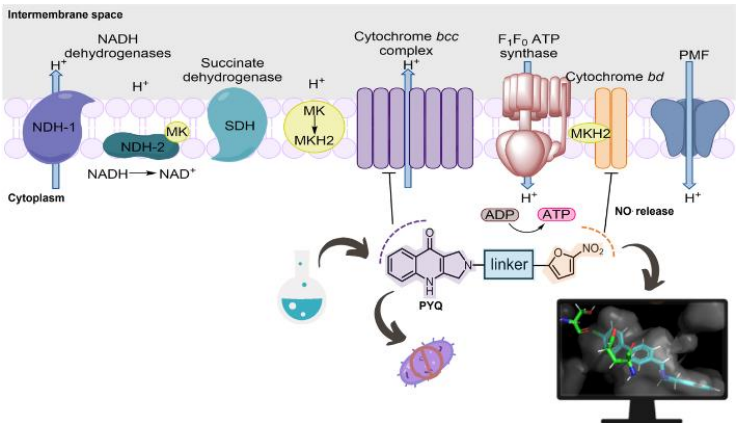

Figure 1: Pyrroloquinolone-based hybrids multitargeting the electron transport chain of *Mycobacterium tuberculosis*.

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Pharmacokinetic profile of selenochrysin: a promising anticancer scaffold

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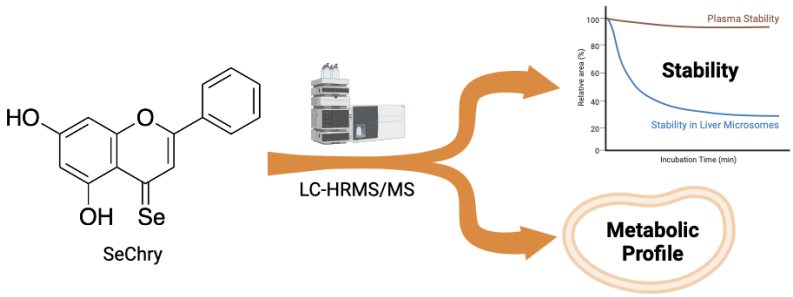
Chemotherapy stands as a key cancer treatment; however, the restricted efficacy due to drug resistance stresses the need for developing new drugs capable of overcoming this challenge [1].

Selenium-containing chrysin (SeChry), exhibited efficacy in overcoming cisplatin and multidrug resistance in a pannel of cell lines [2]. In addition to its potent glutathione peroxidase (GPx)-like activity, SeChry was demonstrated to have inhibitory effect towards the antioxidant enzyme thioredoxin reductase (TrxR) and the H_2S-synthesizing enzyme cystathionine β-synthase (CBS) [2,3]. Altogether, these preliminary findings position SeChry as a promising scaffold for addressing the challenging issue of multidrug resistance in cancer treatment.

A profound understanding of the metabolic fate of drug candidates is crucial to flag structural liabilities and guide structural optimization, preventing late-stage drug attrition attributed to toxicity [4]. Employing a methodology similar to the one used for ruthenium-cyclopentadienyl compounds,[5] we present the *in vitro* stability of SeChry against plasma and liver metabolizing enzymes. Furthermore, the metabolic profile of this lead compound was elucidated in human liver microsome incubations using liquid chromatography coupled with tandem high-resolution mass spectrometry (LC-HRMS/MS).

While SeChry demonstrated stability towards plasma enzymes, rapid degradation occurred under liver metabolizing enzymes. The metabolite profile shed light on potential structural modifications that might enhance the pharmacokinetic profile of this organoselenium scaffold.



Scheme 1: Selenochrysin pharmacokinetic profile.

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Hexahomotrioxacalix[3]arene-based receptors containing naphthalene, anthracene and pyrene fluorophores

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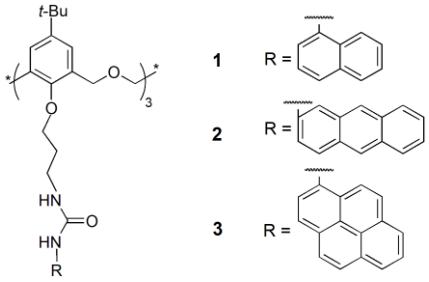
Anion recognition by synthetic receptors continues to attract much attention, as anions play essential roles in biological systems, as well as in environmental and industrial processes [1]. By other side, the development of chemical sensors for the detection of explosives is a very actual research area, due to its importance in anti-terrorism and homeland security areas [2]. The versatile macrocyclic compound calixarenes bearing fluorophore groups have been widely studied in the recognition of both kind of analytes [3].

Following our previous studies on binding properties of ureido-hexahomotrioxacalix[3]arene derivatives [4, 5], we have extended those studies to fluorescent receptors for anions and nitroaromatic compounds.

This work reports the affinity of compounds **1**, **2** and **3**, bearing naphthyl-, anthryl- or pyrenyl-urea groups, respectively, on the lower rim via a propyl spacer, towards relevant anions and some nitroaromatic explosives. These studies were performed by proton NMR, UV-Vis absorption and steady-state fluorescence titrations.



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Synthesis of isatin-based macrocycles for treating Alzheimer's disease

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Some of the targets involved in Alzheimer's disease are considered undruggable, which means that these biomolecules do not respond to conventional small molecules [1]. This is the reason why larger molecules began to be considered as potential therapeutics for these targets. Macrocycles for a long time have have a privileged status for the treatment of various disease, particularly cancer (Dolastatin, Laulimalide A, Peloruside, Calicheamicin), anti-microbial (Erythronolide B) and immunosuppressants (Rapamycin, FK-506), showing favorable pharmacological properties.

Our interest has been the development of novel macrocycles based on the oxindole unit – which shows a large spectrum of biological activities – against neurodegenerative diseases, such as Alzheimer's [2]. The oxindole unit is an excellent starting point considering its vast application in medicinal chemistry, and particularly in Alzheimer's disease [3].

In this communication, we report our efforts on developing novel macrocyclic structures based on isatin and the application of powerful synthetic tools to achieve this objective, using various methodologies including Grignard, Barbier, and cross-coupling reactions (e.g. Mizoroki-Heck), as well as Ring-Closing Metathesis (RCM) approaches (Figure 1).

Furthermore, these compounds will then be screened *in vitro* against β-secretase (BACE-1), responsible for β-amyloid formation in Alzheimer's disease.

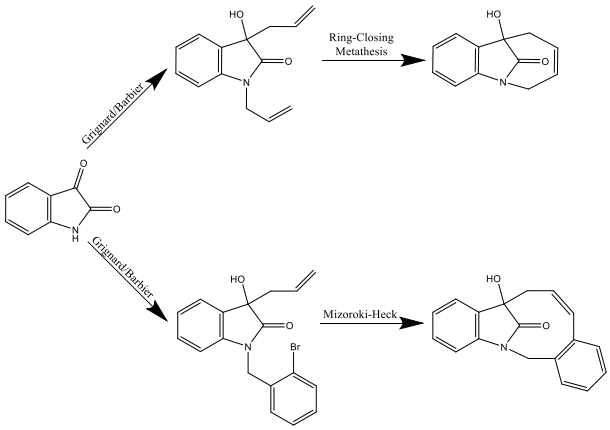

Figure 1: Our synthetic approach to isatin-macrocyclic structures.

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Inexpensive small molecules as promising fluorescent labels for biomolecules

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Fluorescent labels are indispensable in various modern scientific applications, including direct and indirect immunochemistry, fluorescence microscopy, histochemistry, flow cytometry and fluorescence in situ hybridization (FISH) [1,2]. Small fluorescent labels offer significant practical benefits, enabling the optimization of fluorescence signals through the attachment of multiple fluorophores to a single biomolecule [3,4]. The commonly used fluorescent labels are prohibitively expensive for regular use in routine applications and most of them have small Stokes shifts. In this work we present three new small molecules (Figure 1), as promising fluorescent labels for biomolecules, obtained through an efficient, straightforward, and cost-effective synthetic strategy. Additionally, we evaluate the fluorescent three new small molecules labels as potentially effective fluorescent labels for biomolecules. Six new fluorescent oligonucleotide probes have been obtained, three directed to the rRNA region of eukaryotic cells (EUK516) and three to the rRNA region of prokaryotic cells (EUB338). The developed fluorescent probes were tested on microorganisms belonging to the culture collection of the Laboratory of Biodegradation and Biotechnology of the HERCULES Laboratory (University of Évora), showing effective performance as RNA-FISH probes. Density functional theory and time-dependent density functional theory calculations were carried out to gain insights into the observed photophysical properties.These findings evidenced the applicability of these new small molecules in labeling of biomolecules and bioimaging.

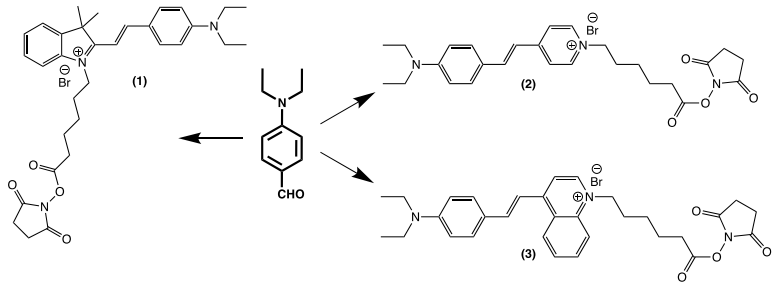

Figure 1: Synthetic route to the fluorescent labels **1**, **2** and **3**.

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Lipophilic profile of the *Salicornia alpini* growing in different salt marshes of the Ria de Aveiro

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Soil salinization is one of the most critical issues in global agricultural production [1]. Halophytes present several advantages compared to other plants, such as high productivity in saline and waterlogged environments, nutritional and medicinal properties of human interest, phytoremediation, and soil desalination [2]. These metabolites of interest are biosynthesised in response to the environmental stress they endure [3], rendering them rich in fatty acids and antioxidant molecules [4].

Annual species within the Salicornia genus are extensively studied. *Salicornia alpini* is a perennial halophyte forming extensive meadows in the marshes of the Iberian Peninsula [5]. In the Ria de Aveiro, this plant thrives in the middle portion of the marshes, facing variable environmental conditions such as summer droughts, high salinity, and occasional submersion due to tides, ranging from twice daily to once a year [6]. To valorise Portuguese natural resources, we used GC-MS analysis to conduct a lipophilic profile analysis of *S. alpini* inhabiting different salt marshes within the Ria de Aveiro. It is intended to discern compositional differences corresponding to the environmental conditions the plants are subjected to *in situ* and to identify the environmental conditions that yield the best phytochemical profiles for human consumption. The primary compounds identified and their respective sedimentary conditions will be presented and discussed in this poster presentation (Figure 1).

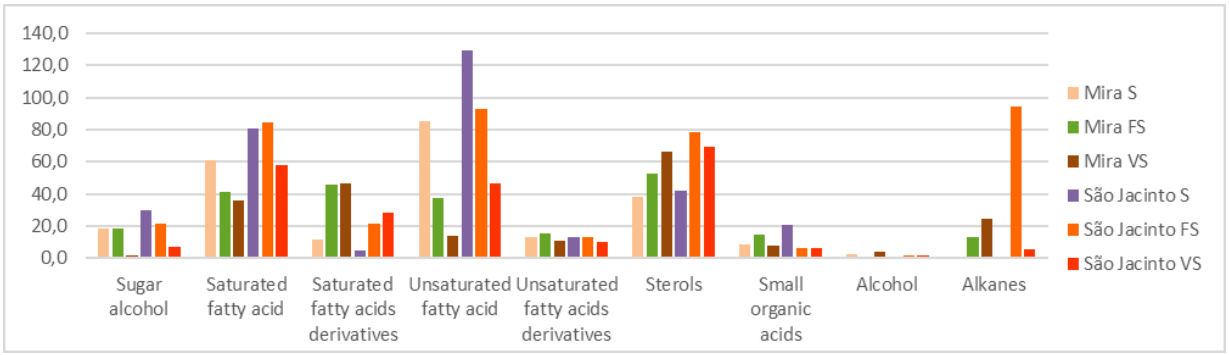

Figure 1: Quantification of groups of compounds found in S. alpini. S=stem; FS=fruiting segments; VS:vegetative segments.

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Design and synthesis of 12-thiazole abietanes as selective inhibitors of the human metabolic serine hydrolase hABHD16A

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Neuroinflammation, defined as inflammation of tissue within the peripheral and central nervous system, has been implicated in the development of chronic pain via sensitization of nociceptive neurons [1,2]. Therefore, identifying and targeting the processes and molecules involved in neuroinflammation is regarded as an effective strategy for innovative chronic pain treatments. In this regard, the metabolic serine hydrolase ABHD16A, belonging to the ABHD (α,β-hydrolase domain) enzyme family may potentially be a novel key target in inflammation-mediated pain [3,4]. Selective inhibitors of hABHD16A (human ABHD16A) have not yet been reported.

In the screening of an in-house library of compounds, we have identified 12-thiazole abietanes as a new class of reversible inhibitors of the human metabolic serine hydrolase [5,6]. Upon the optimization of the first hit compound we discovered a 2-methylthiazole derivative with an IC_{50} value of 3.4 ± 0.2 μM and promising selectivity towards ABHD16A. Our current work focuses on screening a further series of 12-thiazole abietanes on ABHD16A. Our study suggests abietane-type diterpenoids present an attractive starting point for the design of selective ABHD16A inhibitors, contributing towards understanding the significance of hABHD16A inhibition *in vivo*.

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Amplifying the library of thio-linked pyrimidine-based conjugates

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Annually, more than 40,000 deaths are reported in countries with low socioeconomical level due to incident protozoan diseases, such as leishmaniases, chagas disease and human african trypanosomiasis. Available chemotherapy for the treatment of these vector-borne diseases is unsatisfactory, mainly due to poor efficacy, side effects, inadequate mode of administration, and emerging resistance. There is, thus, an imperative necessity of novel, safer and more effective drugs, with reduced propensity to loss of efficacy through resistance [1]. A hopeful approach employed in *de novo* drug discovery is the search for new biomolecular targets.

Recently, trypanothione reductase (TR) attracted attention due to its vital role in maintaining the parasite's redox homeostasis by reducing trypanothione. On the other hand, the similarity of the TR structure among all Trypanosomatidae could trigger the development of a common inhibitor endowed with a wide spectrum of activity among trypanosomatids. Moreover, TR is not present in the mammalian host, since mammalians own glutathione reductase (GR), favoring the specificity of a potential lead compound [2]. Efforts to improve the prevailing situation of trypanosomiasis chemotherapy based on TR inhibition have been intensified. Seeking to find better options, several preliminary studies were conducted showing the potential of aryl sulfides in inactivating the catalytic site of TR (**RDS_562**, Figure **1**) [3,4].

In this work we reported the synthesis and crystal structure of a library of novel thio-linked pyrimidine-based conjugates that could be evaluated as new potential TR inhibitors. By applying our synthetic approach, we observed formation of products from reaction with DMF. The regioselectivity also proved to be affected by the mono- or di-protection of the starting 2,6-dichloropyrimidin-4-amine with di-*tert*-butyl decarbonate. The electron-withdrawing nature of the protecting group appears to increase the susceptibility of the pyrimidine at C4 for reaction with DMF.

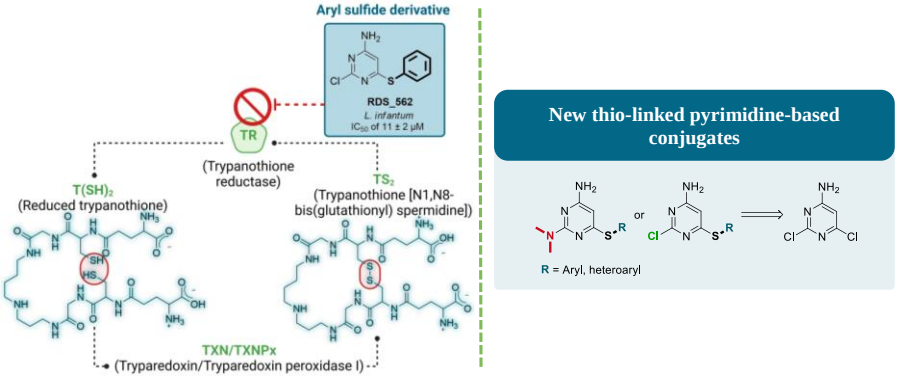

Figure 1: Schematic representation of trypanothione reductase as a target of interest in the development of novel drugs; as aryl sulfides as possible inhibitors (*e*.g. **RDS_562**)[3]. Structural representation of the synthesized thio-linked pyrimidine-based conjugates.

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Iron-catalysed transfer hydrogenation of shikimic acid derivatives

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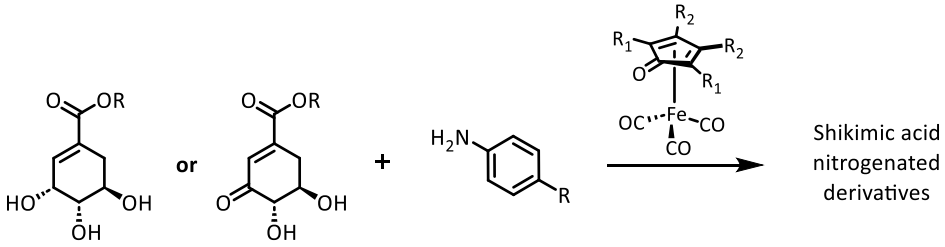
Chemists have been presented with the task of substituting noble metal based processes with Earth-abundant metals such as Iron. As a metal, iron holds a special status, as it ranks second in abundance on the Earth's crust, possesses biocompatibility, and exhibits a diverse range of oxidation states.[1] While iron heterogeneous catalysts have long been employed in the industry for syngas and ammonia production, the exploration of homogeneous iron catalysts has only gained momentum in the past 15 years, ushering in a "new iron age".[2][3]

Shikimic acid, a renewable feedstock, is a naturally occurring compound found abundantly in plants. In addition to its role in the production of Tamiflu, shikimic acid has gained significant recognition due to its valuable carbon backbone and dense stereochemistry, making it highly versatile as a chiral precursor.[4]

In this work, we present our efforts to establish new C-N bonds on shikimic acid skeleton aided by iron-catalysts. Two synthetic approaches were tested: hydrogen borrowing approach which is a one-pot method that converts alcohols into the corresponding amines; and catalytic reductive amination.



Scheme 1: Iron-catalysed transfer hydrogenation on shikimic acid derivatives.

