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Message from the Chairs

The College of Chemistry of the University of Lisboa (CQUL) is pleased to organize its 5th Meeting and Summer School, under the *motto* "**CHEMISTRY: Forging bonds**", which is aimed at all researchers and students within the ULisboa universe.

Following a 2-year period of virtual interactions, the meeting is a golden opportunity to restore lively in-person talks, share research breakthroughs, (re)create collaborations and (re)introduce the younger students to a discussion forum open to all areas of Chemistry and related fields.

We prepared an attractive program that comprises lectures from renowned national and international scientists, invited oral communications, selected oral communications, flash presentations and panel communications, grouped by the different CQUL Divisions: Energy & Environment, Life & Health, Materials, and Technology & Industry.

The "2022 Summer School" will provide training on special topics delivered by distinguished speakers and promote contacts of students with academic and industrial sectors.

We warmly welcome you at the 5th CQUL Meeting and Summer School, where Chemistry bonds will surely be (re)forged.

Mário Nuno Berberan Santos
Matilde Marques
Francisco Lemos
Manuel Eduardo Minas da Piedade
Rui Moreira
Carlos Afonso
José Manuel Nogueira

COLÉGIO de QUÍMICA | UNIVERSIDADE DE LISBOA

5th Meeting

12-14 July '22
ULisboa's Main Building

Day 1 12th July

08:30	**Check-in**
09:00 – 09:15	**Opening Session** Cecília Rodrigues *(Vice-Rector of ULisboa)*, Mário Nuno Berberan e Santos*, (Chair of CQUL),* Matilde Marques*, Organizing Committee*

ENERGY & ENVIRONMENT | Chair: Francisco Lemos

09:15 – 10:00	**Plenary Lecture 1** "From plastic waste to light olefins – opportunities and challenges" Marvyn Kusenberg *(Ghent University, Belgium)*
10:00 – 10:20	**Invited Lecture 1** "Challenges on projects combining renewable energy and green gases production" Tiago Faria *(Efacec)*
10:20 – 10:35	**Oral Communication 1** Rafael Gomes *(iMed-Ulisboa, FFUL)*
10:35 – 11:35	**Poster Session and Coffee Break**
11:35 – 11:50	**Oral Communication 2** Fábio Santos *(iMed-Ulisboa, FFUL)*
11:50 – 12:05	**Oral Communication 3** Cátia Marques *(CQE-IMS, IST)*
12:05 – 12:20	**Flash Presentations 1-3** Nuno Conceição *(CQE-IMS, IST)*, Nuno Canha *(C2TN, IST)*, João Oliveira *(iMed-Ulisboa, FFUL)*
12:20 – 12:40	**Invited lecture 2** Daniel Pio *(the Navigator)*
Lunch	

MATERIALS | Chair: Manuel Minas da Piedade

14:00 – 14:45	**Plenary Lecture 2** "Mechanochemical formation of multicomponent crystals systems" Franziska Emmerling *(Bundesanstalt für Materialforschung und -prüfung - BAM, Berlin, Germany)*
14:45 – 15:05	**Invited Lecture 3** "The chemistry of water on Cu surfaces from quantum mechanical modeling" Cláudio M. Lousada *(Department of Materials Science and Engineering, KTH Royal Institute of Technology, Sweden)*
15:05 – 15:20	**Oral Communication 4** Nuno Bandeira *(BioISI, FCUL)*
15:20 – 15:35	**Flash Presentations 4-6** Ricardo Simões *(CQE-IMS, FCUL)*, Diogo Sousa *(ISEL and IBB, IST)*, Maria José Silva *(iMed-Ulisboa, FFUL)*
15:35 – 16:35	**Poster Session and Coffee Break**
16:35 – 16:50	**Oral Communication 5** João António *(iMed-Ulisboa, FFUL)*
16:50 – 17:05	**Oral Communication 6** Shirley Sancha *(iMed-Ulisboa, FFUL)*
17:05 – 17:25	**Invited Lecture 4** "Silica-gel as a carrier for hydrogen peroxide for applications in bio-decontamination" Fadhil Musa*, Delox*

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COLÉGIO de QUÍMICA | UNIVERSIDADE DE LISBOA

5th Meeting

12-14 July '22
ULisboa's Main Building

Day 2 13th July

08:45 **Check-in**

LIFE & HEALTH | Chair: Rui Moreira

9:15 – 10:00 **Plenary Lecture 3** "The discovery of LML134, an H3R inverse agonist for the treatment of narcolepsy"
Yves Auberson *(Novartis, Switzerland)*

10:00 – 10:20 **Invited Lecture 5** "Low data machine learning for chemical discoveries"
Tiago Rodrigues *(iMed.Ulisboa, FFUL)*

10:20 – 10:35 **Oral Communication 7**
Rita Félix *(iMed.Ulisboa, FFUL)*

10:35 – 11:35 **Poster Session and Coffee Break**

11:35 – 11:50 **Oral Communication 8**
Elizabeth Lopes *(iMed.Ulisboa, FFUL)*

11:50 – 12:05 **Oral Communication 9**
Gonçalo Justino *(CQE-IMS, IST)*

12:05 – 12:20 **Flash Presentations 7-9**
Vera Isca *(CBIOS, ULHT and iMed.Ulisboa, FFUL)*, Salvatore Princiotto *(Univ. Milan and ULHT)*, Ivo Martins *(IMM, FMUL)*

12:20 – 12:40 **Invited lecture 6** "Protecting the Central Nervous System with broad range antiviral drugs. The cases of Zika and Dengue viruses, HIV and SARS-CoV-2"
Miguel Castanho *(iMM-FMUL)*

Lunch

TECHNOLOGY & INDUSTRY | Chair: Carlos Afonso

14:00 – 14:45 **Plenary Lecture 4** "Flow Chemistry: Enabling and Accelerating Understanding and Development"
Kerry Gilmore *(Department of Chemistry, University of Connecticut)*

14:45 – 15:05 **Invited Lecture 7** "Electrifying Organic Synthesis – When your Chemistry has got Potential"
Kevin Lam *(Department of Pharmaceutical, Chemical and Environmental Sciences, The University of Greenwich, UK)*

15:05 – 15:20 **Oral Communication 10**
Abdallah Mahmoud *(CQE-IMS, IST)*

15:20 – 15:35 **Flash Presentations 10-12**
Humberto Ferreira *(FFUL and CERENA-IST)*, Milene Fortunato *(iMed.Ulisboa, FFUL)*, Inês Martins *(iMed.Ulisboa, FFUL)*

15:35 – 16:35 **Poster Session and Coffee Break**

16:35 – 16:50 **Oral Communication 11**
João Ravasco *(iMed.Ulisboa, FFUL)*

16:50 – 17:05 **Oral Communication 12**
Késsia Andrade *(iMed.Ulisboa, FFUL)*

17:05 – 17:25 **Invited Lecture 8** ""High pressure food, biotechnological and chemical potential applications"
Jorge Saraiva *(University of Aveiro)*