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Halimane derivatives from *Plectranthus ornatus* Codd. demonstrate anti-cancer activity

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The *Plectranthus* genus (Lamiaceae) is known for its medicinal species, representing a rich source of lead natural compounds with diverse biological activities [1]. Across Africa, Asia, and Brazil, *P. ornatus* Codd. has been used in folk medicine as a replacement for *P. barbatus* to treat a plethora of ailments, including digestive issues, liver failure, infections, and pain [2]. *P. ornatus'* main phytochemical constituents are diterpenes and phenolic compounds and give rise to interesting biological activities. The main constituent of *P. ornatus'* acetonic ultrasound-assisted extract is the halimane compound 11*R**-acetoxyhalima-5,13*E*-dien-15-oic acid (**Hal**) [2]. **Hal** was found to have interesting biological activities, such as moderate anti-inflammatory effects, antimycobacterial activity and cytotoxicity. Previous studies by our group, demonstrated that **Hal** has moderate anti-inflammatory and cytotoxic activity against four cancer cell lines (lung A549, leukaemia CCRF-CEM, FaDu and MCF7 with IC_{50} = 19.38, 16.52, 15.12 and 13.61 μg/mL, respectively) [3,4]. Based on this, the present work aimed for the full physiochemical characterization of the starting material **HAL**, through SCXRD, FT-IR, and thermal analysis, including HSM (165.7°C), DSC and TG. The results of the crystallographic studies indicate that **HAL** crystallizes in the $P2_12_12_1$ orthorhombic space group, and that $R_2^2(8)$ homosynthons originate pairs of **Hal** molecules as their carboxylic acid moieties form hydrogen bonds. Furthermore, this work aimed to improve the bioactivity of **HAL** through the preparation of new derivatives functionalized using amines. **HAL** derivatives **2**, **3**, **4** and **5** were successfully synthesized and their structural characterization confirmed by ^{1}H-,^{13}C-NMR, MS and FT-IR. Our data showed that amide derivatives of **Hal** presented moderate cytotoxicity and more potent activity when compared to the parent molecule, giving insight into the SAR of **Hal**. The derivatives also displayed protection against oxidative damage to DNA. Finally, the derivatives possessed anti-inflammatory properties at the level of gene and protein expression for the cytokines *IL-1β*, *TNF-α* and *IL-6*, induced by LPS in normal HGF-1 cells. Overall, our study provides useful insight into the enhanced biological activities of semi-synthetic halimane derivatives, as a starting point for novel drug formulations in cancer therapy.

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c-MYC G-quadruplex stabilization by 5-amino-8-chloro-11*H*-indolo[3,2-*c*]isoquinoline derivatives: *in vitro* and *in silico* studies

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Cancer is a group of diseases characterized by uncontrolled cell growth resulting from genetic mutations, presenting a significant therapeutic challenge due to cancer cells' adaptability and resistance to conventional treatments [1]. To address these challenges, innovative approaches, such as targeting G-quadruplexes (G4s), have emerged. G4s are secondary structures formed in DNA, playing a crucial role in downregulating gene expression, particularly in cancer-related genes like *c-MYC*. [2]. Indoloquinolines, natural alkaloids known for their planar structure, have the ability to bind and stabilize various G4s [3]. In this study, a family of 5-amino-8-chloro-11-*H*-indolo[3,2-c]isoquinoline derivatives was synthesized, and their interactions with G4s were analyzed using three different methods: FRET / CD melting assays, and Molecular Dynamics simulations. While *in vitro* assays showed that these are weak stabilizers of DNA G4s, exhibiting a ΔT_m of approximately 4 °C at 25 molar equivalents, our MD simulations indicated that, in general, these compounds are able to stabilize *c-MYC* G4 (Figure 1). Furthermore, we identified preferential binding sites with the 5' terminal quartet. Interestingly, binding studies by fluorescence titration showed that the compounds are good/very good *c-MYC* G4 binders. Overall, the results indicate that the compounds are able to bind to *c-MYC* G4 and induce weak stabilization.

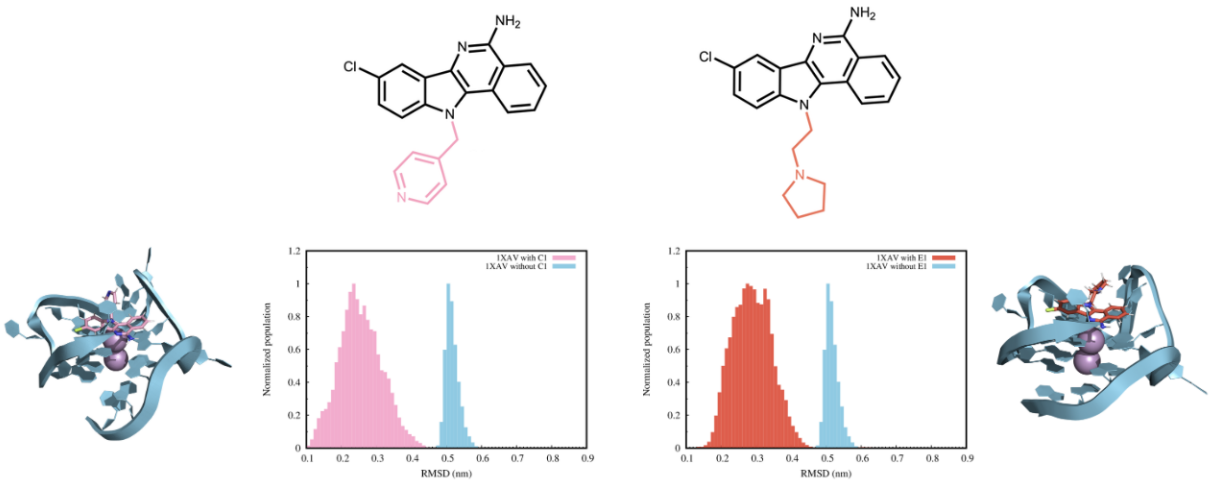

Figure 1: Most populated conformations and variations in the RMSD of 1XAV G4 in the presence (pink or orange) and absence (blue) of the compounds.

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Synthesis of sulfonamides via electrophilic amination mediated by hypervalent iodine(III) reagents

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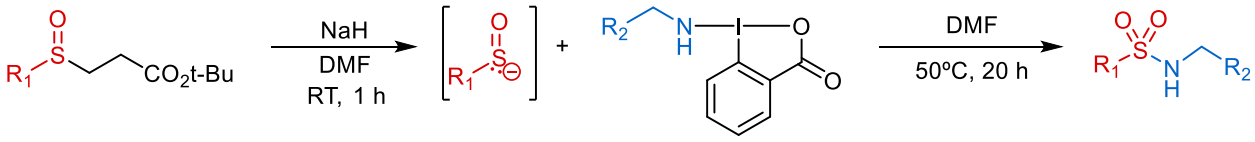
Electrophilic sources of nitrogen-based groups have been known for many decades and are of great synthetic importance. Hypervalent iodine reagents (HIRs) bearing N-containing groups have emerged as an alternative to classical electrophilic amination reactions, and are capable of transferring a wide diversity of nitrogen-containing functional groups to organic molecules.[1]

In particular, cyclic HIRs - benziodoxol(on)es - incorporating the iodine atom in a heterocycle exhibit higher stability. The benziodoxol(on)es and benziodazoles have been the focus of interest, due to their excellent properties to act as electrophilic synthons of normally nucleophilic groups, emerging as powerful tools in electrophilic amination reactions.[2,3]

Our group has been exploring the umpolung reactivity of benzodixolones in the synthesis of sulfonamides,[4] and sulfinyl hydrazides.[5]

Recently we have disclosed the synthesis and reactivity of a novel class of HIRs bearing a transferable primary amine.[6]

In this study, we explored the use of these new HIRs on the electrophilic amination of β-sulfinyl esters, showcasing the synthetic versatility and advantages of this approach. The reactivity of the new HIRs with sulfenates generated in situ was investigated, affording the corresponding aminated products with good to excellent yields (Scheme 1). To gain insights into the reaction mechanism, we conducted control experiments and proposed a plausible reaction pathway.



Scheme 1: General scheme for sulfonamide synthesis

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Mechanochemistry: a way to improve sustainability of furans' transformations

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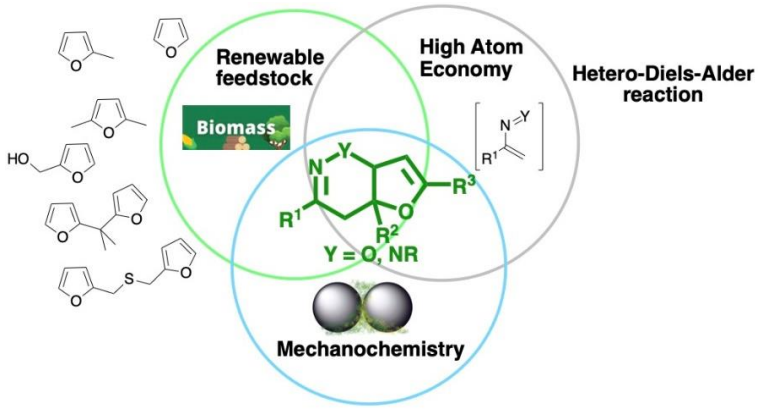
The chemistry of *in situ* generated azo- and nitrosoalkenes has been one of our research topics. These reactive intermediates have been explored as heterodienes in the hetero-Diels-Alder (HDA) reaction with several electron-rich heterocycles, including furan derivatives, providing a range of diverse compounds [1]. To comply with the 12 principles of Green Chemistry, all the participants in a chemical transformation must be considered [2]. In addition to HDA high atom economy and selectivity, it is crucial to choose renewable reactants, and produce the lowest possible amount of waste. In this context, this study combines the hetero-Diels-Alder reaction, furan derivatives, a renewable resource obtained from lignocellulosic biomass, and mechanochemistry. Mechanochemistry presents several advantages when compared to conventional synthetic methods, namely the possibility to perform the reactions without solvents, decreased energy input and easy work-up procedures[3]. In this communication, the results obtained from the studies of the hetero-Diels-Alder reaction of furan derivatives with azo- and nitrosoalkenes, under mechanochemical conditions, will be presented. These studies allowed the synthesis of bicycles (furan-dihydrooxazines and furan-tetrahydropyridazines) in yields of up to 90 %, in a single step and without solvent (Scheme 1). The green chemistry metrics demonstrate the increased sustainability of these transformations when compared to the previous synthetic methods. Details of this study and the mechanisms underlying these transformations will be addressed.



Scheme 1: Combining mechanochemistry, renewable feedstock and hetero-Diels-Alder for the synthesis of furan derivatives.

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Synthesis and characterization of mono- and di-aminopyrazine precursors for the preparation of zinc(II) phthalocyanine derivatives

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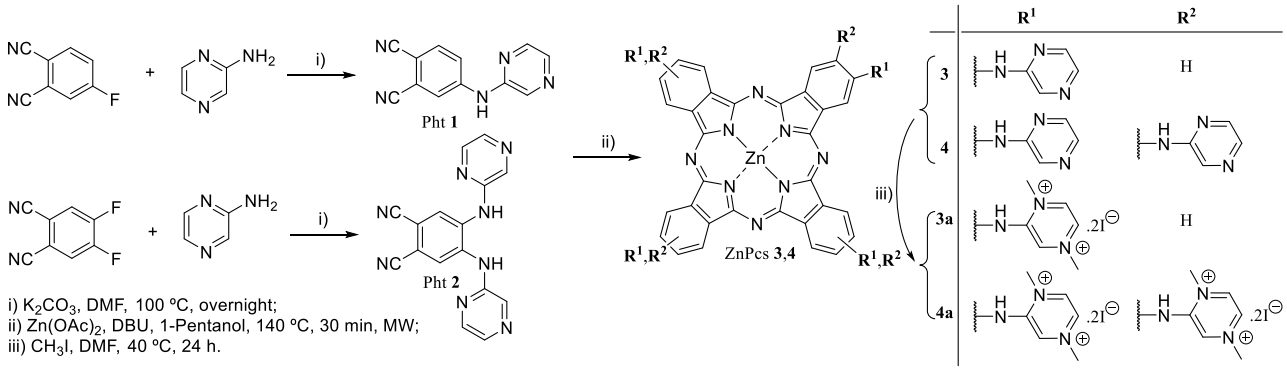
The attempt to create new phthalocyanine (Pc) derivatives has been a challenge area for synthetic researchers to study their applicability in many scientific and technological areas. Pcs are photoactive molecules that can absorb and emit light in a large range of the UV-Vis spectrum [1,2]. However, the low solubility of this class of compounds is the main problem for their application in several areas, mainly in the biomedical ones. The use of pyrazine/pyrazinium units in Pc structures can be a good strategy to solubilize them in different media [3,4]. In this communication we will report and discuss the synthesis and characterization of aminopyrazine phthalonitriles (Pht **1** and Pht **2**) and the corresponding zinc(II) phthalocyanine derivatives (ZnPcs **3**,**3a** and ZnPcs **4**,**4a**) – Scheme 1. The NMR, absorption, and emission spectroscopy and mass spectrometry will be analysed for the prepared molecules.



Scheme 1: Synthesis of aminopyrazine phthalonitriles **1** and **2** and the corresponding zinc(II) phthalocyanine dyes (**3**,**3a** and **4**,**4a**).

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Synthesis of Sonogashira coupling products in the thieno[2,3-*b*]pyrazine series and cyclizations to tricyclic lactones

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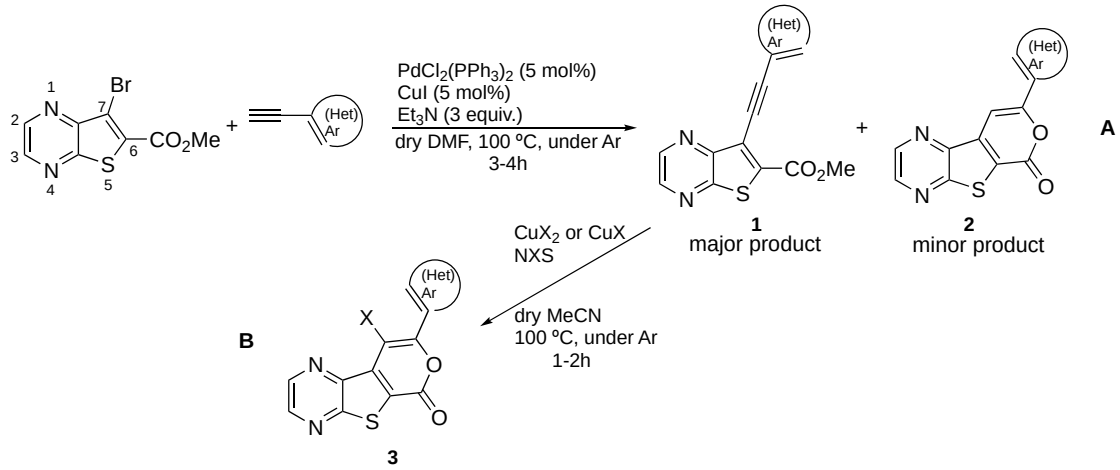
The thieno[2,3-*b*]pyrazine skeleton has been found in natural products and in biologically active synthetic compounds. Besson *et al.* prepared some thieno[2,3-*b*]pyrazine tricyclic derivatives that were studied as potential antitumor compounds [1]. Our research group recently described the synthesis of methyl 7-[(hetero)arylamino]thieno[2,3-*b*]pyrazine-6-carboxylates and their evaluation against different human tumor cell lines including some insights in the mechanism of action for the most promising compounds [2].

Here we present the synthesis of Sonogashira coupling products **1** from the methyl 7-bromothieno[2,3-*b*]pyrazine-6-carboxylate, also prepared [2], and different (hetero)arylalkynes (Ar with EWGs or EDGs and HetAr: thiophene, pyridine) in the presence of Pd and Cu catalysts and Et_3N as a base (Scheme 1A) [3]. Compounds **1** were obtained in good to high yields (50-75%) together with the minor tricyclic lactones **2**, resulting from 6-*endo-dig* cyclization of compounds **1**, in poor yields (5-20%). These were separated by column chromatography and compounds **1** were submitted to halolactonization with Cu salts/NXS to give the halo tricyclic lactones **3** in good yields (Scheme 1B). All the new compounds were fully characterized by ^1H, ^{13}C RMN and HRMS.



Scheme 1: A- Synthesis of Sonogashira coupling products **1** and tricyclic lactones **2**; **B**- Halocyclization of compounds **1**.

The antitumor potential of the compounds obtained will be studied in collaboration with other research groups.

Compounds **3** will be further functionalized by aromatic nucleophilic substitution (SNAr) and/or C-C or C-N metal-catalyzed cross-couplings to give interesting compounds.

Funding: Fundação para a Ciência e Tecnologia (FCT)-Portugal through CQUM (UID/QUI/686/2019), also financed by European Regional Development Fund (ERDF), COMPETE2020 and Portugal2020.

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Biocatalytic approach for sustainable esterification

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The pharmaceutical industry is progressively adopting sustainable approaches for the synthesis of excipients or active pharmaceutical compounds. Typical Fischer esterification requires the use of hazardous reagents, excessive stoichiometric quantities and high reaction temperatures resulting in slower reaction rates and lack of regioselectivity.

In response to these drawbacks, enzymes emerged as a more favourable alternative to operate under milder conditions and achieving faster reaction rates. In addition, the regio- and enantioselectivity displayed by enzymes allows the minimization of side products, decreasing further purification steps and improving the overall process yield.

Due to genetic engineering, it is now possible to optimize enzymes to withstand harsher conditions and to exhibit specificity towards target substrates. These advancements contributed to the cost decrease of biocatalysts, raising the interest of multiple industries [1].

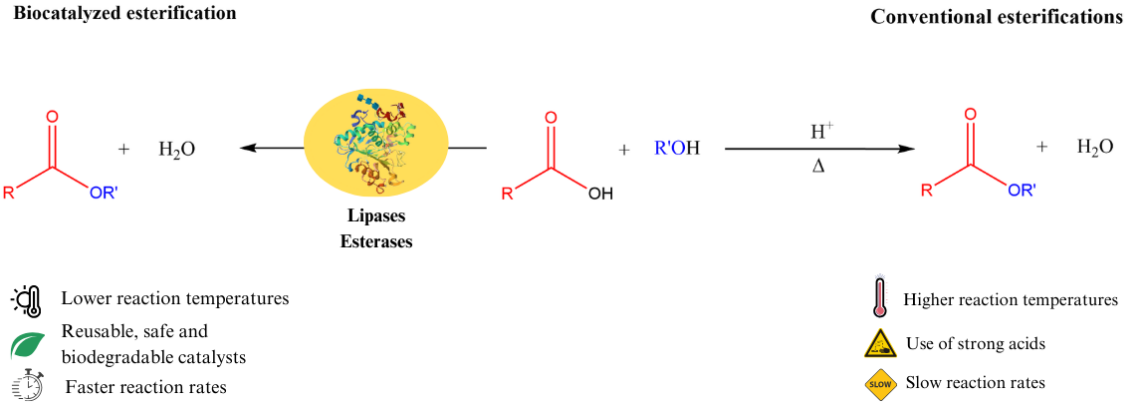

Figure 1: Advantages of biocatalysed esterification compared to conventional esterifications.

Lipases and esterases are mostly known as hydrolases. However, in organic solvents, these biocatalysts can perform the reverse reaction (esterification) although variations in their active site environment can lead to higher or lower specificity. Immobilizing these enzymes on a support addresses the interfacial activation keeping the enzyme in the "open state" and reusable for multiple reactions. This study focuses on enhancing reaction rates by optimizing parameters like temperature, enzyme concentration and substrate concentration. Additionally, research was conducted on the use of additives, various concentrations of salts, to further understand whether electrostatic forces or interactions between the support and enzyme contribute to protein structure maintenance [3]. Furthermore, investigating the effect of water on reaction kinetics allows determination of the minimum water percentage required for enzyme activity while also reducing the tendency for the reaction to shift towards hydrolysis when water is released during esterification **Error! Reference source not found.**. Overall, the lack of literature on the previously mentioned parameters paved the way to understand the underlying mechanism of biocatalysed esterifications, enabling further process optimization.

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Multicomponent synthesis of chiral spiro-oxindoles-hydantoins for leishmaniasis treatment

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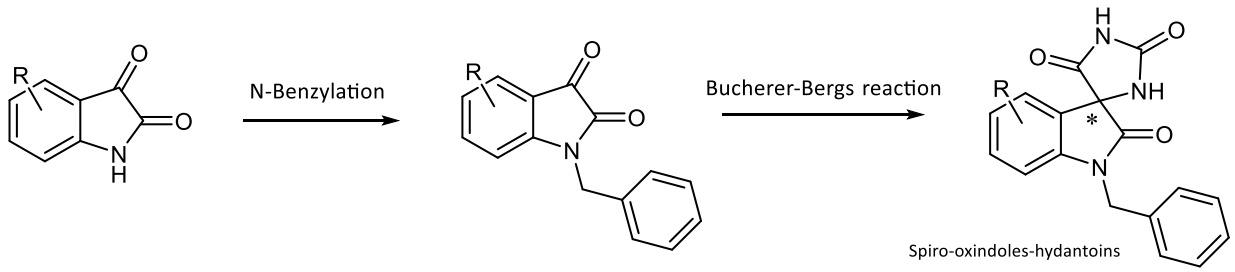
Leishmaniasis is a neglected tropical disease (NTDs), being the second biggest cause of death for a parasitic disease in, after malaria [1]. According to the World Health Organization, it is estimated that 700,000 to 1 million new cases are reported every year. Current treatments include antimony compounds, amphotericin B, pentamidine, miltefosine, among others [2]. However, these pharmaceuticals show toxicity, required prolonged usage and are expensive [3]. That is why it is so important to develop new drugs against leishmaniasis.

Interestingly, several spiro compounds have already demonstrated antileishmanial activity [4]. The oxindole unit is a well-known pharmacophore [5] and, in fact, compounds containing oxindole have been reported for their antileishmanial activity [6]. Hydantoins (imidazolidine-2,4-ones) are also biologically active [7]. In this communication we will discuss our latest results on the multicomponent synthesis (Bucherer-Bergs reaction) of a library of spiro-oxindoles-hydantoins (**Scheme 1**). In the future, these compounds will be evaluated for their antileishmanial activity through *in vitro* assays.



Scheme 1: Synthesis of spiro-oxindoles-hydantoins.

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Synthesis and computational modelling of naturally occurring sucrose-based phytochemicals as lead pharmaceutics

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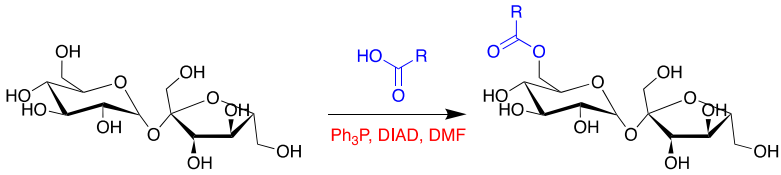
Carbohydrates are one of the most important components for living systems, not only in terms of nourishment and energy, but also in many cases for the treatment of various diseases. Thus, glucose, fructose and sucrose appear as a renewable feedstock replacing petrol-based materials. However, there are still very few drugs containing carbohydrates on the market and more research efforts need to be done, particularly on compounds based on sucrose [1,2].

Phenolic Sucrose Esters (PSEs) are a class of bioactive substances that have been isolated and identified from plants and used in folk medicine since ancient times. These have important biological activities including anti-proliferation, anti-oxidation, anti-inflammatory, and α-glucosidase inhibition activities. Very few of these have been obtained synthetically so far, which, combined with the milligram quantities isolated from plants in pure form, has prevented their use in pharmacology [3,4]. PSEs were first identified in *Raphanus sativus*, and later in a wide variety of plant species that are commonly used as alternative medicine ingredients, such as *Veronicastrum sibiricum*, *Musa acuminata*, *Polygala sibirica*, among others [5].

With this project, we explored one-step selective chemical methodologies (Mitsunobu conditions) to synthesize **24 biologically active sucrose esters** (6 monoesters, 6 per-acetylated monoesters, 6 diesters and 6 per-acetylated diesters) with very promising applications (Scheme 1). A part of the project includes a computational estimation of the radical scavenging effects of these newly synthesized compounds through different reaction paths - hydrogen atom transfer (HAT), single electron transfer (SET) and radical adduct formation (RAF). Then, we will perform *in-vitro* studies to experimentally determine the antioxidant activities in order to compare the results and find structure-activity relationships (SAR).

So far, we have successfully synthesised half of the target compounds with yields up to 33%. The regioselective 6-OH acylation can be confirmed by the HMBC. It is important to note that we succeeded the first synthesis of 6-O-benzoyl sucrose ester and of 6,6'-di-O-feruloyl sucrose ester.



Scheme 1: Acylation of sucrose under Mitsunobu conditions.

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Valorization of thistles from Beira Baixa through the study of the biochemical profile and potential bioactivities

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Thistle is the name given to various weedy, herbaceous, and thorny plants, mostly belonging to the Apiaceae, Dipsacaceae, and Asteraceae families. Usually, they appear spontaneously on agricultural land, pastures, fallow lands, and wastelands, as happens in the Beira Baixa region. These plants have no value for agriculture or animal feed, thus becoming unused waste for local farmers, as they have to be removed, resulting in additional costs. Furthermore, some plants found in the Beira Baixa area have never been studied from a biochemical point of view, namely, their biochemical profile and possible associated bioactivities. Therefore, studying these plants to find alternative ways of valuing them and contributing to the region's development is essential.

Different species of thistle have been used for hundreds of years in traditional medicine to treat various diseases, as they have anti-inflammatory, antibacterial, antipyretic, cytotoxic, and antidiabetic properties, most often prepared by infusion, decoction, or boiling [1]. There are studies where different species of thistles have been explored for their bioactive properties with promising results [2,3].

Therefore, the main objective of this work is to value unexplored thistles in the Beira Baixa region through the study of the biochemical profile and identification of bioactive compounds.

Figure 1: *Galactites tomentosus* Moench is one of the thistles that can be found in the Beira Baixa region.

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Ru-HKUST: Combining the drug loading and release ability of metal-organic frameworks (MOFs) with ruthenium

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Metal-organic frameworks (MOFs) are the target of growing interest as drug delivery systems due to their high load capacity. Within these, MOF-199 (also known as HKUST-1) features a highly porous structure formed by repeating paddlewheel units of copper (II) dimers and 1,3,5 – benzene tricarboxylic acid (BTC) residues [1]. HKUST-1 is reported to load drugs [2-3] and to have a fair biocompatibility *in vitro* [4]. However, different concentrations of HKUST-1 showed some *in vivo* toxicity that seemed to be associated with MOF degradation and copper release [5].

This study describes the preparation of a ruthenium HKUST analogue, potentially posing as a safer material for drug delivery mainly due to the ability of ruthenium to be transported *in vivo* by transferrin and thus to be less toxic. Moreover, MOF degradation is expected to release ruthenium and/or its complexes, which can be useful in treating parasitic diseases [6]. Synthesis of Ru-HKUST (Figure 1) is done by both solvothermal conditions and microwave-assisted synthesis, with the resulting materials characterised by Fourier-Transform Infrared spectroscopy (FTIR), powder x-ray diffraction (PXRD) and scanning-electron microscopy (SEM). Results show that microwave (MW) synthesis not only creates smaller but also more uniform particles. Drug loading and release studies will also be performed with the anti-parasitic drug 2-phenylquinoline.

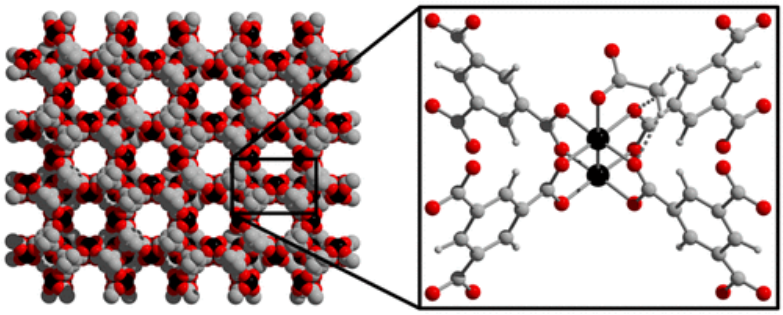

Figure 1: Structure of the ruthenium HKUST, where black, gray, red, and white spheres represent ruthenium, carbon, oxygen, and hydrogen, respectively (Reprinted (adapted) with permission from [7]).

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Antimicrobial potential of nitrogen-substituted Zn(II)-porphyrins as photosensitizers against *Staphylococcus aureus*

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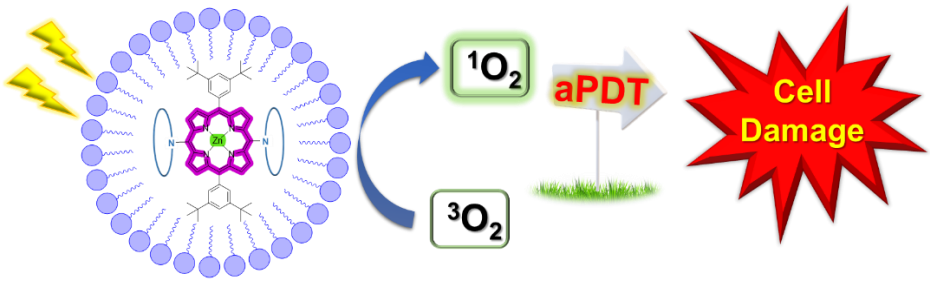
The increase in human life expectancy is strongly related to the emergence of antimicrobial therapy in modern medicine.[1,2] Nevertheless, wrong prescriptions and abuse of antimicrobial drugs led to a new concern – the development of a high number of infections caused by multi-drug resistant microorganisms. Accordingly, it is necessary to develop alternatives[3] and antimicrobial photodynamic therapy (aPDT) is considered a promising option to antibiotics, especially to treat local infections. This approach is based on the activation of a photosensitizer (PS) through visible light in the presence of dioxygen ($^3O_2$), resulting in the generation of reactive oxygen species (ROS) like singlet oxygen ($^1O_2$), which enhances microbial death.[4]

Porphyrins have received attention from the scientific community as beneficial PSs for aPDT due to their absorption features in the visible range of the electromagnetic spectrum, effectiveness in generating ROS, low cytotoxicity in the absence of light, and overall stability and biocompatibility.[3]

Even so, there is room for new developments, and here, we report the synthetic approaches used to afford new PSs based on porphyrins and different nitrogen entities bearing antimicrobial efficiency. The structural characterization and the photoinactivation efficiency of these PSs after their incorporation in PolyVinylPyrrolidone (PVP) against *Staphylococcus aureus* will be discussed, giving special attention to the role of nitrogen entities.



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Biological activity of *bis*(indolyl)methanes functionalized with different hetero(aromatic) moieties

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Pathogenic protozoa are responsible for several diseases worldwide including African trypanosomiasis (also known as sleeping sickness, caused by two subspecies of *Trypanosoma brucei*) and Leishmaniasis (caused by more than 20 species of *Leishmania spp.*). Currently, these parasitic diseases do not have FDA-approved vaccines and the drugs used as treatment have many drawbacks, such as relative toxicity, undesirable side effects, drug resistance and conditional efficiency [1–2]. For those reasons, the development of new chemical structures with improved activity and selectivity against these parasites is a field of great interest.

Bis(indolyl)methanes (BIMs) can be found in several natural products and comprise a wide range of biological activities, such as antitumor, antibacterial, anti-inflammatory, antifungal, antiviral, amongst others [3]. That being the case, BIM derivatives are recognized as important scaffolds and pharmacological intermediates in drug discovery [4]. However, to the best of our knowledge, research on the antiparasitic activity of these family of compounds has been scarce. Having this in mind, our goal was to synthesize a family of BIMs (**1a**-**c**), functionalized with different hetero(aromatic) groups: triphenylamino, *N*,*N*-dimethyl-1-naphthylamino and 8-hydroxylquinolyl and evaluate their antiparasitic and antitumor activity. Our findings demonstrated the BIM scaffold functionalized with a triphenylamino moiety (**1a**) was the most promising antiparasitic and anticancer agent of this series. Analysis of the selectivity index revealed this compound was up to 8-fold more potent against the parasites *T.brucei* and *L.major* and HT-29 cancer cells compared to the healthy human cell line (MRC-5 cells). Fluorescence microscopy experiments conducted on *T. brucei* treated with derivative **1a** indicated that the compound exhibited accumulation in the nucleus of the parasites (Figure 1).

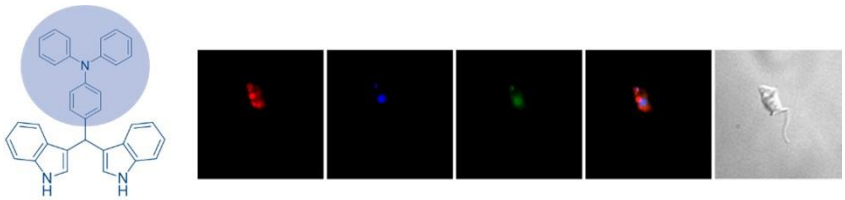

Figure 1: Structure of BIM derivative **1a** and fluorescence microscopy of parasites *T. brucei* incubated with the compound for 2 h.

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Exploring novel anticancer agents by the coupling of (thio)barbiturates with mono- and trimethinecyanine dyes

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Cancer treatment remains challenging due to its complex nature. Various therapies including chemotherapy, radiotherapy, and surgery are used, however, continuous global efforts are essential to discover new, safer, and more effective drugs. In this field, researchers have explored the antiproliferative properties of barbiturate derivatives and cyanine dyes, both separately and together. Within the combination of these two scaffolds, our research group has already confirmed the increase in potency and selectivity of squarylic cyanine dyes, when coupled with barbituric acid in the context of photodynamic therapy (PDT) [1]. In fact, cyanine dyes, in general, are widely studied as photosensitizing agents in PDT [2], with little exploration as antiproliferative agents in themselves, especially when absorbed outside the therapeutic window. In this context, we recently found that mono- and trimethinecyanines revealed high potency and selectivity outside the PDT context [3]. To pursue this purpose, a set of symmetric and asymmetric cyanine dyes functionalized with barbiturates were synthesized. Antiproliferative activity was evaluated in the dark using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method in two cancer cell lines (MCF-7 and Caco-2) and one non-tumoral cell line (NHDF) at concentrations of 1 and 10 µM. Initial findings suggest that monomethinecyanines are more effective than trimethinecyanines, and asymmetric dyes demonstrate greater effectiveness compared to symmetric ones. Concentration-response curves were also conducted for the most potent cyanine dyes, indicating a tendency to enhance the potency and selectivity of the molecule with the reduction of the barbiturate nitrogen substitution group. Additionally, certain barbiturate derivatives exhibit more potency and selectivity than thiobarbiturates. The asymmetrical monomethinecyanine dye derived from benzothiazole and coupled with barbituric acid (Figure 1) emerged as the most promising within this series of tested dyes. It demonstrated an IC50 value of 0.12 µM against the MCF-7 cell line and exhibited a selectivity index of 37.8 for cancer versus non-cancer cells. Future studies will assess the ability of the most promising dyes to induce apoptosis and evaluate their impact on cell cycle arrest. These exploratory results aim to expand our understanding of the therapeutic potential of these dyes in cancer treatment.

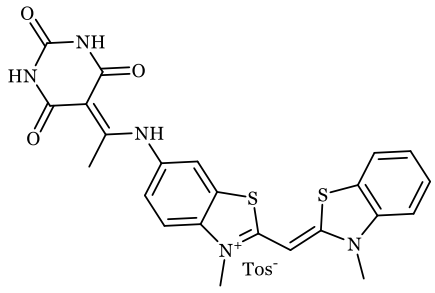

Figure 1: Structure of the most promising cyanine dye in this work.

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Synthesis of floridoside phosphotriesters

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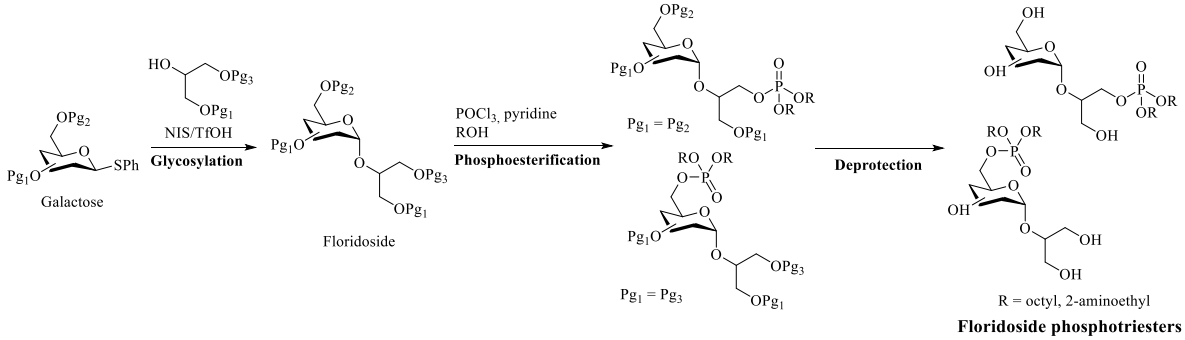
Floridoside is a common natural product usually found in extracts of red alga. Several bioactivity assays shown that floridoside is: an activator of the classical complement pathway, involved in the immunotherapeutic action against cancer cells [1]; an up-regulator of hemoxygenase-1, superoxide dismutase and glutathione peroxidase which gives it antioxidant properties [2,3]; an inhibitor of LPS-induced inflammatory responses in microglia cells by inhibition of reactive oxygen species and nitric oxide production [4].

On a different note, glycoglycerol posphates are reported as membrane-bound and frequently contributing to cell-to-cell interactions, namely the development of inflammatory responses [5]. Some examples of glycoglycerol phosphates are highly complex ones as lipoteichoic acids and lipopolysaccharide or smaller and simpler ones like phosphatidylinositol mannosides, involved in the pathogenicity of tuberculosis. However, the reports found focus only in glycoglycerol phosphodiesters and the only reports on phosphotriesters were related with nucleotide-based drug development.

The gathering of this information prompted us to wonder what the potential activity of glycoglycerol phosphotriesters would be. With this in mind, we prompted to synthetize floridoside phosphotriesters. We resorted to the common thioglycoside donor strategy for the glycosylation reaction with a protected glycerol acceptor. The phosphotriester was then inserted in one of two positions: the primary hydroxyl of glycerol or the primary hydroxyl of galactose. After deprotection, the final products were obtained (Scheme 1). Four molecules were synthetized, and their activity will be evaluated in future work.



Scheme 1: Synthetic pathway to achieve floridoside phosphotriesters.