17:25 – 18:00 **Awards and Closing Session**
Cecília Rodrigues *(Vice-Rector of ULisboa)*, Mário Nuno Berberan e Santos *(Chair of CQUL)*, Matilde Marques *(Organizing Committee)*

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COLÉGIO de QUÍMICA | UNIVERSIDADE DE LISBOA

5th Meeting

12-14 July '22
ULisboa's Main Building

Day 3 14th July SUMMER SCHOOL

Biorefineries

08:30	**Check-in**
9:00 – 9:15 h	**Opening Session** Francisco Lemos and Carlos Afonso *(co-chairs of the 2022 Summer School)*
9:15 – 10:15 h	**Lesson 1** "Cannabis - A European and chemistry perspective on an emerging industry" Joana Lemos *(Atann One)*
10:15 – 11:15 h	**Lesson 2** "The Sea as a source of another Chemistry" Pedro Lima *(Sea4Us)*
11:15 – 11:45 h	**Coffee Break**
11:45 – 12:45 h	**Lesson 3** "Microalgae Biorefineries Fostering Circular Economy" Cristina Matos *(A4F)*
Lunch	
14:15 – 15:15 h	**Lesson 4** Adélio Mendes *(FEUP)*
15:15 – 16:15 h	**Lesson 5** "Fostering biomass thermochemical liquefaction within a biorefinery perspective" Rui Galhano dos Santos *(CERENA)*
16:15 – 16:45 h	**Coffee Break**
16:45 – 17:45 h	**Lesson 6** "Biorefinery processes in symbiosis with the forestry sector" João Nunes *(BLC3)*
17:45 – 18:00	**Closing Session** Francisco Lemos and Carlos Afonso *(co-chairs of the 2022 Summer School)*

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SUBMITTED CONTRIBUTIONS

ORAL COMMUNICATIONS

Direct Diels-Alder reaction of chitin derived 3-acetamido-5-acetylfuran

Rafael F. A. Gomes, Juliana Pereira, João Ravasco, João Vale, Fausto Queda

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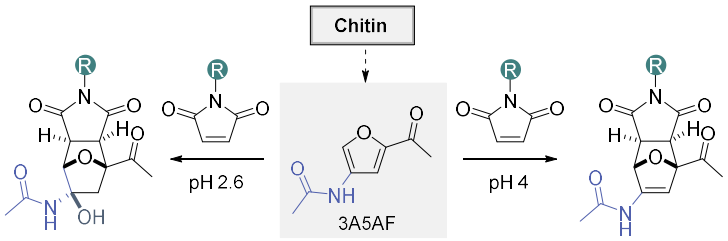
The Diels-Alder (DA) reaction of biomass derived furans is an emerging technology for the preparation of new molecular entities and "drop-in" commodity chemicals.[1] In this work we address the challenge of the direct use of electron-poor furanic platforms as dienes through the use of an unexplored chitin derived furan, 3-acetamido-5-acetylfuran (3A5AF).[2]

Moreover, the introduction of renewable nitrogen is of the utmost importance given the dependence of Haber processes for preparation of ammonia, the most common nitrogen source for fine and commodity chemicals.49, 50 This leads to the consumption of circa 1.5 % of the total world energy consumption for the production of ammonia.[3] Using chitin as starting material we are able to introduce renewable nitrogen in the new scaffolds/synthons.

The remarkable effect of the acetamide group in position 3 of the furan, endorsed by *ab initio* studies, allowed for chitin derived 3A5AF to be used as the first biomass furan diene in DA reactions "as is". Fine tuning of the reaction conditions allows selective preparation of 7-oxanorbornenes (7-ONB) or tandem partial hydrolysis of the enamide to prepare 7-ONB hemi-acylaminal derivatives.

The beneficial effect of the 3-acetamide is observed by the mild reaction conditions in contrast with commonly employed harsh conditions which require high temperature or catalysts. Also the operational simplicity for the reaction setup/isolation is highly appealing for its application in areas such as materials, biomaterial chemistry and even biology.



Acknowledgements

Financial support from Fundação para a Ciência e a Tecnologia (SFRH/BD/120829/2016; PTDC/QUI-QOR/32008/2017; UIDB/04138/2020; UIDP/04138/2020, SFRH/BD/120119/2016, PD/BD/143162/2019), is gratefully acknowledged. 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.

References

[1] J. Ravasco and R. F. A. Gomes, *ChemSusChem,* **2021***, 14,* 3047-3053

[2] Juliana G. Pereira, João M. J. M. Ravasco, João R. Vale, Fausto Queda, Rafael F. A Gomes, *Green Chem., just accepted.*

[3] T. Kahl, K. Schröder, F. R. Lawrence, W. J. Marshall, H. Höke, R. Jäckh, *In Aniline*, in Ullmann's Encyclopedia of Industrial Chemistry, **2011.**

BASHY as a valuable fluorescent linker for drug conjugates

Fábio M. F. Santos,[a] Silvia Baldo,[a] Patrícia Antunes,[b] Jesus F. Arteaga,[c] Fábio Fernandes,[b] Uwe Pischel,[a,c] Sandra N. Pinto[b] and Pedro M. P. Gois[a]

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Boronic-acid derived salicylidenehydrazone (BASHY)[1] dyes were evaluated as fluorescent linkers for drug conjugates. The proteasome inhibitor bortezomib (Btz) was incorporated into the BASHY framework, and the complexes were structurally optimized in order to improve the stability at physiological pH buffered conditions (half-life up to 40 h), photophysically characterized regarding their fluorescence properties and used in confocal microscopy colocalization studies that revealed their intracellular sequestration by lipid droplets.[2] The accumulation in these hydrophobic organelles limited the hydrolysis of the complex and consequently the drug release, a problem that was circumvented by the conjugation of the BASHY-Btz complex with a cellpenetrating peptide GV1001-C (**Figure 1**).[3] The conjugate exhibited an improved cytoplasmic availability as confirmed by confocal fluorescence microscopy studies and an improved potency against HT-29 cancer cells (IC_{50} = 100 nM) as compared to the nontargeted complex (IC_{50} = 450 nM).[4]

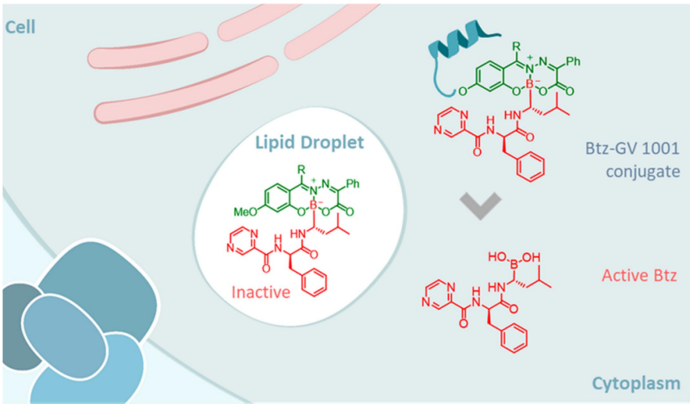

Figure 1 - BASHY platform enables the assembly of a fluorescent cytototoxic bioconjugate.

Acknowledgements

We acknowledge the financial support from Fundação para a Ciencia e a Tecnologia (FCT), Ministério da Ciência e da Tecnologia, Portugal (iMed.ULisboa UIDB/04138/2020; SAICTPAC/0019/2015, PTDC/QUI-QOR/29967/2017); LISBOA-01-0145-FEDER-029967, LISBOA-01-0145-FEDER32085, and PTDC/QUI OUT/3989/2021, and the Ministerio de Ciencia e Innovación, Spain (PID2020-119992GB-I00). Centro de Química Estrutural acknowledges the financial support of FCT (UIDB/00100/2020). iBB acknowledges the financial support of FCT (UIDB/04565/2020 and UIDP/ 04565/2020).

References

[1] Santos, F. M. F. *et al*. Chem. Eur. J. 22 (2016) 1631–1637.
[2] Zhang, I. *et al*. Eur. J. Pharm. Biopharm. 100 (2016), 66–76.
[3] Kim, H. *et al*. Int. J. Mol. Sci. 17 (2016), 2054.
[4] Baldo, S. *et al*. ACS Med. Chem. Lett. 13 (2022), 128–133.

Unravelling hidden mechanisms of montelukast action: an MS multi-omics approach to drug toxicity and repurposing

Cátia F. Marques[a], Gonçalo C. Justino[a], Pedro F. Pinheiro[a], M. Matilde Marques[a]
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Montelukast (MTK) is a cysteinyl leukotriene receptor antagonist widely used to suppress the inflammatory response in asthma and allergic rhinitis. Despite being suggested as a potential therapeutic strategy for neuroinflammatory disorders, such as Alzheimer's Disease, the number of reported adverse drug reactions (ADRs), among which neuropsychiatric ADRs are the most reported, has been increasing.

In order to reconcile the central nervous system (CNS) adverse reactions to MTK with its repurposing for a neurodegenerative condition, we performed a multi-omics multi-system MS-based evaluation of the pathways involved in the response to MTK administration using an *in vitro* chicken embryo neuron model and an *in vivo* approach using a rodent model. Taking advantage of the ultra-performance liquid chromatography coupled to high-resolution electrospray ionization tandem mass spectrometry (UPLC-ESI-HRMS/MS) equipment installed at CQE Mass Spectrometry Lab, full untargeted metabolomics and proteomics approaches were used to study both models' response to MTK.

Results clearly show that MTK treatment is associated with an hyperactivation of the HPA axis, leading to a dysregulation of neurotransmitter-dependent pathways, establishing a clear relation between MTK and the described adverse reactions on the CNS. Furthermore, proteomics data also suggest that MTK influences endopeptidase activity, apoptotic processes, and cell death.

In parallel, thiol-based pathways involved in protection against oxidative stress were found shifted towards an increased global oxidative status. This correlates with the identification of an MTK-glutathione adduct formed both enzymatically and non-enzymatically, which was also characterized in this work.

Regarding the repurposing application of MTK for neurodegenerative disorders, proteomics data suggest that some of the proteins with neuroprotective roles are altered, suggesting a beneficial effect of MTK treatment. Moreover, *in vitro* protein aggregation assays also suggest an MTK protective role.

To conclude, the network connectivity between both omics approaches allowed identifying the potential pathways involved in the mechanisms responsible for the reported ADRs, as well as, the mechanisms involved in the neuroprotective effect of this drug.

Acknowledgements

Centro de Química Estrutural is a Research Unit funded by Fundação para a Ciência e Tecnologia through projects UIDB/00100/2020 and UIDP/00100/2020. Institute of Molecular Sciences is an Associate Laboratory funded by FCT through project LA/P/0056/2020. This work was partially funded through FCT grants SAICTPAC/0019/2015 and PTDC/QUI-QAN/32242/2017 and through the Portuguese Mass Spectrometry Network (RNEM-LISBOA-01-0145-FEDER-022125). C.F.M. also thanks FCT for a PhD fellowship (PD/BD/143128/2019 and COVID/BD/152559/2022).

Co(II) Single Ion Magnets with imino-pyrrolyl ligands: Analysis and Design strategies.

Nuno A. G. Bandeira*, Patrícia S. Ferreira, Ana C. Cerdeira, Tiago F. C. Cruz, David Hunger, Alexander Allgaier, Joris van Slageren, Manuel Almeida, Laura C. J. Pereira, Pedro T. Gomes

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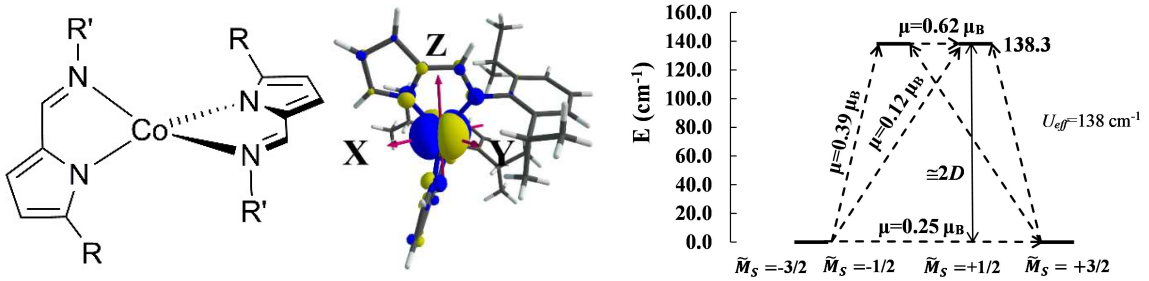
Previously, only a few Co(II) complexes containing four coordinating nitrogen atoms are found in the literature showing a strong magnetic anisotropy as a result of a strong axial distortion [1]. In this work, we report a series of distorted tetrahedral homoleptic Co(II) complexes bearing two 2-formiminopyrrolyl N,N'-chelating ligands (Figure 1a) also displaying single ion magnetic (SIM) behaviour with very high energy barriers [3].

Magnetic measurements and HFEPR showed a large and negative magnetic anisotropy with the zero-field splitting parameter *D* lying between *ca.* -50 to -70 cm^{-1}. These results are reproduced by means of first principles CASSCF/QD-NEVPT2 calculations. The most important source of axial anisotropy stems from the first $e \rightarrow t_2$ electronic transition, in line with other tetrahedrally coordinated Co(II) complexes. Calculations carried out on model systems show how the SIM properties in this family of ligands may be magnetostructurally improved. Most of these compounds show slow relaxation of the magnetization at zero DC field with barriers (U_{eff}), above 100 cm^{-1} (Figure 1b), which are higher than the majority of the tetracoordinated Co(II)-based SIMs reported in the literature [1].