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Oxime-functionalized *trans*-A_2B-corroles as promising photosensitizers for photodynamic therapy of lung cancer

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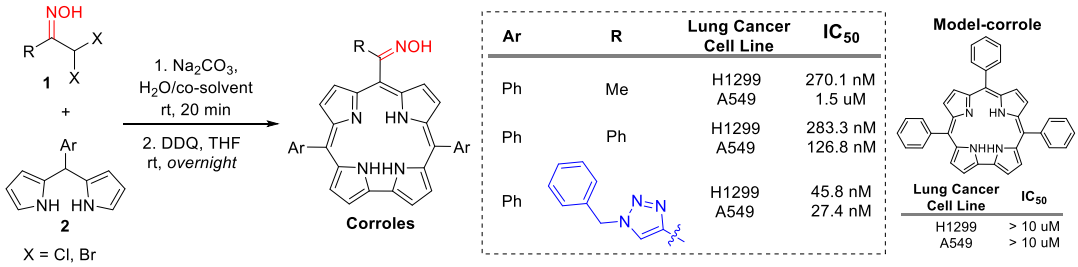
The development of a novel synthetic strategy based on the reactivity of nitrosoalkenes towards dipyrromethanes led to unprecedented oxime-functionalized *trans*-A_2B-corroles [1]. These macrocycles, bearing either methyl- or phenyl-oxime groups, showed photophysical and acid-base properties suitable for their use as photosensitizers in biological systems [2]. These promising results led us to investigate the potential of the novel corroles as photosensitizers (PSs) for photodynamic therapy (PDT) of lung cancer (H1299 and A549 lung cancer cell lines).

A set of new *trans*-A_2B-corroles has been synthesized combining phenyl, bromophenyl, hydroxyphenyl, and nitrophenyl substituents at 5 and 15 *meso* positions and methyl-, phenyl- and triazole-oximes at the 10 *meso* position. The study of the photophysical and acid-base properties of these corroles, together with the evaluation of their *in vitro* activity as PSs, allowed us to establish that the presence of the oxime group is crucial to ensure high biological activity. In fact, the model-corrole (without any oxime moiety) showed no photodynamic activity against none of the studied lung cancer cell lines (IC_{50} > 10 uM, Scheme 1), in contrast with the high activity observed for the oxime-functionalized corroles. On the other hand, the nature of oxime substituent (R) was also found to influence the activity. The corrole bearing a methyl-oxime group shows IC_{50} values in the nanomolar and micromolar range against H1299 and A549 lung cancer cell lines, respectively. Substitution of the methyl-oxime by phenyl-oxime group resulted in a decrease of the IC_{50} value against A549 lung cancer cell line, reaching nM activity against both cell lines. The photodynamic activity of the corroles is further enhanced by the presence of the triazole-oxime moiety, resulting in an even more potent PDT agent with IC_{50} values of 45.8 nM and 27.4 nM against H1299 and A549 lung cancer cell lines, respectively. Details of the synthesis, photophysical and acid-base properties, and activity as photosensitizers for photodynamic therapy of lung cancer will be discussed.



Scheme 1: Synthesis of *trans*-A_2B-corroles and IC_{50} values of selected examples.

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Synthesis of carvone derivatives and screening of anti-inflammatory activity

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Natural products are increasingly used for their anti-inflammatory properties and as sources of new anti-inflammatory compounds [1]. The chemical modification of natural compounds with a known pharmacological activity is a useful strategy to improve their bioavailability and/or potency.

Previous studies elucidated the structure-activity relationship of monoterpene compounds, derived from *p*-menthane, as potential anti-inflammatory drugs. (S)-(+)-carvone (**1**) was identified as the most potent of the compounds tested and may be efficient in halting inflammation-related diseases like osteoarthritis [2].

The α,β-unsaturated ketone group of carvone seems to be critical for activity. The replacement of the isopropenyl group at C5 by a 2-hydroxyisopropanyl group, such as in 8-hydroxycarvotanacetone (**2**), lowered the potency but provided a hydroxyl group, important to manage the lipophilic properties. Another relevant feature for activity must be the chirality, so both enantiomers of carvone must be studied [2].

(**1**) (**2**)

Figure 1: (S)-(+)-carvone (**1**) and 8-hydroxycarvotanacetone (**2**)

Based on these premises, recently, our group reported the synthesis of some carvone derivatives and performed a screening *in silico* and *in vitro* of their anti-inflammatory activity and pharmacokinetic properties [3]. Although presenting anti-inflammatory and some advantageous ADME properties, the tested compounds still have low potency and specificity. However, these results encouraged us to design new structures that may overcome the detected drawbacks and yield more promising drugs. Thus, new carvone derivatives, namely 8-hydroxycavotanacetone esters, were synthesized, using acyl halides under basic catalysis or carboxylic acids with activating agents. After purification and structural analysis, the cytotoxicity and anti-inflammatory activity will be evaluated *in vitro*.

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Structure and ligand-based strategies to discover novel orexin receptor modulators: targeting the circadian clock and Alzheimer's disease

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Alzheimer's disease (AD), the most prevalent form of age-related dementia, accounts for 60%-80% of all dementia cases. Despite being identified over a century ago, a cure for this devastating disease remains elusive [1]. Recent research suggests a link between dysfunction in the orexinergic system and cognitive decline in AD, spotlighting orexin receptors 1 and 2 (OX1R and OX2R) as potential targets for AD research and treatment [2]. This study utilizes computational methods to identify photoswitchable ligands that bind these orexin receptor subtypes. Photoswitchable ligands are characterized by their reversible and controlled conformational changes upon light exposure, altering their affinity, potency, or other pharmacodynamic properties [3]. This property enables spatial and temporal control of orexin receptor activation *in vivo*, crucial for investigating the role of the orexin system in AD.

Our methodology involved analyzing receptor-ligand interactions in existing OX1R and OX2R PDB structures using PLIP [4], supplemented by an analysis of water bridges using GetContacts (https://getcontacts.github.io/). We also conducted a preliminary study to assess receptor flexibility, measuring the Root Mean Square Deviation (RMSD) of the active center residues' side chains across various structures. Additionally, re-docking and cross-docking studies using GOLD were carried out to identify optimal OX1R and OX2R structures for virtual screening [5].

Our analyses revealed key molecular interactions in the experimentally resolved structures of both OX1R and OX2R. Predominant hydrogen bonds involved residues His6.55 and Gln3.32 (Ballesteros-Weinstein numbering scheme), along with hydrophobic interactions with residues Ile3.28, Pro3.29, Phe5.43, and Ile6.51. A notable water bridge between ligands and His7.39 was confirmed in six of the structures [6]. The RMSD analysis revealed variability in the conformation of certain residues, particularly Gln3.32, Phe5.43, and His6.55. These residues are involved in crucial hydrogen bonds and hydrophobic interactions, suggesting their significance in receptor-ligand binding. Furthermore, a model of the OX1R receptor demonstrated promising performance in both re-docking and cross-docking studies, positioning it as a valuable tool for future virtual screening campaigns.

In conclusion, this study marks considerable progress in the virtual screening workflow of photoswitchable ligands targeting the orexin receptors. The models developed exhibit promising characteristics for this application. However, there is a need for further refinement and improvement. Future efforts will focus on thoroughly validating these models to ensure their reliability and enhance their efficacy in subsequent analyses, aiming to contribute significantly to the understanding and potential treatment of Alzheimer's disease through modulation of the orexinergic system.

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Novel synthetic cinnamic acid-flavonoid hybrids with multifunctional properties

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Oxidative stress plays a role in the development of skin inflammatory diseases such as atopic and contact dermatitis, psoriasis, and skin cancer [1]. UV light is recognized as one of the primary triggers for the production of reactive oxygen (ROS) and nitrogen (RNS) species. Sunscreens containing UV-filtering/antioxidant double action compounds have been proposed to reduce skin oxidative damage caused by UV-induced reactive species [2,3]. Natural-derived flavonoids and cinnamic acids were already reported in the literature by their anti-inflammatory and antioxidant effects [4]. Hybrids containing these two scaffolds were created to discover novel compounds to fight the damaging effects of solar radiation. Seven hybrids with flavone and cinnamic acid moieties linked by amide and/or ester linkers were synthesized and structurally characterized. Two cell lines, representing the epidermis (keratinocytes) and dermis (macrophages), were used to assess their cytotoxicity through resazurin assay, and their anti-inflammatory activity was evaluated in a macrophage cell line. The mitochondrial antioxidant activity of the most promising compounds was further examined in macrophages using flow cytometry and the MitoSOX kit test. Additionally, photoprotective properties were investigated through ultraviolet-visible spectrophotometry. In the concentration range examined, all the seven compounds exhibited cell viability superior to 70%. In LPS-stimulated cells, five of the seven hybrids showed interesting inhibitory activity (40 - 80%), and two of them exhibited antioxidant inhibitory activity towards the rotenone-induced oxidative stress, with inhibitory percentages above 20%. Three of them had the capacity to absorb in the UVA region (UVA/UVB ratio > 1), and one showed the potential to be a broad-spectrum UV filter. With the future goal of developing multifunctional sunscreens, the hybrid with safer and effective profile will be selected for formulation.

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Revolution in neuroscience: Innovating Alzheimer's treatment with photoswitchable molecules

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Alzheimer´s disease (AD), the most prevalent neurodegenerative disorder, is marked by a progressive decline in memory and cognitive functions, eventually leading to fatality. The World Health Organization estimates that the number of individuals with AD could reach nearly 152 million by 2050 [1]. Once AD advances to the stage of dementia, the primary pharmacological strategy is to decelerate its progression. In 2021, the FDA approved *aducanumab*, the first AD drug in 18 years, though its efficacy and safety remain under scrutiny [2]. Alternatively, sleep dysregulation and alterations in the orexin system have been observed in AD patients, highlighting the potential of targeting this receptor for therapeutic benefits in cognitive symptoms of the disease [3].

This work aimed to develop and optimize a chemical library of photoswitchable small molecules targeting the orexin receptors, employing computational methods [4]. This strategy allows for alternated conformational states in response to different light wavelengths, facilitating the examination of both therapeutic effects and potential side effects[5]. A library of compounds was collated by extracting compounds with the azobenzene substructure from ChEMBL resulting in a total of 23,431 compounds. These compounds were compared based on their similarity to known antagonists and agonists of the receptors and categorized according to their potential to bind other targets, using bioactivity data from ChEMBL.

Additionally, we analyzed 1,667 compounds tested against orexin receptor 2 and clustered them into various maximum common scaffolds [6]. This process helped derive meaningful QSAR rules applicable to the azobenzene compounds. Selected compounds were docked in both cis and trans conformations, and their ligand- receptor binding was assessed. Our results suggest that azobenzene compounds can potentially modulate activity in response to stimuli, making them a useful toolbox for studying the orexin system in AD.

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Quinonemethides: Synthesis and electrochemical studies of potential new organic redox mediators

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Over the years, an increasing need for more efficient and sustainable energy sources has been observed, due to the increasing, worldwide, demand for energy [1]. Redox mediators, crucial components to many electrochemical devices, have emerged as a great alternative. They are important components of batteries for energy storage purposes.

These devices facilitate the conversion of chemical energy into electrical energy through reversible oxidation/reduction processes. However, many existing systems utilize materials that are toxic, hazardous, and costly. Organic redox mediators (ORM) emerged as a promising alternative to address these issues [2,3].

In 2014, Huskinson et al., reported an aqueous organic redox flow battery that employed 9,10-anthraquinone-2,7-disulphonic acid (AQDS) as the anolyte [4]. Subsequently, numerous studies have explored potential ORM for applications in organic redox flow batteries (ORFB). Quinones have been one of the extensively researched families for ORFB, due to their redox properties [5]. Quinonemethides have not been explored in this area of research so far.

In this work, nine quinonemethides were synthesized, in yields ranging from 25% to 86%, from 2,6-di-tert-butylphenol and aldehydes. Their electrochemical properties were studied by cyclic voltammetry (Figure 1), showing some promising results with some compounds showing reversible transformations, with reduction potentials ranging from -1.3 to -0,8 V vs SCE. The quinone like core of these molecules make them suitable candidates to be used as potential alternative ORM to the already broadly studied quinone family.

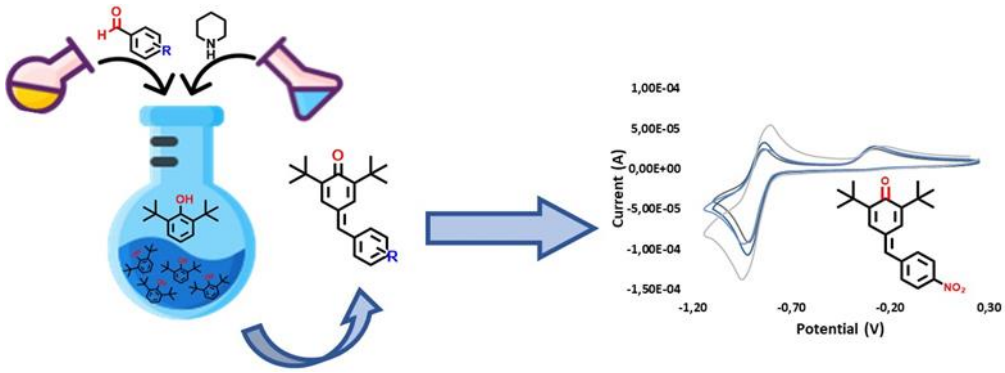

Figure 1: Schematic representation of the synthesized quinonemethide core and their electrochemical studies to access their applicability as ORM for ORFB.

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Exploration of electrocatalytic reactivity using electrochemistry in combination with computational tools

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The synthesis of small molecules and the development of new chemical transformations remains a crucial step in the development of drug candidates. Electrochemistry has recently re-gained popularity due to the development of specialized equipment that improves the reproducibility of reactions. Simultaneously, electrochemistry offers sustainable and milder alternatives to conventional chemistry that remain largely unexplored [1]. Herein, using computational tools, we explore the reactivity space of biomass derived building blocks with commercially available reaction partners using the ElectraSyn 2.0 system. By randomly performing thirty experiments we were able to identify combinations that led to new products, some of which with a high conversion rate. We will discuss the implications of our findings and future perspectives in the context of computer-assisted reaction discovery.

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Hetero-Diels-Alder reactions of a novel steroidal nitrosoalkene

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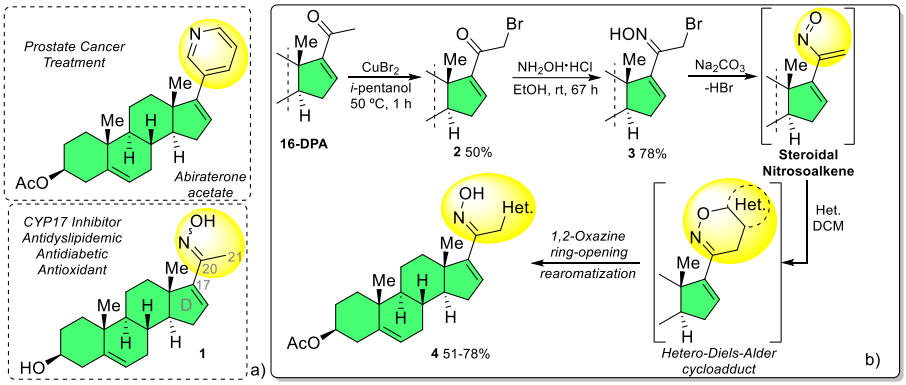
Steroids are a widely and important class of biologically active compounds, exhibiting a plethora of pharmacological activities. Structural modulation by introducing heteroatoms and/or heterocycles onto the steroid backbone has emerged as the most fruitful strategy for the development of new therapeutics. Indeed, the drug abiraterone acetate, used to treat prostate cancer, contains an aza-heterocycle at C17, and the oxime-functionalized steroid **1** exhibits activity as a CYP17 inhibitor as well as antidyslipidemic, antidiabetic and antioxidant properties (Scheme 1a). Our on contribution to this research topic includes the synthesis of new ring-fused steroidal compounds with interesting biological properties *via* [8π+2π] cycloaddition of steroids with diazafulvenium methides and annulation/cycloaddition pyrrolidine-induced reactions of steroidal 1-azadienes with carbonyl compounds [1-5]. In this communication, the use of nitrosoalkenes as a synthetic tool for the synthesis of new steroids will be presented. The synthetic strategy outlined in Scheme 1 aimed at the structural modulation of steroidal oxime **1** via functionalization of C21 with heterocyclic groups. Nitrosoalkenes participate in hetero-Diels-Alder reactions with electron rich alkenes and heterocycles to give 1,2-oxazines or open chain oximes [6]. Hence, we decided to explore the generation of a novel steroidal nitrosoalkene and its reactivity towards heterocycles (Scheme 1b). The bromination of the commercially available 16-dehydropregnenolone acetate (**16-DPA**) gave the α-bromo steroid **2**, which reacted with hydroxylamine hydrochloride to give the steroidal α-bromo-oxime **3** in 78% yield. The transient steroidal nitrosoalkene, generated *in situ* by treatment of oxime **3** with base, was trapped by heterocycles affording steroidal open chain oximes **4** in high yield, through the ring-opening of the primarily formed hetero-Diels-Alder cycloadduct and concomitant rearomatization of the heterocyclic moiety. Details of this steroids modulation strategy will be presented.



Scheme 1. a) Structure of abiraterone acetate and steroidal oxime **1**. b) Synthetic strategy for steroid modulation.

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Light driven modifications in quinic acid derivatives

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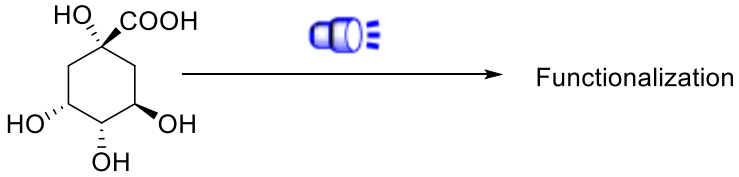
Quinic acid (QA) is a widely occurring metabolite in plants and microorganisms [1].The synthesis of Oseltamivir (Tamiflu) [2] and Bactobolin A [3] are probably the most distinct uses of QA in total synthesis. Exploration of stereoselective metal-free deoxygenation is a recent example of QA's synthetic value [4]. Additionally, the *O*,*O*-silyl group migration on a quinic acid-derived cyclitol gives suitable intermediate for the synthesis of a vitamin D receptor modulator (VS-105) [5] Photoredox catalysis is a known sustainable alternative to the use of less environmentally super-stoichiometric oxidants and reductants. Ruthenium and iridium complexes, in combination with visible light, are efficient photocatalysts when strong reductants or strong oxidants are needed, however, their toxicity and scarcity are a drawback for the evolution of photocatalysis to the next level. Organic dyes represent a good alternative to these metal complexes [6].

The functionalization of QA and its derivatives via photoredox catalysis will be presented. Organic dyes under visible light irradiation can generate radical intermediates from QA under mild conditions. This radical generation unravels innovative ways for the synthetic modification of QA.



Scheme 2: Quinic acid functionalization under visible light

Acknowledgements*:* The authors acknowledge Fundação para a Ciência e a Tecnologia (FCT) for financial support (PTDC/QUI-QOR/1131/2020, UIDB/04138/2020 and UIDP/04138/2020). The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951996.