(a) (b)

Figure 1: (a) Chemical makeup of the series of Co(II) complexes (R=H, C_6H_5, 2,6-$Me_2C_6H_3$, adamantyl; R'= 2,6-$^{i}Pr_2C_6H_3$, adamantyl); (b) Energy level diagram of the Kramers' doublets of the best performing complex.

Acknowledgements

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References

[1] J. Vallejo, et al., Chem. Sci. 8, 3694 (2017);

[2] H. Cui, et. al., Inorg. Chem. 58, 12555 (2019).

[3] P. S. Ferreira, et. al., Inorg. Chem. Front., Advance Article, https://dx.doi.org/10.1039/D2QI00601D (2022).

Diazaborines as a stable and triggerable linker: development of the first well-defined ROS-responsive antibody-drug conjugate

João P. M. António,[a] Joana Inês Carvalho,[a] Ana S. André,[b] Joana N. R. Dias,[b] Sandra I. Aguiar,[b] Hélio Faustino,[a] Ricardo M. R. M. Lopes,[a] Luis F. Veiros,[c] Gonçalo J. L. Bernardes,[d,e] Frederico A. da Silva,[b] Pedro M. P. Gois[a]

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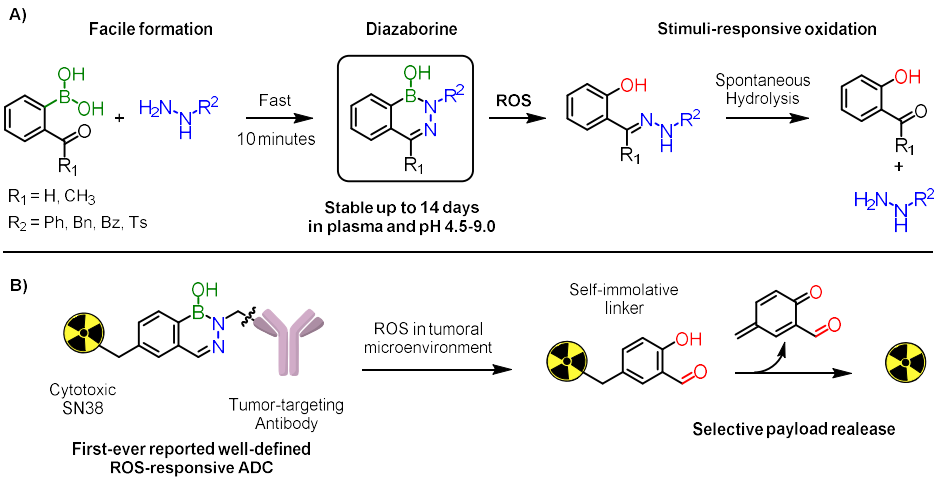
Antibody-drug conjugates (ADCs) are one of the most promising class of therapeutics in the battle against cancer. The success of an ADC is closely related with the careful optimization of its four major components: antibody, payload, linker and bioconjugation technology. The linker, in particular, must be stable in solution and capable of releasing the payload upon a predetermined stimulus.[1] Current ADCs explore the distinctive microenvironment of cancer cells to ensure a selective deliver of the drug, including its acidic pH, high glutathione levels and overexpressed proteolytic enzymes. In this work, we demonstrate for the first time that the high reactive oxygen species (ROS) concentrations present in tumor cells can be exploited to generate a first-in-class ROS-responsive ADC.[2] The synthesis of this ADC was possible due to the discovery that diazaborines (DABs) are a very effective ROS-responsive unit while being stable in buffer and in plasma. DABs can be generated with click-like kinetics (bioorthogonal, 10 min in aqueous pH 7.4) and displayed remarkable stability in pH 4.5-9.0 and plasma. However, in the presence of 100 equiv. H_2O_2 they were swiftly oxidized ($t_{1/2}$= 15 min) (**Scheme 1A**). Mechanistic and DFT experiments were performed on the system to further understand the details behind their stability and selectivity. To showcase their potential, a DAB-based self-immolative linker was designed and used in the construction of a homogenous ADC. The ADC, featuring a SN-38 cytotoxic drug and a B-cell lymphoma targeting antibody, showed remarkable activity (IC_{50} = 54.1 nM) and selectivity (>100 µM in T-cell lymphoma) (**Scheme 1B**). Due to their modularity and fast kinetics, we envision that DABs will play an important role in the development of a new generation of ROS-responsive linkers which could span from the construction of additional ADCs to the development of novel responsive materials.



References

[1] J. P. M. António *et al*, Chem. Soc. Rev. 48, (2019), 3513.

[2] J. P. M. António *et al*, Angew. Chem. Int. Ed. 60, (2021), 25914.

Exploring Amaryllidaceae-type alkaloids and derivatives for overcoming multidrug resistance in cancer

Shirley Sancha[1,*], Adriana V. Gomes[2], Joana B. Loureiro[2], Nikoletta Szemerédi[3], Gabriella Spengler[3], Lucília Saraiva[2], Maria-José U. Ferreira[1]

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The increasing occurrence of multidrug resistance (MDR) is the major obstacle to cancer chemotherapy treatment. Therefore, there is an urgent need for new anticancer compounds and new strategies for overcoming MDR.

Aiming at finding new anticancer compounds for overcoming MDR, in the present study several Amaryllidaceae-type alkaloids bearing lycorine, tazettine, galanthamine, haemanthamine, and homolycorine scaffolds were isolated from *Pancratium maritimum* L. (Amaryllidaceae). Moreover, some derivatives were prepared by chemical derivatization of compounds isolated in large amount. Their structures were assigned, mainly, based on spectroscopic data (IR, MS, 1D, and 2D NMR -COSY, HMQC and HMBC, and NOESY experiments).

The isolated natural compounds were evaluated for their antiproliferative activity in triple-negative breast cancer cell lines MDA-MB-231 and MDA-MB-468, breast cancer cells MCF-7, and non-malignant fibroblast (HFF-1) and breast (MCF12A) cell lines, by the sulforhodamine B assay. Subsequently, a homolycorine-type alkaloid was evaluated for its ability to induce apoptosis and cell cycle arrest. In addition, to corroborate the results obtained, western blot analyses and chemosensitivity assays were also performed. The lycorine derivatives were evaluated for their MDR reversal activity on resistant human adenocarcinoma (Colo 320) cells. In the rhodamine accumulation assay, significant inhibition of P-gp efflux activity was observed for some derivatives at non-cytotoxic concentrations. The effect on the ATPase activity of the most active compounds showed that they behaved as inhibitors. In drug combination assays, most of the compounds showed strong synergistic interactions with doxorubicin. Moreover, some derivatives exhibited a selective antiproliferative effect toward resistant cells, having a collateral sensitivity effect.

Keywords: “Amaryllicaceae-type alkaloids”; “*Pancratium maritimum; Molecular* derivatization”; “Multidrug resistance”; “Triple-negative breast cancer”.

Acknowledgments: This study was financially supported by Fundação para a Ciência e a Tecnologia (FCT), Portugal (grant SFRH/BD/130348/2017; project PTDC/MED-QUI/30591/2017; Bilateral Portuguese-Hungarian Science & Technology Cooperation FCT/NKFIH, 2019/2020 and LAQV/REQUIMTE (UID/QUI/50006/2020).

β-Lactams and Their Isosteres as Scaffolds to Design Activity-Based Probes for Chemoproteomics

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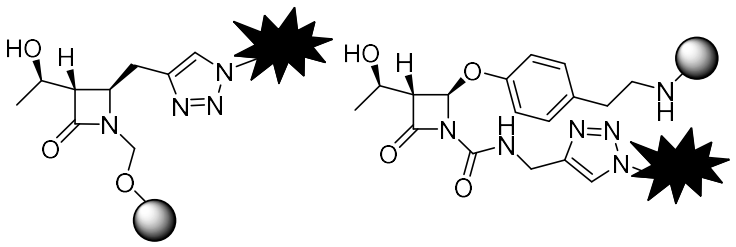
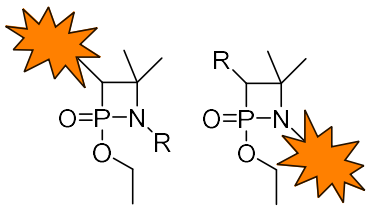
Human Neutrophil Elastase (HNE), a serine hydrolase expressed in polymorphonuclear neutrophiles, is present in the tumour microenvironment. While recent studies reported that HNE can promote tumour proliferation and metastasis [1], there is a lack of chemical tools to properly understand the potential of this enzyme in cancer therapies.

In this work we report the development and optimisation of a synthetic methodologies to obtain β-lactam-containing quenched activity-based probes [2](qABPs). The photophysical properties of these qABPs are described. Remarkably, gel-based studies revealed that qABPs released the fluorophore when incubated with elastase. Furthermore, these compounds were incubated with HEK cells lysates spiked with elastase and showed that even at low concentrations of enzyme, the qABPs display excellent selectivity.

While the structural requirements for acylation and sulfonylation [3] of catalytic aminoacids by four-membered ring probes, phosphonylation remains largely unexplored. The second part of the work aims to achieve the synthesis of a probe using as a warhead a phospholactam ring. We present the optimisation synthetic strategy for probes containing this warhead. A preliminary study of the reactivity of this type of compounds will be performed to understand if phopholactams can became an important tool to analyse serine hydrolases.



β-lactam based qABPs



β-phospholactam based ABPs

Acknowledgements

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References

[1] Lerman, I., Hammes, S. R. Steroids, 133, (2018), 96-101.

[2] Bender, O., Ofori, *et al.* J. Am. Chem. Soc., 137, (2015), 4771-4777.

[3] Carvalho, L. A. R., Moreira, R, *et al.* ACS Chem. Bio., 15, (2020), 878-883.

Dual inhibition of p53-MDM2/4 PPIs: spiropyrazoline oxindoles case

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The tumor suppressor p53 is a highly attractive target and has uncovered a wide field in the development of novel p53-based cancer therapies. In particular, the dual p53-MDM2/4 protein-protein interactions (PPIs) inhibition is considered the most efficient approach to fully activate wild-type p53. The design of p53 reactivators mimics the amino acids (Phe19, Leu22, Trp23, and Leu26) of p53 involved in the interaction with MDMs. MDM2 antagonists have been widely studied and several compounds have reached clinical trials. However, they do not inhibit extensively p53-MDM4 PPI. Moreover, the development of novel chemical entities that disrupt p53-MDM4 and p53-MDM2/4 PPIs has been very demanding, mostly due to the rigidity of MDM4 and its conformational differences with MDM2. To date, only the stapled peptide ALRN-6924 is in clinical trials as dual inhibitor of MDM2 and MDM4, despite having low proteolytic stability and membrane permeation issues.[1,2]

In this communication, we report the structural optimization of a previously identified hit spiropyrazoline oxindole as dual inhibitor of p53-MDM2/4 PPIs. Although this derivative was identified as p53 pathway activator in HCT116 cells, inducing cell cycle arrest at G0/G1 phase and apoptosis, it didn't bind extensively to MDM2.[3] Consequently, we have designed new derivatives able to reactivate p53 by targeting MDM2 and MDM4. Hence, several structural modifications to mimic p53 pivotal amino acids were screened in both proteins. In addition, an *in silico* database of spiropyrazoline oxindoles was constructed by adding fragments to the scaffold, in particular, the solvent-exposed pocket, and, then, screened against MDM4. Compounds with higher scores and best visual fitting were synthesized and evaluated in cancer cell lines harboring wild-type p53. The most active compounds were also evaluated in an enzyme immunoassay for heterocomplexes p53-MDM2 and p53-MDM4. Three new spiropyrazoline oxindole derivatives showed to inhibit both p53-MDM2/X PPIs in the nanomolar range.[4]

Acknowledgments

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References

[1] M. N. Saleh et al., Clin. Cancer Res. 27 (2021) 5236.
[2] M. Espadinha *et al.*, Curr. Top. Med. Chem. 18 (2018) 647.
[3] a) R. Nunes *et al.*, Eur. J. Med. Chem. 139 (2017) 168.
[4] M. Espadinha *et al.*, Eur. J. Med. Chem. (under revision)

Neuropsychiatry, COVID, polyclonal myeloma, and clinical bacterial isolates - CQE's Mass Spectrometry Lab in clinical practice

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High-resolution mass spectrometry (HRMS) is a fundamental tool for both structure-oriented and omics-focused approaches to biological systems and clinical samples alike.

In this framework, the Mass Spectrometry Laboratory of Centro de Química Estrutural (Técnico) has been developing a series of HRMS methodologies aiming to contribute to various clinical-focused studies, in both medical and research contexts, coupled to a high-throughput bioinformatics-driven analysis. This communication will summarily describe the work performed in this area.

A fully untargeted metabolomics approach was employed to analyse the toxicity and adverse drug reactions (ADRs) to the asthma-controlling drug montelukast (Singulair), together with an organ-targeted proteomics approach. This MS-based double-omics approach, combined with a classical RT-qPCR transcriptomic study, has highlighted the role of the hypothalamic–pituitary–adrenal axis and of the thiolome dysregulation on the development of ADRs not only in man but also in model rodents and in model embryonic neuronal cell models.

A similar double-omics approach was applied to samples from hospitalized COVID patients, allowing the identification of metabolome-level biomarkers with potential to predict the fate of patients regarding ventilation needs and survivability.

In collaboration with haematology departments from select hospitals, targeted proteomics was employed as a diagnostic tool for amyloidosis screening in cases where standard clinical assays contradicted anamnesis. In positive cases, data re-analysis allowed a further screening of multiclonality, as well as identifying deposited proteins and multiclonal cases, and also fostered the proposal of shRNA-/RNAi-based approaches to gene silencing-based personalized therapy, addressing a yet-unidentified unmet clinical need.