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Novel methodologies for dicarboxymethyl cellulose preparation

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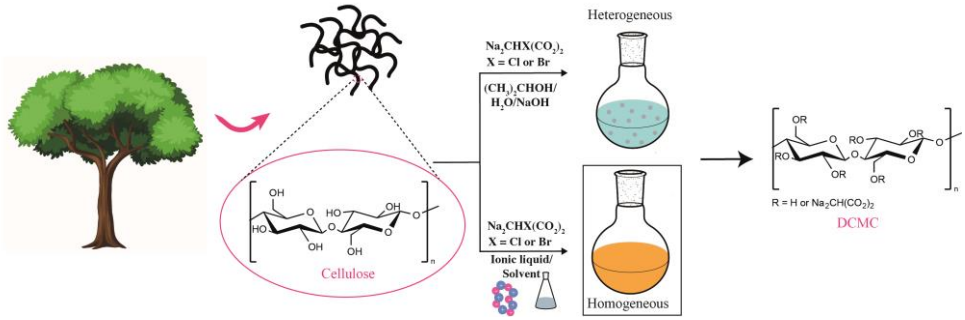
Cellulose, the main constituent of plants' fibres is a naturally occurring polymer and one of Earth's most available materials[1], its low solubility in common solvents, which is attributed to its extensive network of hydrogen bonds and hydrophobic interactions,[2,3] presents a challenge to its use. To address this issue, one solution involves chemically modifying cellulose, thereby interrupting the inter-unit and chain interactions to enhance solubility[4].

Carboxymethyl cellulose (CMC) is a widely used cellulose ether-derivative that has found uses in several fields such as the pharmaceutical, textile, and biomedical industries.[5] Its pKa value of approximately 4.5 limits its usage. A novel cellulose derivative, dicarboxymethyl cellulose (DCMC), which can be produced by grafting a malonic acid moiety to cellulose, can increase the pH working window since it has pKa values of 2.85 and 5.70. It has been reported to be an efficient material for dye removal in water[6] and in white wine protein removal[7].

CMC and DCMC can be obtained in a heterogeneous medium reaction composed of isopropyl alcohol, water and NaOH to introduce the desired functional group to cellulose. The resulting polymer degree of substitution (DS) is defined as the number of substituents per anhydroglucose unit (AGU).

This work focuses on the development of novel homogeneous synthetic methodologies for DCMC synthesis, capable of controlling the obtained DS and reaction regioselectivity. Common solvents for cellulose homogeneous modification, lithium chloride/*N*,*N*-dimethylacetamide (DMAc/LiCl), tetrabutyl ammonium fluoride/DMSO (TBAF/DMSO) and N-methylmorpholine-*N*-oxide (NMMO) suffer from high toxicity, in the case of DMAc, or thermal instability, in the case of NMMO. In the present work, ionic liquids (ILs) and binary mixtures of ILs/molecular solvents are used as greener alternatives for cellulose modification. Superbase-derived ionic liquids [DBNH][OAc] and [DBUH][OAc] binary mixtures with DMSO showed promising results as solvents for DCMC preparation, yielding the polymer with a DS value of 0.5 which is comparable to heterogeneous conditions and above the substitution threshold for water solubility.



Scheme 3: Routes for DCMC preparation using heterogeneous or homogeneous conditions.

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Substituted carbocyanine dyes: synthesis and antiproliferative evaluation

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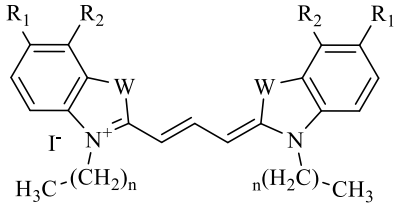
While cyanine dyes were initially used in photography, in recent years, this class of dyes have attracted academic attention due to their potential as photosensitizers for photodynamic therapy as well as anti-proliferative agents [1,2]. In the latter case, a study was recently carried out in which the antiproliferative potential of several cyanine dyes was evaluated in absence of light, revealing carbocyanine dyes as one of the most potent options [2]. Following the search for a potential antiproliferative agent, a series of new carbocyanine dyes were synthesized, varying the nature of the heterocyclic rings (indole, benzoxazole, benzothiazole, benzoselenazole, or benzo[*e*]indole), as well as the size of the alkyl chain (pentyl or undecyl). Additionally, the introduction of amine, acetamide, iodine, or methoxy substituent groups at position 6 of the benzoazole moiety was also studied (Figure 1). The evaluation of their impact on cell proliferation was carried out using two cancer cell lines (MCF-7 and Caco-2) and a non-tumor cell line (NHDF) at concentrations of 1 and 10 μM by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. These studies suggest that carbocyanine dyes featuring a five-carbon *N*-alkyl chain are associated with increased antiproliferative effects. Concentration-response curves for the most potent carbocyanine dyes revealed a slight increment in the potency and selectivity for the Caco-2 compared to the MCF-7 cell line. The benzo[*e*]indole derivative in both cell lines, as well as benzothiazole derivative with iodine at C6 position for the Caco-2 cell line, should be highlighted due to their potency and selectivity. Future studies with the most effective cyanine dyes will assess their ability to induce apoptosis and evaluate their impact on the cell cycle.



W= S, O, Se, $C(CH_3)_2$; n= 4, 10; R_2 = H and R_1= H, I, NH_2, OCH_3, $NHC(O)CH_3$, or R_1-$(CH)_4$-R_2

Figure 1: General structure of carbocyanine dye under study.

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Decoding drug targets: An innovative strategy for protein binding pocket exploration

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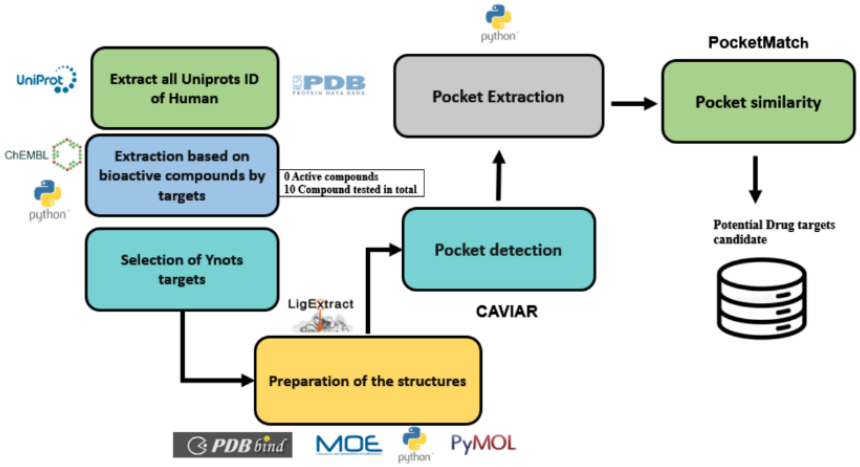
The discovery of new drug targets often focuses on a limited segment of the human proteome, representing only about 15%. This is primarily due to researchers concentrating their efforts on a limited set of genes, thus avoiding the exploration of uncharted research avenues. Consequently, about 85% of disease-associated targets remain underexploited. [1] This study undertakes a series of computational analyses aimed at detecting and analyzing protein binding sites to identify novel drug targets. We established three protein target groups based on the work of Oprea et al., and data from UniProt, ChEMBL, and the Protein Data Bank (PDB). The first group comprises targets with approved drugs or those in clinical trials, termed Well-Known Targets (WKT). The second group, Difficult to Obtain Pharmacological Effect (DOPE), includes targets challenging to model. The final group, yet not druggable targets (YNOTs), has no known active compounds. We performed pocket detection for each target using CAVIAR software, identifying cavities and binding sites in proteins [2]. We then compared cavities in DOPE targets with binding sites of WKTs using Pocket Match [3]. Preliminary results revealed that the allosteric center cavity of Excitatory amino acid transporter 1 (EAAT1) showed notable similarity with phosphodiesterase 6 delta subunit (PDE6δ), making it a promising candidate for further investigation. Similarly, for YNOTs, a clustering analysis comparing them with WKTs identified 178 targets with over 75% similarity, including 4 targets with over 80% similarity. These findings suggest the potential for a new database of unexplored structures, which could serve as valuable targets for small molecule intervention.



Scheme 1: Workflow for the characterization of YNOTs

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Optimization of enzymatic kinetic resolution for scale-up production of (-)- agelastatin A

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Agelastatin A (AglA) is a promising alkaloid in medicinal chemistry. Since the first isolation from the marine sponge *Agelas dendromorpha* in 1993, by Pietra *et al.*[1], it withdrawn attention from diverse groups, due to a unique and complex tetracyclic structure composed by four stereocentres in its central ring. (-)-AglA has shown remarkable cytotoxicity against a variety of tumour cells and strong inhibition of osteopontin-mediated neoplastic transformation and metastasis [2].

As natural product, it is hard to obtain in a large scale from natural sources. Therefore, several total syntheses were developed throughout the years [3], including our group, which proposed an asymmetric synthesis from a pyridinium salt, resorting to enzymatic kinetic resolution (EKR) to obtain the enantiopure intermediary (*S*)-allyl bicyclic aziridine [4].
Kinetic resolution mediated by lipases stands out from the various methods for obtaining enantiopure compounds, as it is a sustainable process with several advantages such as high activity, selectivity and mild conditions [5].
We synthesised allyl bicyclic aziridine on a large scale through the photochemical transformation of 1-allylpyridinium bromide, obtaining it as a racemic mixture, which was subjected to EKR to give the enantioenriched intermediary (*S*)-allyl bicyclic aziridine. Herein we present the optimization of the temperature on EKR experiments, to improve the reaction enantioselectivity, for its application on a large-scale synthesis of (-)-AglA.

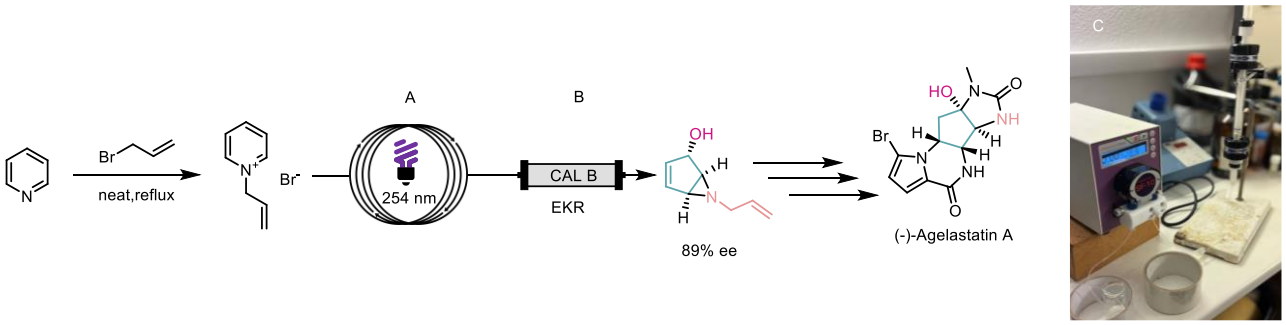

Figure 1: Synthesis of enantiomeric pure allyl bicyclic aziridine: (A) Photochemical transformation of pyridinium salts in flow; (B) Enzymatic kinetic resolution of allyl bicyclic aziridine; (C) Set-up of the EKR system.

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Photochemical cysteine modification

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Protein and peptide site-selective modifications are a powerful tool in drug development. Site-selective modifications enables obtaining homogenous bioconjugates and minimize the formation of undesired conjugates by reactivity with multiple protein/peptide residues.

Cysteine is one of the most interesting target residues in the bioconjugation strategies field. The high nucleophilicity of the thiol group in the presence of electrophilic species under pH control, comparing with other competitive nucleophilic side chains such as lysine and histidine residues, and the low natural abundance in proteins increases the likelihood that a single target residue will be exposed, enabling the site-selective modification pretended [1].

Novel visible-light-mediated photochemical approaches in bioconjugation have emerged. These strategies exploit specific and unique modes of reactivity providing high reactive intermediates using light as external source of energy. Amongst several photochemical systems, photoredox catalysis using visible light and a photocatalyst is considerably more biocompatible for proteins and peptides and thus the preferred method for this application [2].

Thiol-Ene click chemistry driven by visible-light, in the presence of a photocatalyst, has been reported as an insightful method for bioconjugation and is one of the most promising cysteine modification strategies. The radical addition reaction does not compete with other possible nucleophilic groups and provide more stable adducts. This strategy proves effective in generating reactive radical species that can participate in a unique bond-forming process utilizing native functional groups, leading to novel approaches for biomolecule functionalization, labeling, and cross-linking techniques [3].

Herein we explore a photoredox methodology for the site-selective functionalization of biomacromolecules targeting cysteine residues.

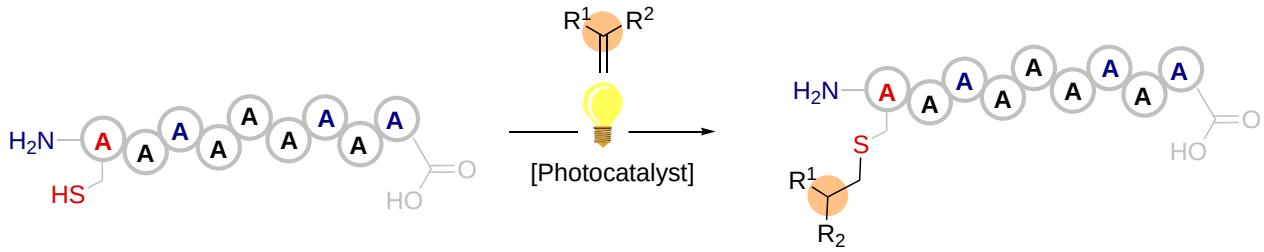

Figure 1: Thiol-Ene click reaction for cysteine modification

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Reaching important objectives in the difficult fight against lung cancer: a knowledgeable *in silico* strategy

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Lung cancer remains a major cause of mortality, affecting both men and women. Annually, it claims approximately 1.8 million lives, with a sobering five-year survival rate of just 15%. Often, lung cancer is diagnosed at an advanced stage. Patients undergoing treatment for one type of cancer may concurrently develop another, including lung cancer. In cases of synchronous multiple primary lung cancer (MPLC), especially among those ineligible for surgery, the average survival time is about 31 months. Notably, 50.8–57.9% of MPLCs exhibit similar histological characteristics [1].

Increased levels of HIF-1α are known to promote tumorigenesis in lung cancer. However, targeting HIF1AN, a regulatory factor of HIF-1α, can lead to its downregulation. Thus, HIF1AN emerges as a promising therapeutic target in lung cancer treatment [2].

Given that HIF1AN is a novel target with a scarcity of known effective molecules, a combination suite of *in silico* methods will be employed. One approach involves active site similarity comparison. This technique identifies new targets with similar molecular binding sites (pockets) to a given target lacking active molecules. By leveraging known ligands of these similar targets, we can discover potential new candidates for HIF1AN. This method capitalizes on the principle that structurally distinct targets may share significant similarities in their binding pockets, influencing how they interact with small molecules - a critical insight for drug discovery [3].

We performed an analysis of pocket similarities in available HIF1AN structures from the Protein Data Bank (PDB) (Figure 1). Interestingly, despite all structures pertaining to the same protein, their pocket similarities varied significantly, ranging from very low (0.24) to perfect (1). The number of pocket residues also differed, ranging between 16 and 31.

This study highlights that even structures of the same protein can exhibit low pocket similarity values. Despite this variability, these values are invaluable in determining the appropriate cutoff when searching for similar, well-characterized proteins.

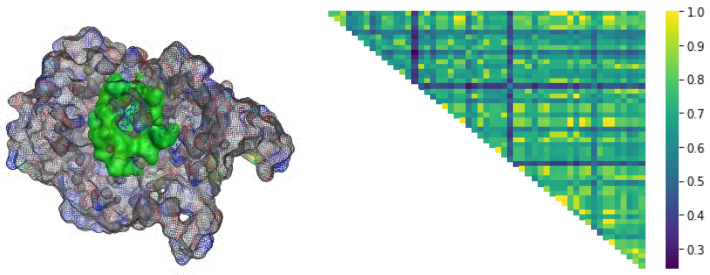

Figure 1: Example of a binding pocket identified in a pdb structure of HIF1AN (highlighted in green), accompanied by a heatmap illustrating the similarities among binding pockets detected across various hif1an structures.

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Photodegradation of microplastics: Role of adsorbed contaminants

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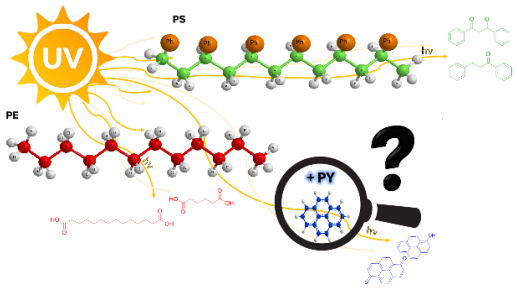
Plastic pollution is a major global threat. The accumulation of plastics in natural environments has been assigned to the increasing production of these materials, improper waste management practices and their stability in natural conditions. Despite the slow process, plastics undergo transformation in the environment, resulting in the break down into smaller particle, microplastics and nanoplastics, and the release of organic compounds, which impact ecosystems and human health. Sunlight-induced photodegradation is a major degradation pathway of these materials [1]. We have been studying the release of organic compounds after photodegradation of plastics and microplastics on surfaces to evaluate the environmental contamination by these compounds. Photoreaction experiments were implemented using a Xenon lamp and products were analysed by LC-HRMS and using metabolomics tools. Non-volatile compounds released from polyethylene (PE) and polystyrene (PS) particles on surfaces were annotated or identified. Released compounds included aliphatic dicarboxylic acids from PE and chalcone, 3-phenyl propiophenone and dibenzoymethane from PS, among other. As expected, the photodegradation of PE was very slow due to weak light absorbance by this polymer. As microplastics adsorb and concentrate environmental contaminants such as polycyclic aromatic hydrocarbons (PAHs), we also evaluated the role of adsorbed contaminants on the photodegradation of PE and PS. Pyrene (Py) was selected as a representative of PAHs, as this compound migrates to the non-polar microplastic particles on polar surfaces [2]. The adsorption of Py on PE and PS was studied using steady state fluorescence and the formed products by LC-HRMS. Py photodegradation on silica surfaces without microplastics leads to the formation of hydroxypyrene, three pyrenediones and 4-oxapyrene-5-one, among others. When PE and PS microplastics were present the fluorescence spectrum changed indicating the adsorption of Py onto the polymer particles. The presence of PE decreases the degradation of Py but the presence of PS has little effect on Py degradation rates. The presence of microplastics did not change the nature of Py photoproducts. However, the photoproduct distributions in the presence of microplastics indicated significantly higher concentration of some products such as 4-oxapyrene-5-one, suggesting a stabilizing effect on the formed products by microplastics. On the other hand, the presence of Py increased the photodegradation rate of PS as the main products increased by 2-3 fold. No significant products of PE were detected in the absence or presence of Py.



Scheme A: Photodegradation of Pyrene adsorbed on PE and PS microplastic.

Acknowledgements: CQVC thanks FCT grant 2022.14374.BD; JPDS thanks Fundação Azul, project "Size Matters – Looking for invisible plastics", reference FA_05_2017_024. This study received Portuguese national funds from FCT - Foundation for Science and Technology through projects EXPL/CTA-AMB/1613/2021, MACAU/0001/2019 (PLASTIFISH), UIDP/04326/2020, UIDB/04326/2020 and LA/P/0101/2020, from Macao Science and Technology Development Fund (FDCT), project FDCT0004/2019/AP, and from the operational programmes CRESC Algarve 2020 and COMPETE 2020 through project EMBRC.PT ALG-01-0145-FEDER-022121.