In an R&D context analysis of bacterial isolates of various species, it has also been possible to analyse the changes in mevalonate and homo-serine lactones pathways, that support the possible quorum-sensing-dependent bacterial adaption to the host.

These cases demonstrate the impact of HRMS in clinical practice and contribute significantly for CQE’s positioning in clinical settings, where classical structural characterization tools are still seldom used.

Acknowledgements

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Complexes of lower rim functionalized PTA derivatives: Synthesis, characterization and application in catalysis

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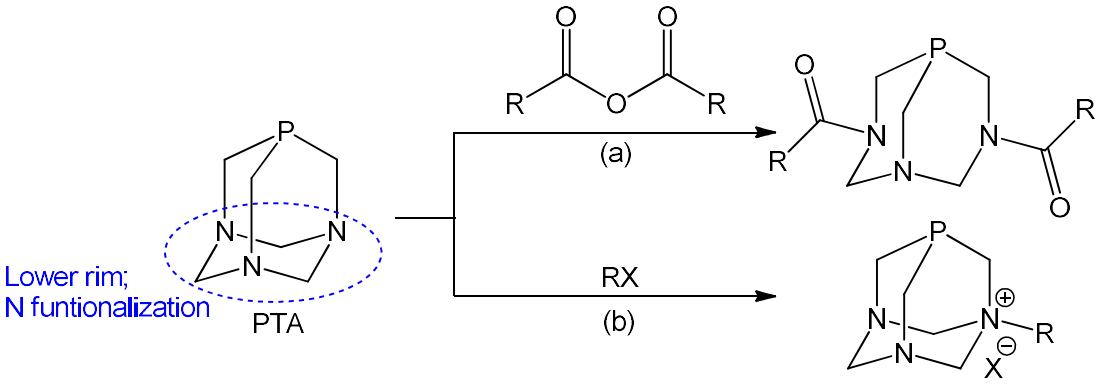
Using water-soluble ligands is the most common approach to construct transition metal complex catalysts with hydrophilic nature. Phosphines play a leading role in aqueous organometallic catalysis.[1] The cage-like 1,3,5-triaza-7-phosphadamantane (PTA) and its derivatives are among the most interesting water-soluble phosphines. Their applications and functionalization with different substituents have been largely expanded worldwide.[2,3] The modification of PTA through the N-atoms of the triazacyclohexane ring is known as lower rim functionalization. For the lower rim functionalization of PTA, two approaches have been considered (Scheme): a) acetylation with anhydrides; and b) alkylation using electrophiles. The obtained phosphines were used to synthesis novel coordination compounds, which were applied as catalysts for organic transformations in aqueous medium.



Scheme. Lower rim functionalization of PTA by acylation (a) and Alkylation (b).

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This work has been partially supported by the Fundação para a Ciência e a Tecnologia (FCT), Portugal, (UIDB/00100/2020). AGM is grateful to Instituto Superior Técnico, Portugal for his post-doctoral fellowship through the project CO2usE-1801P.00867.1.01 (Contract no. IST-ID/263/2019).

References

[1] K. H. Shaughnessy, Chem. Rev., 109 (2009) 643–710.

[2] A. Guerriero, M. Peruzzini and L. Gonsalvi, Coord. Chem. Rev., 355 (2018) 328–361.

[3] A. G. Mahmoud, M. F. C. Guedes da Silva and A. J. L. Pombeiro, Coord. Chem. Rev., 429 (2021) 213614.

Predictive Multivariate Models for Metal-free Bioorthogonal Cycloaddition Reactions and Orthogonality Hit Screening

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Metal-free cycloaddition reactions, particularly inverse-electron demand Diels–Alder cycloadditions (iEDDA) and 1,3-dipolar cycloadditions (1,3-DC) have emerged as cornerstone technologies in chemical biology with recent first-in-human trials.[1] Understanding and predicting reaction rates for such reactions is fundamental for evaluating their efficacy in biological systems. Although robust results are often obtained by DFT calculations and distortion/interaction model analysis, this analysis is time-consuming. Use of mutually orthogonal bioorthogonal reactions - where each substance can interact with their respective partner, but does not interact with either reactant of the other pair - is of a particular interest as it shed new venues towards spatiotemporally plural drug-delivery and imaging. However, orthogonality among highly reactive species is difficult to envision and predict. Here, data-driven multivariate models capable of independently predicting the second order rate constants of both metal-free bioorthogonal iEDDA[2] and 1,3-DC[3] are generated. Models are descriptive and chemically comprehensive given individual the parametrization of 1,3 dipoles, dipolarophiles, alkenes and tetrazines properties. Combination of predictive models can be used to select potential mutually orthogonal reaction pairs.

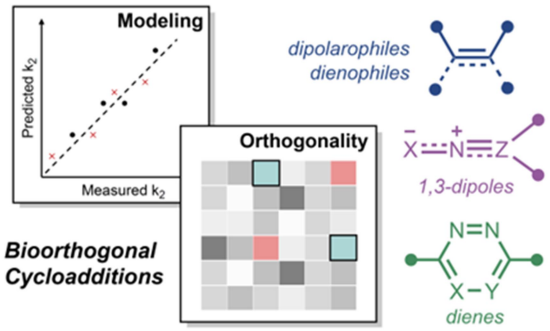

Figure 1: Schematic representation multivariate models and hit screening platform

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References

[1] Scinto, S.L., Bilodeau, D.A., Hincapie, R. et al. Nat Rev Methods Primers 1, (2021), 30
[2] Ravasco, J.M.J.M.; Coelho, J.A.S., J. Am. Chem. Soc. 142, 9, (2020), 4235–4241
[3] Ravasco, J.M.J.M.; Coelho, J.A.S., ChemRxiv, (2022), doi:10.26434/chemrxiv-2022-tqh6t

Synthetic valorization of olive leaves by acid catalyzed methanolysis of phenolic compounds as Oleuropein

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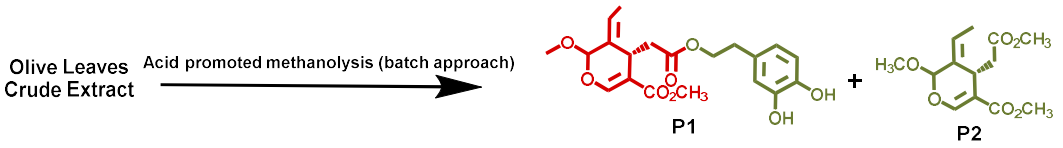
The development of bio renewable chemical building blocks for chemical-based commodities is an important issue. A variety of phenolic compounds exhibit a wide range of bioactivity and can be obtained from olive leaves. Transformations of these structures have yielded important scaffolds with potential pharmacological properties. [1-4]. Aiming at the valorization of olive leaves, we focused on the methanolysis reaction directly from the olive leaves crude extract rich in phenolic compounds, such as oleuropein (Figure 1A).

By exploring different acid catalysts (known by their eco-friendly characteristics and their low cost), under batch conditions, different temperatures and reaction times, it was possible to fine tune methodologies to synthesize two interesting synthons (P1 and P2) (Figure 1B) by an easy, cheap and scalable method derived from the cleavage of the hydroxytyrosol and glycoside units of secoiridoids present on olive leaves crude extract, opening the possibility to explore the synthetic manipulation of the mono-terpene core of oleuropein and related phenolic compounds.



Acknowledgements

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References

[1] Rahmanian N., Jafari S.M., Wani TA., Trends in Food Science & Technology 42 (2) (2015) 150-72

[2] Guinda Á., Castellano J.M,, Santos-Lozano J.M., Delgado-Hervás T., Gutiérrez-Adánez P., Rada M., LWT-Food Science and Technology 64 (1) (2015) 431-438

[3] Cavaca L. A. S., Afonso C. A. M., Eur. J. Org. Chem. 5 (2018) 581- 589

[4] Afonso C. A. M., Cavaca L. A. S., et al, ChemSusChem., 11(14) (2018) 2300-2305

FLASH PRESENTATIONS

Knoevenagel condensation of benzaldehyde and malononitrile in $scCO_2$ catalyzed by a Zn(II)-CP

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In the scope of the Green Chemistry, the replacement of conventional organic solvents by the so-called "green solvents" (water, biomass derivatives and "advanced" solvents) is a common approach to more sustainable chemical processes. Carbon dioxide, due to its properties, has been successfully regarded as a common replacement when in the supercritical state ($scCO_2$). Moreover, it possesses moderate critical pressure and temperature (p = 73.8 bar; t = 31.1 ˚C) and may be easily separated from the catalytic system by a simple pressure change effect [1].

In the present work [2], the new Zn(II) coordination polymer (CP) $[Zn(L1)(NMeF)]_n \cdot n(NMeF)$ was solvothermally prepared by reacting 5-{(pyren-4-ylmethyl)amino}isophthalic acid (H_2L1) with $Zn(NO_3)_2.6H_2O$ in *N*-methylformamide (NMeF). Its potential as catalyst was studied in the Knoevenagel condensation of benzaldehyde and malononitrile in a $scCO_2$ medium.

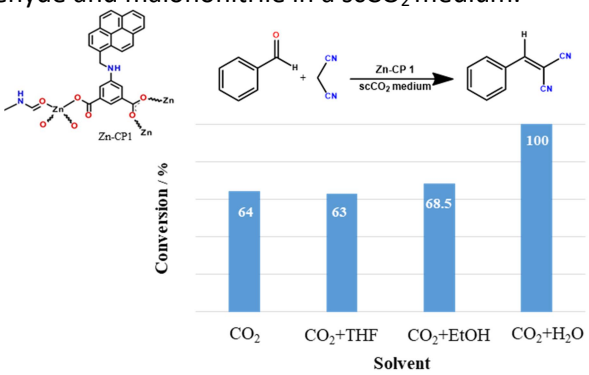

Figure 1. Knoevenagel condensation reaction in $scCO_2$ medium using a Zn(II)-CP as catalyst.

An increasing trend was observed in the reaction yield as we moved from THF (aprotic) to EtOH and H_2O (protic) polar co-solvents, reaching the full conversion in the case of water. It was found that $scCO_2$, in the absence of a protic co-solvent, is not the most suitable medium for this reaction. SEM, PXRD, FT-IR and TGA analyses show the high stability of the catalyst throughout the process, which can be recycled without a considerable loss of activity.

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References

[1] a) X. Han, M. Poliakof, Chem. Soc. Rev. 41 (2012) 1428-1436; b) R. Scott Oakes, A.A. Clifford, C.M. Rayner, J. Chem. Soc. Perkin Trans. I (2001) 917-941.

[2] N. Reis Conceição, B.P. Nobre, A. Karmakar, A.M.F. Palavra, K.T. Mahmudov, M.F.C. Guedes da Silva, A.J.L. Pombeiro, Inorganica Chim. Acta 538 (2022) 120981.

Oxidative potential of fine aerosols from a Portuguese urban-industrial area – preliminary results

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Oxidative potential (OP) of aerosols is considered as a highly relevant indicator to characterize the toxicity of particulate matter (PM), with recent studies associating OP measurements to adverse health effects. Several cellular and acellular methods exist to study the OP of particles, with each one exhibiting its own characteristics. The dithiothreitol method (OP^{DTT}) [1] has been widely used and it has been linked to airway inflammation markers, cellular oxidative stress markers, cellular cytotoxicity and cardiorespiratory health endpoints in epidemiological studies. These results support OP as a highly health relevant air quality parameter. However, specific chemical species, aerosol sources and processes that affect the OP of PM are still not well established. Currently, no studies are available for Portugal.

Fine aerosols ($PM_{2.5}$) were sampled during one year (Dec 2019-Nov 2020, total of 128 sampling days) in an urban-industrial area of the Metropolitan Area of Lisbon (Seixal, Portugal) and their chemical composition was assessed to perform a source apportionment study using Positive Matrix Factorisation. A total of seven different sources were identified: soil, secondary sulphate, fuel-oil combustion, sea, vehicle non-exhaust, vehicle exhaust and industry.

Thirty samples were chosen considering the highest load for each source (both massic or %), which could eventually allow to understand the impact of each source regarding its associated OP, assessed by the dithiothreitol (DTT) method. The final DTT activity of samples was normalised in terms of sampled air volume and in terms of collected aerosol mass.

Samples presented mean levels of DDT activity (normalized to the mass) of 11.9 ± 6.8 pmol/min*µg, ranging from 2.6 to 26.1 pmol/min*µg. The DDT activity (normalized to the sampled volume) showed to have an association with the $PM_{2.5}$ levels, as shown by Figure 1.

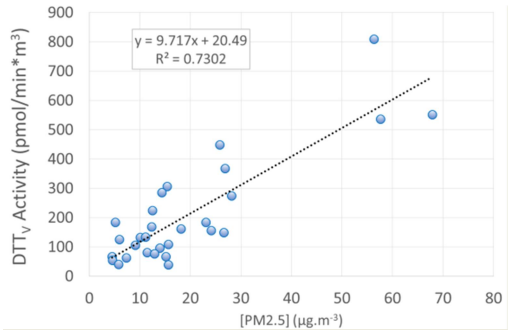

Figure 1. Correlation between $PM_{2.5}$ concentrations and their DTT_v activity.

Considering that the contribution in mass of the different sources was known to the PM2.5 levels, Spearman correlations were conducted and it was found significant correlations between DTT_v and two different sources: vehicle exhaust (R^2= 0.651, p-value = 0.001) and fuel-oil combustion (R^2 = 0.510, p-value = 0.016). Future work will assess the OP of the remaining samples to evaluate the contribution of the different sources for the OP of fine aerosols in the study area.

Acknowledgements

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References

[1] Chirizzi D., Cesari D., Guascito M.R., Dinoi A., Giotta L., Donateo A., Contini D. (2017) Influence of Saharan dust outbreaks and carbon content on oxidative potential of water-soluble fractions of $PM_{2.5}$ and PM_{10}, Atmospheric Environment 163, 1-8.