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Synthesis and optical properties of 2-(((4-(trifluoromethyl)quinolin-6-yl)amino)methyl)phenols

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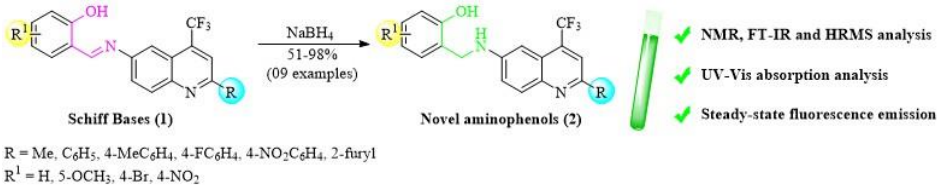
Secondary amines are compounds of biological interest and have also been employed in the synthesis of products that are of interest in pharmaceutical and agricultural industries [1,2]. *N*-aryl imines of salicylaldehyde have been used to obtain secondary amines, which have been employed in the synthesis of benzoxazines with potential fungicidal activity, and also exhibit a range of biological activities, including analgesic effects, anti-neuroinflammatory properties and antimicrobial activity [3]. The common method for accessing secondary amines is through reductive amination of aldehyde or ketone. This can be done directly with the carbonyl compounds and amines or indirectly through the preparation of imines which are subsequently reduced [4]. Although the secondary amines are well now for their biological interest, the synthesis of organic compounds that presents interesting photophysical characteristics have been drawing considerable attention in the last years. This highlights the significance of creating organic compounds possessing these photophysical properties, which have garnered significant attention and found extensive applications in the chemistry of materials, such as fluorescent probes, organic light emitters, and organic field effect transistors, among others [5]. In this regard, this study sought to evaluate the synthesis by a simple reduction method starting from Schiff bases (**1**) and using sodium borohydride as reduction reagent, to obtain a new series of 2-(((alkyl/aryl/heteroaryl)-4-(trifluoromethyl)quinolin-6-yl)amino)methyl)phenols (**2**), characterized by ^{1}H-, ^{13}C-, ^{19}F-NMR experiments and FTIR. Also given this context, will be discussed and studied the UV-Vis absorption analysis and steady-state fluorescence emission properties, both in liquid and the solid state for these compounds, as depicted in Scheme 1.



Scheme 1: Summary of this study: synthesis and photophysical properties of 2-(((2-alkyl/aryl/heteroaryl)-4-(trifluoromethyl)quinolin-6-yl)amino)methyl)phenols.

In summary, it was possible to obtain a new series of nine 2-(((2-phenyl-4-(trifluoromethyl)quinolin-6-yl)amino)methyl)phenols (**2**), as well as, the photophysical were studied and discussed. Compounds **2** were obtained at yields of 51-98% by adapting a common method of reduction of imines in the presence of sodium borohydride ($NaBH_4$) and could be fully characterized by ^{1}H, ^{13}C and ^{19}F, ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC NMR spectroscopy and HRMS. In the photophysical properties of the derivatives, transitions were observed in the 250–450 nm region, and higher quantum fluorescence yields values for aminophenols **2** were observed in solution. Regarding the solvent polarity variation, the changes could be observed according to the dieletric constant (ε) of the solvents and the electronic nature of the molecules evaluated, which present donor (EDG) or acceptor (EWG) substituents. Some changes in the photophysical properties of imine precursors **1** when compared to aminophenols **2** are predicted, with the reduced derivatives maintaining luminescent properties at high Φf values and with dependence of the quinoline substituents (R) and phenol substituents (R^1).

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(Thio)barbiturate-dehydroepiandrosterone hybrids with potential anticancer properties: Synthesis, biological evaluation and pharmacokinetic predictions

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Cancer remains as one of the major global public health concerns, although the intensive research efforts to improve their therapeutic options [1]. One strategy that has attracted attention is the covalent fusion of different pharmacophores in a single molecule, capable to act through multiple anticancer mechanisms of action [2]. Considering this approach, steroid molecules have been widely explored due to their therapeutic action, including in cancer. In addition, (thio)barbiturates have also recently demonstrated antiproliferative activity [3]. Therefore, this work aimed to synthesize new molecules coupling dehydroepiandrosterone (DHEA) derivatives with (thio)barbiturate derivatives, to evaluate their *in vitro* cytotoxicity, and to predict their pharmacokinetic and toxicological profile by the computational tool pkCSM. The synthesis was performed using different 5-acetylpyrimidin(thi)ones, which were linked to DHEA hydrazones. The cytotoxicity of these hybrids was studied at 30 µM on breast cancer cells (MCF-7) and normal human dermal fibroblasts (NHDF) by the MTT assay after 72 h of incubation. Seven compounds were successfully synthesized with moderate to excellent yields (40-84%). Biological evaluation showed a higher cytotoxicity for steroids coupled with thiobarbiturates with ethyl substituents (cell viability of 4%) followed by (thio)barbiturate derivatives linked to phenyl (cell viability of 11-17%) or methyl groups (cell viability of 71-90%) in MCF-7 cells. The same trend was observed for the NHDF cells. Globally, the most potent compound (Figure 1) presented a selective effect for cancerous cells, compared with the non-cancerous cell line. Furthermore, the *in silico* predictions for this compound suggested a good human intestinal absorption (around 80%), a low volume of distribution at steady state (0.58 L/kg), a high human plasma protein binding (unbound fraction of 0.07) and a low blood-brain barrier permeability. An important fact is that the compound appeared to do not have tendency for cytochrome P450 inhibition or mutagenicity. On the other hand, concerns on the disruption of normal liver function were predicted as well as the possibility of this compound to be a substrate or inhibitor of glycoprotein-P, which motivates further investigation. In conclusion, the combination of a steroid scaffold with the (thio)barbiturate nucleus originates hybrid molecules with interesting antiproliferative effects. Additional studies are ongoing to understand their activity towards other cancer cells.

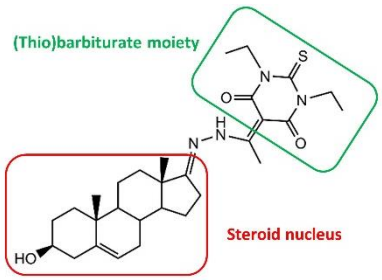

Figure 1: Structure of the most promising barbiturate-dehydroepiandrosterone derivative in this work.

Funding: This work was developed within the scope of the CICS-UBI projects UIDB/00709/2020 and UIDP/00709/2020, financed by national funds through the Portuguese Foundation for Science and Technology/MCTES. The NMR spectrometers are part of the Portuguese NMR Network (PTNMR) and are partially supported by Infrastructure Project No. 022161 (co-financed by FEDER through COMPETE 2020, POCI and PORL and FCT through PIDDAC). João L. Serrano acknowledges a doctoral fellowship grant from the FCT (SFRH/BD/148028/2019).

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Exploring the reactivity of β-vinylporphyrins with α,α'-dioxothione

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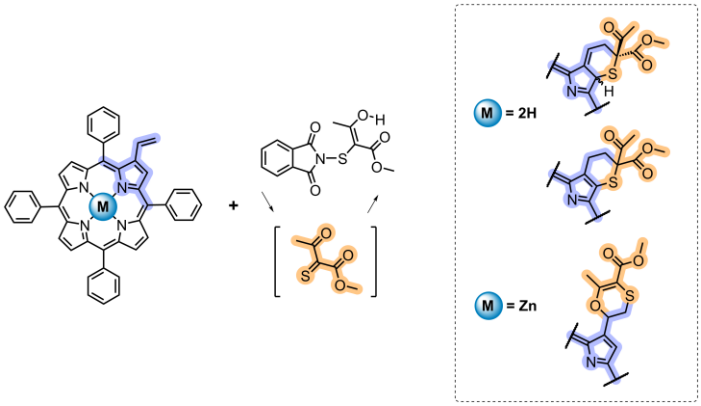
α,α'-Dioxothiones are highly reactive species, known for their ability to be efficiently generated *in situ* and trapped in cycloaddition reactions with several compounds, either as electron-poor heterodienes in inverse electron demand cycloaddition reactions, or as heterodienophiles [1,2]. Porphyrins can react as either 2π or 4π components in different cycloaddition reactions, including hetero Diels–Alder reactions. Notably, porphyrins bearing vinyl functionalities are interesting scaffolds for further functionalization in different cycloaddition approaches [3-5].

Herein it will be discussed the reactivity of an α,α'-dioxothione in the presence of 5,10,15,20-tetraphenylporphyrin bearing a vinyl group (2-VinylTPP) and of its Zn(II) complex (Zn-VinylTPP) (Scheme 1). The interesting dual-behaviour of β-vinylporphyrins in the presence of α,α'-dioxothione revealed that the reactivity of α,α'-dioxothione is influenced by thepresence or absence of Zn(II) in the porphyrin core. Additionally, the photophysical properties of the resulting cycloadducts will also be discussed [6].



Scheme1: Cycloaddition reaction between 2-VinylTPP or Zn-VinylTPP and the α,α'-dioxothione, and the obtained cycloadducts.

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Synthesis and structural analysis of cyclic aza-amino acid derivatives for the assembly of azapeptides

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Aza-peptides, a particular class of peptide derivatives, are formed by the replacement of one or more α-carbon atoms of a peptide by nitrogen atoms [1]. This type of modification provides peptides with a diversified set of pharmacokinetic and pharmacodynamic properties [1].

The incorporation of aza-amino acid residues into biologically active peptides enhances resistance against degradation by peptidases [2], thus increasing the stability and bioavailability of peptide drugs [1,2]. In some cases, aza-peptides may also benefit from improved activity and selectivity [3]. The replacement of α-carbons with nitrogen atoms has been shown to increase the acidity of the amino group, providing stronger hydrogen bonds than the ones formed by proteinogenic amino acids [2]. Not only that, but the α-nitrogen atom can dynamically change between pyramidal geometries, alternating between pseudo-*S* and *R* configurations [4]. Additionally, it has been demonstrated that, because of these properties, aza-amino acids are very useful for the design of secondary structures in peptides and proteins [2,4].

Therefore, the development of aza-peptides is considered to be a very effective and promising methodology in the field of medicinal chemistry for the design of peptide-based pharmaceuticals with improved pharmacological and biological activities.

In this work, two synthetic routes for *C*-activated aza-proline and aza-pipecolic acid are explored. The synthetic methodology relies on *N*-alkylation and *N*-carbonylation from hydrazine derivatives. Moreover, the X-ray structures of these compounds are disclosed. These protocols are expected to be useful for the assembly of bioactive aza-peptides.

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Environmental benign antifouling agent, developed employing the tactics of medicinal chemistry, moved to "clinical" trials

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Currently, 90% of antifouling coatings in use contain copper with at least 30% amount. It is estimated that over 1 million tonnes of copper are being leached per year to the oceans. Copper-based coatings are now being scrutinized and banned, and the maritime industry seek for safer and economic alternatives. GBA26 is a synthetic gallic acid (GA) derivative that was designed and developed by our group, employing medicinal chemistry tactics, to be an eco-friendly and economic antifouling (AF) agent.[1] In the previous synthetic route, trimethoxy benzoic acid (TMBA) was selected as the starting material,[1] and GBA26 was synthesized in two steps: first by a TBTU-coupling reaction of TMBA with a Boc protected amine, followed by an *O*-demethylation using BBr_3. TBTU is well-known to react with free amino groups yielding guanidines and BBr_3 is a strong Lewis acid which has safety problems specially in scale-up reactions. This work aimed to scale up the synthesis of GBA26 to obtain a suitable amount of the compound to perform *in situ* studies in the marine environment, while optimizing the synthetic procedure to significantly reduce the environmental footprint. A synthetic route was envisioned starting from GA, a natural and affordable compound present in the grape waste, bringing an opportunity to offer a sustainable product to the AF industry. GA was firstly protected with benzyl groups. The amine coupling was accomplished with Mukaiyama reagent.[2] Following, deprotection of *N*-Boc groups was accomplished by a solvent-free reaction step.[3] This optimized synthetic route allowed to obtain GBA26 in sufficient amounts to proceed to "clinical" studies in the sea. Different % of GBA26 were incorporated into a commercial marine coating and acrylic plates were coated in duplicate. A prototype was constructed to secure the coated plates and immersed in the sea. The biofouling colonization was monitored during 7 months. Coatings containing only 2% of GBA26 showed better antifouling effect than coatings without any additive (negative control) and similar results to coatings containing 30% of Cu_2O. These promising results, along with the drug discovery approach followed for the development of this AF, may transform the marine antifouling development thinking.

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Mechanistic insights on the reactivation of wild-type activity of mutants p53 by tryptophanol-derived small molecules

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TP53 is the most frequently mutated gene observed in human cancer. The vast majority of cancer types exhibit a high prevalence of *TP53* mutations, resulting in the expression of mutant p53 proteins. These mutant proteins not only lose wild-type p53 tumor suppressor function but also gain functions that increase malignant progression. Consequently, tumors expressing mutant p53 are linked to a poor prognosis, chemoresistance, and invasiveness. The pharmacological restoration of wild-type-like activity of mutant p53 is a promising therapeutic strategy against cancer. Currently, only the cysteine alkylating quinuclidinone PRIMA-1 and the zinc chelator thiosemicarbazone COTI-2 are in clinical trials. These compounds reactivate a wide range of p53 mutation types. However, cancer cell resistance has already been reported for COTI-2, emphasizing the need for novel p53 reactivator compounds with higher selectivity to minimize toxic side effects and improve the therapeutic window.[1-2]

In this communication, we present our latest findings on the development of mutant p53 reactivators based on the tryptophanol-derived oxazoloisoindolinone scaffold. SLMP53-1 was previously identified as a hit candidate for reactivating wild-type and mutant p53, in particular in mutations associated with cancer aggressiveness and metastasis, such as the R273H and R280K. However, the mechanisms of reactivation of the p53 wild-type function in these mutations are still unclear. Our research has yielded crucial insights into the molecular dynamics of the hit compound SLMP53-1 and its binding to wild-type p53, as well as to two mutant forms of p53 associated with highly aggressive types of cancer, R273H, and R280K [3]. Through molecular dynamic simulations, we have obtained significant mechanistic insights into the binding of SLMP53-1 to these different forms of p53. Building upon our understanding of the wild-type and mutant p53 activator SLMP53-1, we are currently developing a hit optimization strategy to improve the efficacy of tryptophanol-derived oxazoloisoindolinones to restore the DNA contacts between mutant p53 and DNA. Our research provides a promising basis for the development of new pharmacological treatments for mutant p53-associated cancers.

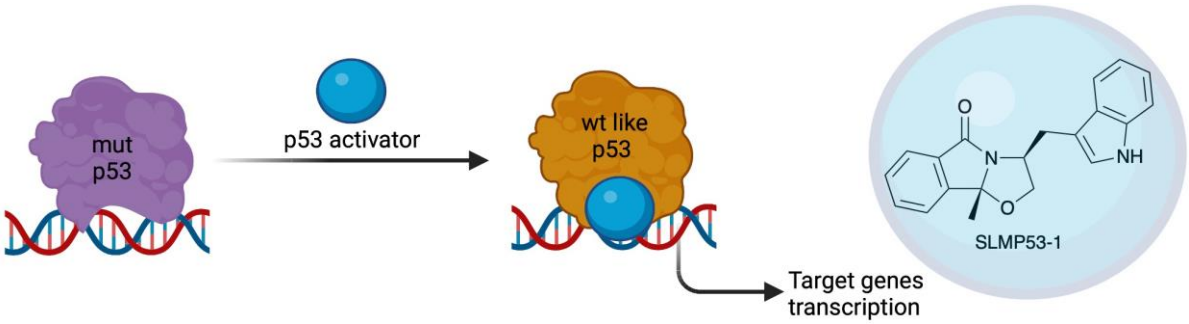

Figure 1: Reactivation of wild-type p53 activity by SLMP53-1.

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Compounds with biological activities on Ca^{2+}-ATPases

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The Ca^{2+} ion is essential in several intracellular processes, such as muscle contraction, synaptic plasticity and apoptosis, hence cells have regulation and fixation systems for normal cell functioning. One of the processes that contributes to Ca^{2+} homeostasis is achieved through Ca^{2+} pumps called Ca^{2+}-ATPase. There are three types of Ca^{2+}-ATPases involved in Ca^{2+}-homeostasis: the plasma membrane Ca^{2+}-ATPase (PMCA), which pumps the excess of Ca^{2+}out of the cell, and two intracellular pumps that accumulate Ca^{2+}- into the sarco/endoplasmic reticulum (SERCA) and to the secretory pathway (SPCA), respectively. The deregulation of the functioning of these pumps is associated with several pathologies including neurodegenerative diseases, heart diseases and diabetes, making these proteins drug targets to counteract those diseases [1,2,3,4]. Various compounds, of organic and inorganic nature, have been tested on Ca^{2+} -ATPases with the aim of determining their biological activity. It was observed that Au(I) and (III) compounds inhibits PMCA activity with IC_{50} range from 0.9 and 4.9 µM [3]. In SERCA IC_{50} range from 0.8 to 16.3 µM [3,4] was determined. Polyoxometalates and vanadium compounds also demonstrated biological activity on Ca^{2+}- ATPase [1,2]. In terms of organic compounds, several organic compounds have demonstrated biological activity in both SERCA and PMCA; we have quercetin, propranolol and naphthoquinones as an example, among others, globally with higher IC_{50} values of inhibition than the ones found for the gold complexes [3,4].

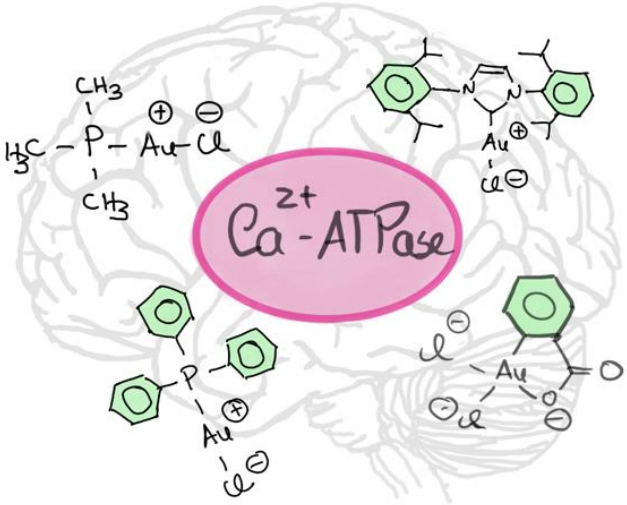

Figure 1: Inhibition of Ca^{2+}-ATPase by four gold complexes might change neuronal calcium homeostasis and consequently several cellular processes, namely in a brain level.

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Practical palladium-catalyzed switchable access to imines and amines from secondary alcohols

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Imines are important chemical intermediates in organic chemistry, with significant applications in medicinal chemistry and natural products [1]. However, the conventional methods for preparing imines often involve the condensation of an aldehyde or ketone with an amine under harsh conditions, using large amounts of solvents, and with low selectivity [2-5]. The use of abundant, renewable, and low-cost substrates to produce imines, would constitute a more environmentally-friendly methodology, overcoming the drawbacks from the traditional protocols. Alcohols, especially secondary alcohols, are highly attractive as a starting material and emerged as a promising alternative towards the synthesis of imines [6,7].

In this study, we introduce a new method for the synthesis of imines using a commercially available palladium catalyst via n acceptorless alcohol dehydrogenation of secondary alcohols and reaction with amines. This process requires only a small amount of catalyst and is highly selective towards imines, without the need of any base or additive, being scalable. Additionally, we have achieved excellent results in producing the corresponding amines by performing only slight modifications to the catalytic system. To demonstrate the practicality of this method, we have synthesized a family of structurally important *N*-heterocyclic scaffolds (Figure 1).

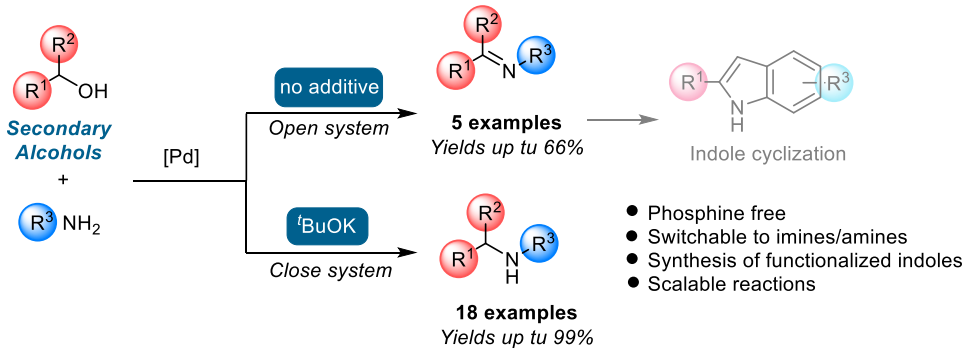

Figure 1: Synthesis of imines from amines and secondary alcohols using a Pd-based catalyst.

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Identification of bacterial strains competent in biodegrading carbamazepine, diclofenac, and 17-α-ethinylestradiol–preliminary results

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An increasing number of pharmaceuticals are consumed worldwide which has led to a higher occurrence of these new emerging pollutants in the environment through the excretion of not fully metabolized substances by humans and animals, through non-proper disposal of unused medication, and the manufacturing process of the pharmaceuticals themselves [1]. To manage and stagnate this development, practical, sustainable, and cost-effective measures must be applied in wastewater treatment plants (WWTP). Biodegradation can be such a measure.

In the present study, we aimed to (1) select isolates able to grow in a selective solid medium with the pharmaceuticals Carbamazepine (CBZ), Diclofenac (DCF), and 17-α-Ethinylestradiol (EE2) as the sole carbon source; (2) enhance the separation of the compounds detected by the high-performance liquid chromatography (HPLC), focusing mainly on the mobile phase; (3) observe the pharmaceuticals' properties concerning biosorption to WWTP sludge; and (4) identify bacterial strains able to biodegrade the pharmaceuticals in liquid medium.

Thirty-one (31) bacterial strains were able to grow in the solid medium in the presence of the tested pharmaceuticals and were selected for further experiments in liquid medium. The solubilized pharmaceuticals were analysed by HPLC with different ratios of the acidified Methanol and dH_2O and Acetonitrile and dH_2O as mobile phases, and biosorption tests were performed and the presence of each pharmaceutical was then analysed in the liquid and solid phases.

Through systematic experimentation of the mobile phase for the HPLC analyses, the best results in terms of separation were achieved using acidified methanol and water (pH 3.3, adjusted with orthophosphoric acid) in different ratios. For CBZ and EE2, the best ratio was 60:40 v/v, while for DCF the best ratio was 80:20 v/v. The biosorption tests gave different results for each of the three pharmaceuticals. The observed amount in percentage (m/m) bound to the solid phase was 10.4 % for CBZ, 9.6% for DCF and 64.5% for EE2. As for the biodegradation of the pharmaceuticals, the work is still ongoing.

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Novel chiral organocatalysts for the asymmetric synthesis of 2-(tetrazol-5-yl)-2*H*-azirines

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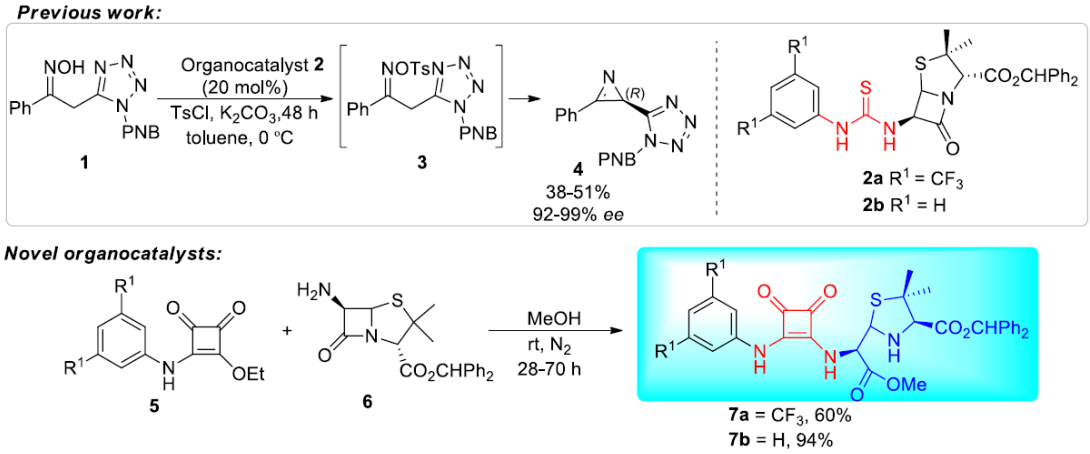
The search for safe and effective methods for the synthesis of chiral molecules with biological activity has been evident in the synthesis of several pharmaceutical compounds. This has led to the discovery and development of numerous organocatalysts over the last decade [1].

In this regard, our group has developed several organocatalysts for the synthesis of chiral 2-(tetrazole-5-yl)-2*H*-azirines resorting to the asymmetric one-pot Neber reaction of β-ketoxime-1*H*-tetrazoles [2-3]. Among the novel organocatalysts, new 6β-aminopenicillanic acid (6-APA)-derived thioureas **2** stand out, affording the (2*R*)-3-phenyl-2-(tetrazol-5-yl)-2*H*-azirine (**4**) with high enantioselectivity (*ee* >99%), albeit in moderate yield (Scheme 1).

To further improve the efficiency of these transformations, we set out to develop new squaramide-derived catalysts embodying the β-lactam-fused thiazolidine moiety. Interestingly, an unexpected outcome was observed in the reaction of **5** with the 6-APA ester **6**, which led to novel chiral squaramides **7** resulting from the β-lactam ring-opening reaction (Scheme 1). In this communication, details of the synthesis of these new chiral organocatalysts as well as initial results of their catalytic activity will be disclosed.



Scheme 1: Novel organocatalysts for the synthesis of chiral 2-(tetrazol-5-yl)-2*H*-azirines

Acknowledgements: Thanks are due to Coimbra Chemistry Centre – Institute of Molecular Sciences (CQC-IMS), supported by the Portuguese Agency for Scientific Research "Fundação para a Ciência e a Tecnologia" (FCT), through projects UIDB/00313/2020 and UIDP/00313/2020, co-funded by COMPETE2020-UE, and the IMS special complementary funds provided by FCT. This work was also supported by Project PTDC/QUI-QOR/0103/2021, funded by national funds (PIDDAC). The authors also acknowledge the UC-NMR facility for obtaining the NMR data (www.nmrccc.uc.pt). Terver J. Sase also acknowledge a PhD grant from Tertiary Education Trust Fund (tetfund), Nigeria.

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Exploring a novel functional assay for investigating the efficacy of anti-tuberculosis drugs targeting arabinofuranosyltransferases

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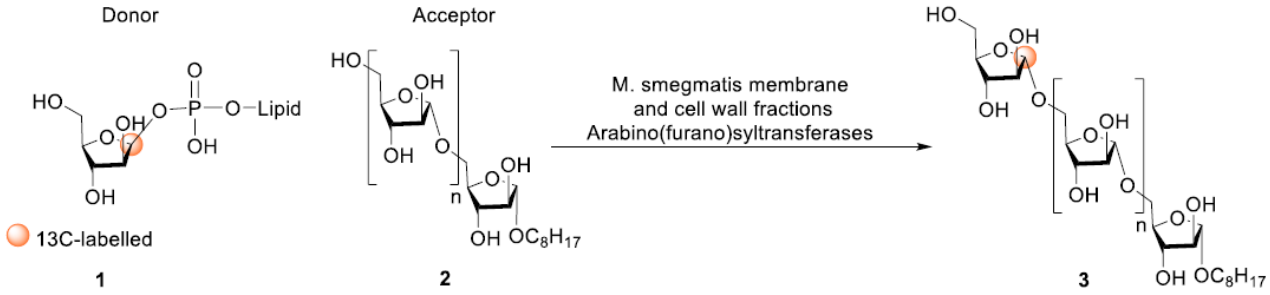
The increasing prevalence of drug-resistant bacteria represents a significant global health problem. *Mycobacterium tuberculosis* remains the leading cause of mortality from a single infectious organism. The development of novel antimicrobials is a major approach to overcome drug resistance problems since new compounds can offer a unique mechanism of action to which target pathogens are susceptible.[1] The cell envelope of *M. tuberculosis* is a common antibiotic target and has a unique structure comprising covalently linked peptidoglycan (PG), branched heteropolysaccharide arabinogalactan (AG) and long chain mycolic acids, termed the mycolyl-arabinogalactan-peptidoglycan (mAGP) complex. Arabinofuranosyltransferases (AraT)[2] use decaprenylphosphoryl-D-arabinofuranose (DPA) to donate an arabinofuranose residue to mAGP and are essential for *M. tuberculosis* growth [3].

In this work, a multidisciplinary approach was used for the development of enzymatic assays for AraT targets. Several linear and branched synthetic arabinofuranoside acceptors were synthesised and their binding affinity with AraT was screened using Saturation-Transfer Difference (STD) NMR to select the best synthetic glycosyl acceptors. The total synthesis of chemical anomeric 13C-labelled decaprenylphosphoryl arabinofuranose analogue **1** was optimised and well-characterised achieving an overall yield of 38% and an excellent anomeric ratio up to 31:1 (β:α). In order to study the protein conversions of the synthesised labelled donor with the acceptors, a flexible NMR protocol was designed and implemented.



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Photocatalytic transformations of quinic acid

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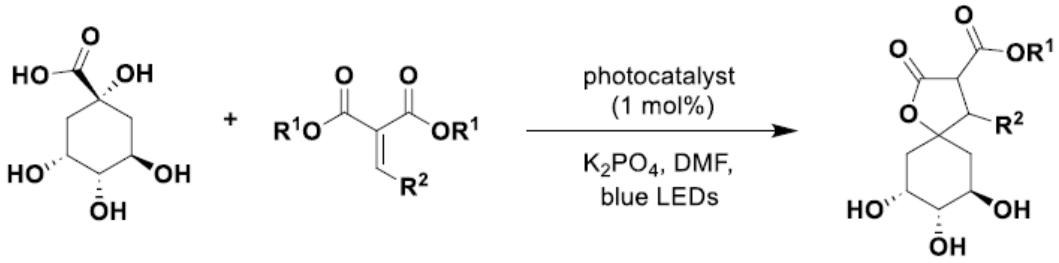
D-(-)-Quinic acid, a primary metabolite originated from D-glucose, is a well distributed compound throughout the plant kingdom, where it can be found free or in the form of its depsides, namely chlorogenic acids. Quinic acid can be easily isolated in a high enantiomeric purity, making it an attractive chiron for new compound design. Therefore, several methods for quinic acid modification have been reported in the literature indicating, however, the need to use harsh reaction conditions and sometimes even hazardous reagents [1-3].

Giese reactions are a specific type of photoredox-mediated radical conjugate addition reaction, enabling sustainable routes in organic synthesis. It consists of adding alkyl radicals to electron-deficient olefins, through conversion of visible light into chemical energy [4-6]. The substrate scope of this synthetic tool is broad with carboxylic acids and their derivatives being widely used as a source of radicals through decarboxylation phenomena which, due to photo-promoted processes, take place under greener and milder reaction conditions [7].

Combining all these facts, an appealing project emerged, consisting in the study of the reaction indicated in the scheme 1, where D-(-)-quinic acid is used as a radical precursor for a non-stereoselective photocatalyzed decarboxylative Giese-type conjugate addition, followed by lactonization to afford a spiro lactone. This work will present our efforts on the screening for different metallic and organic photo-redox catalysts and further optimization of other reaction parameters to increase the chemo- and stereoselectivity of the process.



Scheme 1: Photocatalytic tandem Giese-lactonization .

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Pyridyl-saccharinates: synthesis, structure and chelating properties

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Compounds that can act as potent and selective ligands towards metal cations are of interest in major areas and economic activities, namely for applications in medicine or environmental remediation, especially if they present specificity and good binding affinity to selected metals. Fine-tuning of the ligands structure is instrumental to achieve such selectivity.

Saccharinate-based conjugates are known to be chemically stable and generally non-toxic. In addition, the saccharyl system may be coupled to other heterocycles, generating a variety of structures with diverse properties. Investigation of the structure and reactivity of such conjugates proved their versatility and showed that they can act as selective multidentate nitrogen ligands in coordination chemistry [1, 2].

Following the previous investigations in our group regarding saccharinate-based conjugates with potential as selective metal chelators [3-5], this work presents the synthesis, structure and chelating activity assessment for a group of pyridyl-saccharinates where the linker between the two heterocyclic moieties varies (Figure 1). The structural differences introduced in the conjugates allow the tuning of properties, namely concerning their selectivity towards our target metal cations, Cu^{2+}, Fe^{2+} and Cd^{2+}, providing new information about the chelating capacity of this type of conjugates.

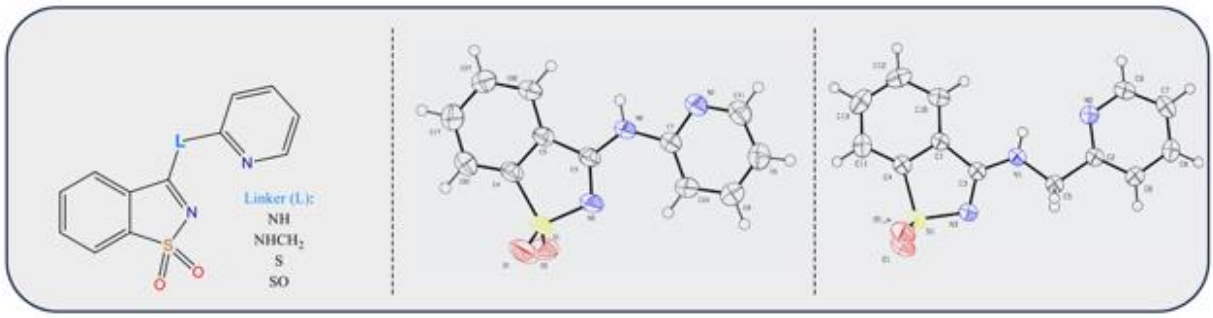

Figure 1: General structure of the pyridyl-saccharinates synthetised and studied (left) and the ORTEP plot of the -NH- (center) and -$NHCH_2$-linked conjugates (right).

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Development of synthetic methodologies to obtain dicarboxymethyl cellulose with differentiated structure and properties

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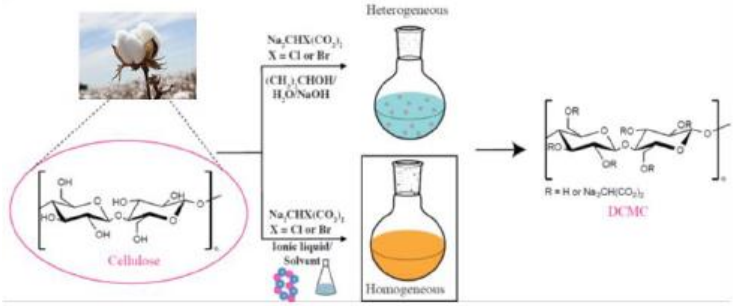
Cellulose, the main constituent of plants' fibres is a naturally occurring polymer and one of Earth's most available materials[1], its low solubility in common solvents, which is attributed to its extensive network of hydrogen bonds and hydrophobic interactions,[2] presents a challenge to its use. To address this issue, one solution involves chemically modifying cellulose, thereby interrupting the inter-unit and chain interactions to enhance solubility[4]. Dicarboxymethyl cellulose (DCMC) is a polyelectrolyte cellulose ether developed by us and usually synthesized via the heterogeneous reaction of cellulose with a halogenated malonate compound [3]. Our team recently developed and explored this compound which has a tuneable water solubility and double the number of ionizable groups compared to the well-known polymer carboxymethylcellulose (CMC) with the same degree of substitution (DS). As a result, DCMC exhibits a higher charge density over a wide range of pH values. However, achieving precise control over this etherification reaction is a non-trivial task. The resulting products may display an unpredictable DS and variable selectivity of the cellulose hydroxyl groups. To address this issue, we have focused on promoting the dissolution of cellulose in inert solvents that do not interfere with the etherification reagents.

Here we used several methodologies to investigate the production of DCMC under homogeneous and heterogeneous condition. The use of ionic liquids (ILs) and binary mixtures of ILs/molecular solvents as molecular solvents allowed the cellulose modification cellulose modification to achieve the tunability of DCMC properties like that observed for CMC, which also has distinct properties based on its degree of substitution and backbone selectivity.[4]



Scheme 1: Routes for DCMC preparation from microcrystalline cellulose using heterogeneous or homogeneous conditions

Funding: This work was supported by the Associate Laboratory for Green Chemistry – LAQV, which is financed by national funds from the Fundação para a Ciência e Tecnologia (FCT), the project 2022.02917.PTDC and the PhD grant DFA/BD/5529/2020 (D.G.).

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Innovative probes for imaging tumor-associated cathepsins through Positron Emission Tomography (PET)

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Cathepsins play pivotal roles in diverse physiological and pathological processes, degrading proteins like collagen and other internalized extracellular components in the lysosome. Increased cathepsin levels are evident in both cancer cells and cancer-associated stromal cells (macrophages, fibroblasts) contributing to tumor progression stages: tumorigenesis, proliferation, invasion, angiogenesis, and metastasis.[1]

Given their role in tumor growth, cathepsins emerge as promising biomarkers for cancer diagnosis. Therefore, the main goal of this research project is to synthesize, develop and evaluate cathepsin inhibitors with a linker capable of connecting to different types of cargos, such as diagnostic radionuclides, holding potential for creating efficient imaging probes which can serve as valuable tools for molecular imaging for tumor detection and treatment.[2]

Different warheads, designed to covalently link to the catalytic residue as cathepsin inhibitors, have been identified. Among them, vinyl sulfones stand out as one of the most promising ones, undergoing irreversible thio-Michael addition to the active site Cys25 of both Cathepsin B and Cathepsin L (Fig.1).[3]

Expanding upon the established scaffold of known inhibitors, modifications were introduced to the P1', P1 and P2 positions of the vinyl sulfone moiety. These alterations aimed to create novel active inhibitors specifically targeting Cathepsin B and Cathepsin L enzymes. The biological characterization of these newly developed inhibitors is currently underway through in vitro assays to assess their activity.

Additionally, modifications were implemented at the P3 position, incorporating a linker that enables the use of a chelator agent enabling the synthesis of new radiolabeled ligands. A comprehensive characterization of these compounds is in progress to ensure its effectiveness and suitability for subsequent investigations.

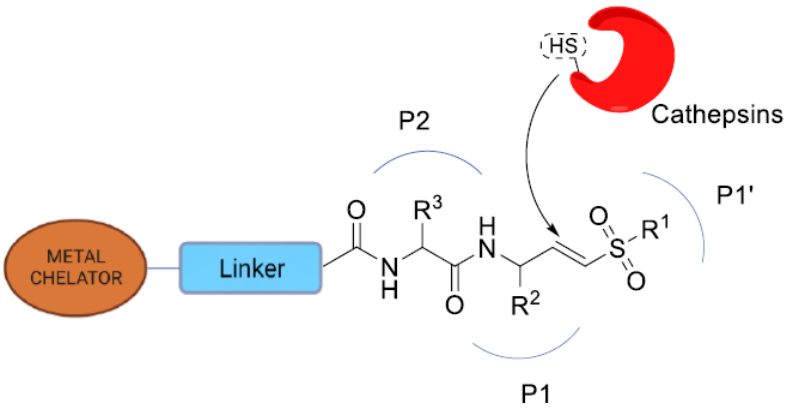

Figure 1: Vinyl sulfone probe scaffold and inhibition mechanism

Acknowledgments: We thank the Program Horizon Europe - MSCA Doctoral Network of the European Union for the support provided through Grant Agreement Number - 101073231 - OncoProTools.

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One-pot synthesis of aromatic aminopropyl lactams as potential agents for Alzheimer's disease

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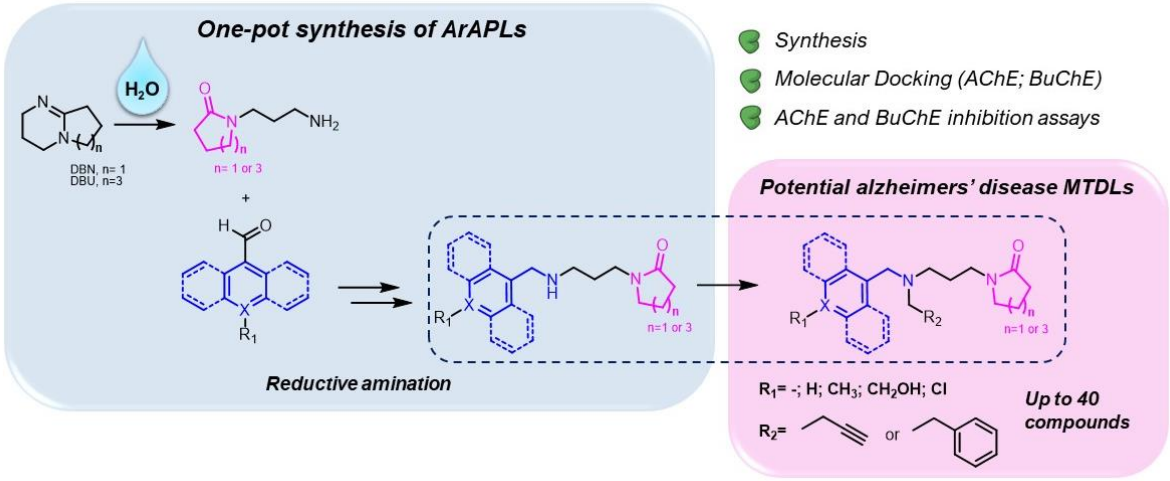
Alzheimer's disease (AD), the most common form of dementia, is a devastating syndrome with enormous burden on global healthcare and economy. There is no cure for AD, and the currently approved drugs have limited cognitive benefit. Cholinesterase inhibitors were, for many years, the only approved drugs for the treatment of AD and continue to be highly researched agents to tackle the disease[1]. Given the multifactorial facet of AD, greater focus has been put on multi-target directed ligands (MTDLs), since these can potentially regulate several targets operating in the disease network[2]. Thus, MTDLs targeting cholinesterases became appealing for the treatment of AD.

In this work, a one-pot protocol to access a library of Aromatic Aminopropyl Lactams (ArAPL) as potential MTDLs for the treatment of AD, is presented. We took advantage of the hydrolytic susceptibility of byclicic amidines DBN and DBU[3] to generate the corresponding γ- and ε-lactams, respectively. Subsequently, reductive amination with aromatic aldehydes resulted in linking of the structures via a three-carbon chain. The aromatic rings connected to the secondary amine have the potential to work as bioisosteres of tacrine. Alkylation of the secondary amine can modify biological activity. Molecular docking to evaluate the compounds' affinity to both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), plus, respective inhibition assays, are presented.



Scheme 1: One-pot synthesis of ArAPL and potential library of MTDLs targeting both AChE and BuChE, for the treatment of AD.

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Glyco-porphyrin based gold nanoplatforms for combined cancer photodynamic and photothermal therapies

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Cancer treatment remains a significant global health challenge, primarily due to its high mortality. Besides traditional cancer treatments, such as surgery, radio-, chemo-, hormone, or immune therapies, there has been a growing focus on exploring other therapies that offer fewer side effects. Among these, photodynamic therapy (PDT) and photothermal therapy (PTT) have gained considerable attention in recent decades [1,2]. The modification of the photoactive compound (photosensitizer, PS) through derivatization with biomolecules, such as carbohydrates, presents a promising strategy for targeted delivery. This approach leverages the recognition of uniquely expressed or overexpressed receptors on tumor cells, thereby increasing the treatment's selectivity [3]. Combining these PS derivatives with photothermal agents, such as gold nanorods (AuNRs), allows the simultaneous performance of PDT (through the generation of reactive oxygen species (ROS) from the cellular oxygen) with PTT, especially under hypoxia, since the slight increase in temperature induced by the photothermal effect results in a higher treatment efficiency [4,5].

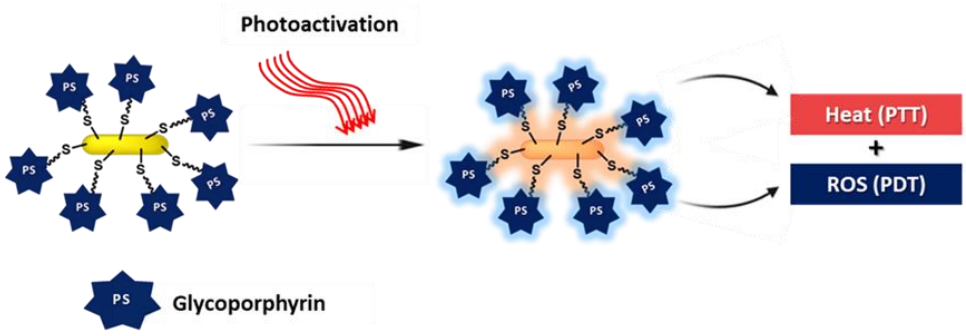

Figure 1: (Nano)formulation of bio-based AuNRs with glycoporphyrins

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 the projects CQE (UIDB/00100/2020 & UIDP/00100/2020); IMS (LA/P/0056/2020) and NanoSens-RNA (2022.04076.PTDC).
Acknowledgements: Thanks are due to CQE research unit and IMS Associate Lab, which have been funded through national funds and where applicable cofinanced by the FEDER, within the PT2020 Partnership Agreement. P. Santos thanks FCT for his PhD grant (ref. 2023.02393.BD)

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The synthesis of BODIPY-tetrazine and its potential application in gastric cancer cells via click chemistry

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Gastric cancer is one of the most lethal cancers worldwide, emphasizing the importance of an early diagnosis and effective treatment [1, 2]. In today's realm of cancer research, the scope has broadened beyond treatment alone, encompassing diagnosis. The goal is to improve outcomes, elevate survival rates, and enhance the quality of life for patients[3]. The current diagnostic techniques have some limitations, with low specificity. Optical imaging using fluorescent probes emerges as a more efficient complement for diagnosing this type of cancer. This approach provides increased contrast and selectivity with the tumor [1]. A good fluorophore is 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY), a dye developed 1968 by Treibs and Kreuzer [4]. The BODIPY core exhibits strong absorption capability, high fluorescence quantum yield, and photostability [4, 5]. These fluorophores can be conjugated with monoclonal antibodies (mAbs) to enhance tumor selectivity. The Inverse Electron Demand Diels-Alder (IEDDA) reaction between compounds with tetrazines and mAbs modified with trans-cyclooctene (TCO) has already been explored, demonstrating significant selectivity and rapid kinetics [6]. This strategy facilitates the development of bioconjugated fluorophores in vitro and in vivo with mAbs[6]. In this study, a BODIPY containing a tetrazine group was synthesized (Figure 1a), followed by its bioconjugation with the anti-human epidermal growth factor receptor 2 (HER2) antibody trastuzumab (Figure 1b).

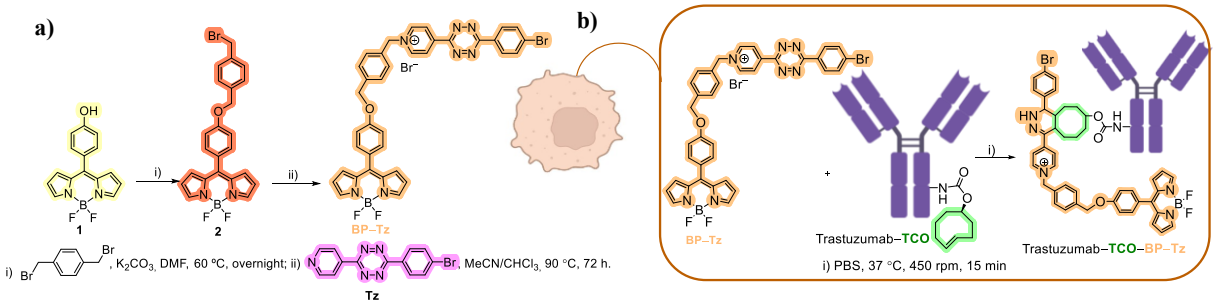

Figure 1: a) Synthesis of BODIPY-tetrazine and **b)** Click reactions to link BODIPY and trastuzumab.

Funding: This work received financial support from FCT/MCTES through the projects: UIDB/00100/2020, UIDP/00100/2020, LA/P/0056/2020, UIDB/50006/2020, UIDP/50006/2020; and internal funds from Mallinckrodt Institute of Radiology (WUSTL).

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Synthesis and evaluation of boronic-chalcone derivatives as anti-cancer and anti-inflammatory agents

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Chalcones are considered privileged scaffold in Medicinal Chemistry, exhibiting anti-cancer activity due to their inhibitory potential against several targets involved in carcinogenesis such as: proteasome, VEGF, VEGR-2, tubulin, NF-kβ, p-53-MDM2, among others [1,2]; and also, anti-inflammatory properties [3]. Fourteen novel chalcones containing a boronic acid group were synthesized through Claisen-Schmidt condensation, involving the coupling between 3- or 4-formyl boronic acids and 3-functionalized acetophenones using basic condition in ethanol medium at room temperature. Compounds were initially evaluated against Head and Neck Cancer (HNC) cell line SCC-25 (oral cavity carcinoma tumor cells) and NOK-si (oral cavity normal cells) in MTT assays. The most promissory compound (D3) showed IC_{50} = 17.7 µM (SCC-25) with SI >2.2. 5-Fluoacil (5-FU) commonly utilized for treatment for HNC, showed IC_{50} = 1.8 mM (SCC-25). The most promissory anti-cancer compound of the series, compound (D3), was selected in order to study its ability in inhibit different cytokines related to cancer promotion [4] using a Cytometric Bead Array (BD® CBA kit). Compound (D3) was able to reduce TNF-α (Figure 1), IL-6, IL-1β and IL-8 at two different concentrations (2 and 4 µg/mL). In addition to the anti-inflammatory effect of (D3), molecular docking studies were performed using Maestro (Schrödinger®) suggesting that compounds may be acting through inhibition of MDM2-p53 interaction (Figure 1). However, further studies will be conducted in order to confirm the molecular target of these novel molecules.

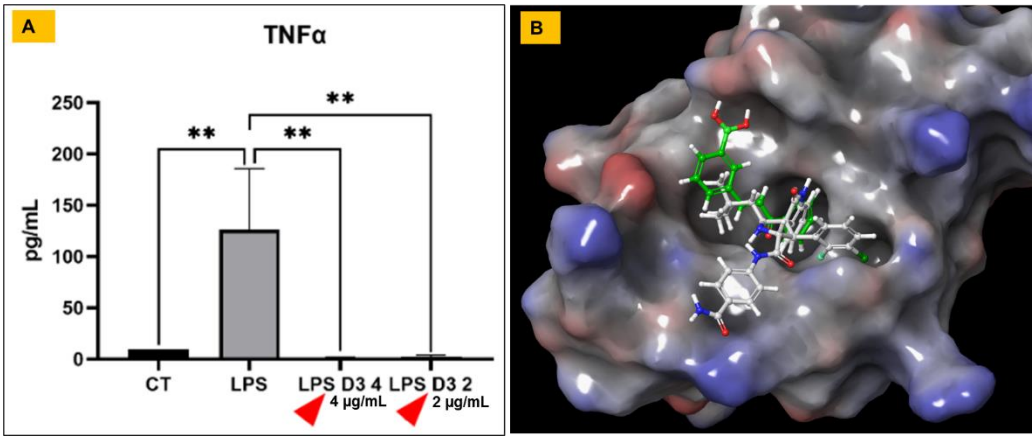

Figure 1: A) Inhibitory profile of compound (D3) against TNF-α, at 4 and 2 µg/mL; (CT – macrophages not stimulated with LPS). B) Molecular docking results using Maestro (Schrödinger®); PDB code: 4LWU; the 3D figure shows the superposition of boronic-chalcone derivative D3 (green) and Nutlin-3A (white), a selective inhibitor of MDM2, at the MDM2 site. The boronic acid group of chalcone is able to form two hydrogens bound with glycine residue (Gly-55).

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The theoretical description for omeprazole and diclophenac cathodic electrochemical determination by poly(tartrazine) modified carbon electrode

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Diclophenac (Fig. 1 to the left side) is one of the most used NSAIDs [1 – 4]. It is frequently used as anti-inflammatory drug and pain-killer for different pains. It is generally used in the form of sodium, potassium, ammonium and alkylammonium ions, being the ammonium salts usually added to creams and ointments.

On the other hand, if taken orally, diclophenac is hydrolized in stomach, provoking gastritis and gastric ulcers. , due to the acidic hydrolysis, yielding a weak acid. Also, its excessive concentrations, like also the long-time use may lead to the side effects like tiredness, slumber, nausea and vomit. In this case, omeprazol (Fig. 1 to the right) is used as a gastric proton pump to prevent and treat ulcer formation, due to the presence of both pyrrolic and pyridinic nitrogen atoms. Omeprazol also provokes adverse effects like vertigo, nausea, diarrhea and flatulence, which may cause discomfort. Moreover, the concentration control is also important for successful treatment of patients with liver and kidney insufficiency or older people. Thus, the search of a precise, exact, rapid and sensitive method for the quantification of both omeprazole and diclophenac is a really actual problem.

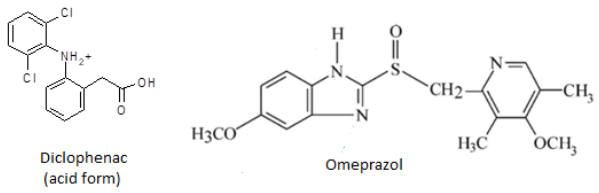

Figure 1: Diclofenac and omeprazol

Both of them have already been detected electrochemically, using different electrode modifiers. Nevertheless, it has been realized anodically, although the cathodic process is applicable to both of them. In order to realize the electrosensing of omeprazole and diclophenac on cathode, which is more suitable for their determination in gastric juice, the carbon material electrode is modified by tartrazine electropolymerization, being possible followed by vanadium (III) oxyhydroxide deposition. By this omeprazole will be cathodically reduced by sulfoxygroup, and diclophenac by carboxylic group and chlorine atoms, procedings to its dehalogenation. The electrode modifier will thereby act as proton and electron transfer modifier. In pure polymer coating the mediation will be realized by N = N bond, and in vanadium-modified coating, by V(IV)/V(III) redox pair.

The behavior of this system is described by the trivariant equation-set:

$$\begin{cases} \frac{d\omega}{dt} = \frac{2}{\delta}\left(\frac{\Delta}{\delta}(\omega_0 - \omega) - r_1\right) \\ \frac{d\lambda}{dt} = \frac{2}{\delta}\left(\frac{\Lambda}{\delta}(\lambda_0 - \lambda) - r_{21} - r_{22}\right) \\ \frac{dp}{dt} = \frac{1}{P}(r_1 + r_{21} + r_{22} - r_3) \end{cases} \quad (1)$$

Its analysis confirms the efficacy of poly(tartrazine) and poly(tartrazine)/VO(OH) coatings as electrode modifiers for omeprazol and diclophenac electrochemical determination on cathode. The same process may be applicable for the determination and dehalogenation of chloroorganic compounds, including pesticides and chemical warfare agents.

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New purine nucleosides against Alzheimer's disease: Cholinesterase inhibitors and metal chelators

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Alzheimer's disease (AD) is the most prevalent form of dementia amongst the elderly. However, there are no efficient treatments available for this devastating neurodegenerative disease. AD is characterized by multiple hallmarks. In this work, the reduced synthesis of acetylcholine (ACh), its hydrolysis by action of acetyl- and butyrylcholinesterase (AChE and BChE, respectively), and biometal imbalance are highlighted, these being related to other AD important features, namely, the formation and deposition of Aβ aggregates and neurofibrillary tangles (NFT), and the oxidative stress (Figure 1) [1]. Nucleosides have been widely employed as antiviral and antitumor drugs [2]. In the context of AD treatment, mannosylpurine nucleosides synthesized in our group have shown potent BChE inhibition [3,4]. Thus, we now present new rhamnosyl- and mannosylpurine nucleosides, synthesized by two different *N*-glycosylation methodologies for the coupling of N^6-benzoyladenine with different glycosyl donors, aiming at obtaining dual-target compounds against AD. Anticholinesterase activity, metal chelation and location of the chelation site were determined and disclosed. Finally, the first nucleoside-based compounds with potential to act as dual-target drugs against AD were obtained in this work [1].

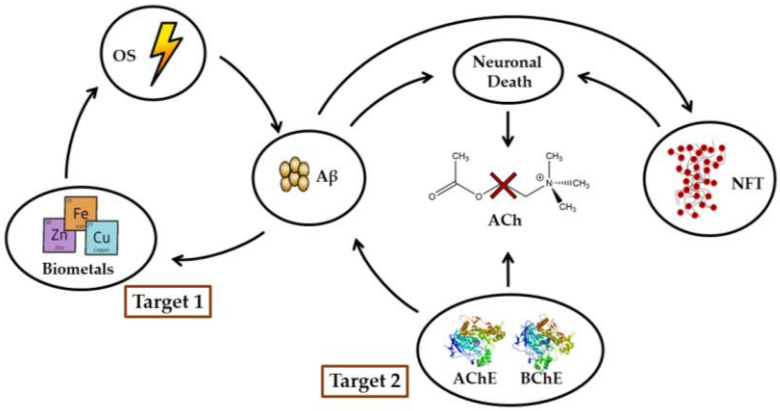

Figure 1: Connection between different AD hallmarks and targets chosen in this work for the development of dual-target compounds against AD.

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