Pd-catalyzed allylic substitution between C-based nucleophiles and Bicyclic Aziridines

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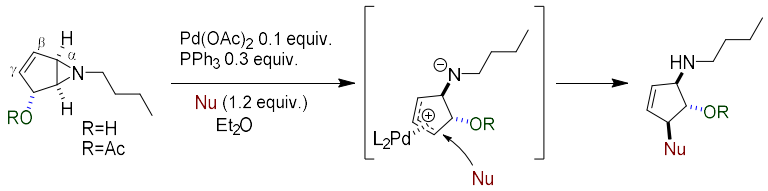
Aziridines are highly reactive three-membered heterocycles. They are well known to organic chemists for their great potential as building blocks for the synthesis of carbocycles with significant biological activity, such as aminocyclopentitols and beta-lactams.[1] A short route for the synthesis of these structures is the photochemical transformation of pyridinium salts to bicyclic-aziridines. The photochemical rearrangement forms a *cis*-fused cyclopenteno-aziridine allylic cation which reacts stereospecifically with poor nucleophiles/solvent devising a stable bicyclic-aziridine containing a new C-Nu bond in *trans*-position (Scheme 1).[2] In 2016, We reported the ring opening of these aziridines structures by performing a S_N2 reaction with nucleophiles such as azides, anilines, and thiols, forming new carbon-heteroatom bonds.[3]

Considering the peculiar structure of the above described α-oxycyclopenten-aziridines in connection with our long-standing interest in Pd-catalyzed allylations, we were intrigued by the thought of investigating the behaviour of such cyclic substrates against soft carbon-based pro-nucleophiles under Pd(0) catalysis. Within this framework, we recently developed a palladium-catalyzed ring opening of vinyl aziridines. This process proceeds takes place through η^3-allylpalladium complex formation via aziridine cleavage, and γ-reactivity of carbon-based nucleophiles leading to new carbon-carbon bonds (Scheme 2).[4] In this line, will be described recent efforts on the enantioselective opening of the aziridine via Pd catalysis.



Scheme 1. Palladium catalysis followed by nucleophilic attack.

Acknowledgements

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951996 *Biomass4Synthons.* We also thank the Fundação para a Ciência e Tecnologia for financial support (PhD grant 2020.04589.BD) and project (PTDC/QUI-QOR/32008/2017 and PESSOA 2018/2019 (Proc. 441.00 França and PHC PESSOA 2018 No 40875QJ)A short introduction can be placed here.

References

[1] S. Vandekerckhove, M. D'hooghe, *Bioorg. Med. Chem.* 21 (2013) 643.
[2] L. Kaplan, J. W. Pavlik, K.E. Wilzbach, *J. Am. Chem. Soc.* 94 (1972) 3283.
[3] J.R. Vale, F. Siopa,P.S. Branco, C.A.M. Afonso, *Eur. J. Org. Chem*. (2016) 2048−2053.
[4] J.A.C. Oliveira, G. Kiala, F. Siopa, A. Bernard, G. Gontard, J. Oble, C.A.M. Afonso, G. Poli *Tetrahedron* 51 (2020) 121182.

Probing 4'-Hydroxyacetophenone Crystallization from Aqueous Solutions

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Crystallization from solution remains one of the most widely used methods in materials preparation and purification. Despite this, the way molecules assemble in solution to form crystals remains poorly understood. Moreover, small changes to the experimental conditions can lead to the formation of different crystal structures (polymorphism), with different properties (e.g., melting temperature and solubility). As such, insights into the mechanisms that govern crystallization will have considerable impact on the production, reproducibility and end-use of materials.

One system where the produced solid phases are highly dependent on changes in the selected experimental conditions is the crystallization of 4'-hydroxyacetophenone (HAP, Figure 1) from water [1]. HAP has two known polymorphs and three different hydrates (H1, H2, and H3). By varying solute concentration, hydrates H2 and H3, and the anhydrous form I can be selectively obtained from aqueous solutions of HAP (Figure 1) [1]. The formation of a colloidal phase prior to crystallization was also observed under certain conditions [1,2]. In this work, the impact of concentration and temperature on solute aggregation in solution, its relation with the formation of a colloidal phase intermediating crystallization, and the nature of the different solid forms produced, was investigated by density and speed of sound measurements.

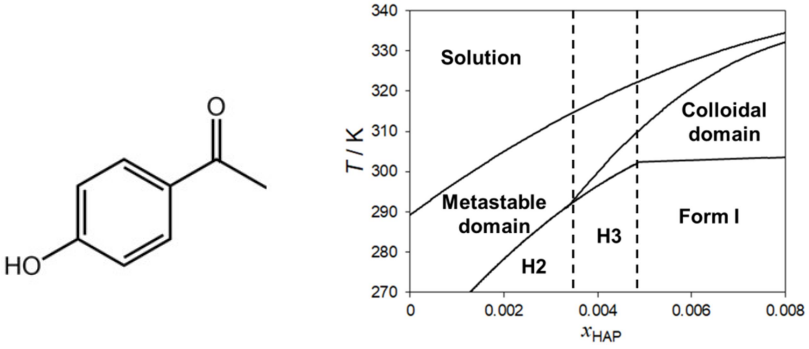

Figure 1. Molecular structure of 4'-hydroxyacetophenone, and phase diagram indicating the formation of the colloidal phase and the precipitated solid forms.

Acknowledgements

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References

[1] C.E.S. Bernardes, M.E. Minas da Piedade Cryst. Growth Des. 12 (2012) 2932-2941.

[2] C.E.S. Bernardes, M.L.S. Matos Lopes, J.R. Ascenso, M.E. Minas da Piedade, Cryst. Growth Des. 14 (2014) 5436-5441.

Luminescent carbon nanomaterials from biomass residues: Structure and luminescence

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Olive oil production is quite significant for European agro-industrial economies (68% of the worldwide quota)[1]. Two-phase extraction systems are currently the most used to produce olive oil, resulting in a by-product called wet pomace, which reaches around 800 kg/ton of processed olives. The latter residue contains substantial amounts of poly(saccharides), lignin, poly(phenols), lipids, and proteins, making it a promising renewable raw material for the synthesis of luminescent carbon dots (CDs)[2]. The establishment of sustainable and affordable processes for converting abundant biomass wastes into high-valued carbon nanomaterials, along with deep insights on the properties of synthesized materials, is of extreme importance for the advanced applications that are envisioned, such as chemical/biological sensing, bioimaging and (photo)catalysis. The structural characterization of CDs, obtained by hydrothermal carbonization of wet pomace, has been addressed by FTIR, XPS and Raman spectroscopies, and their morphology by TEM analysis. The optical properties of the synthesized carbon nanomaterials were studied by ground- state absorption, steady-state and time-resolved fluorescence spectroscopy, and fluorescence anisotropy. The most relevant results will be presented and discussed.

(a) (b) (c)

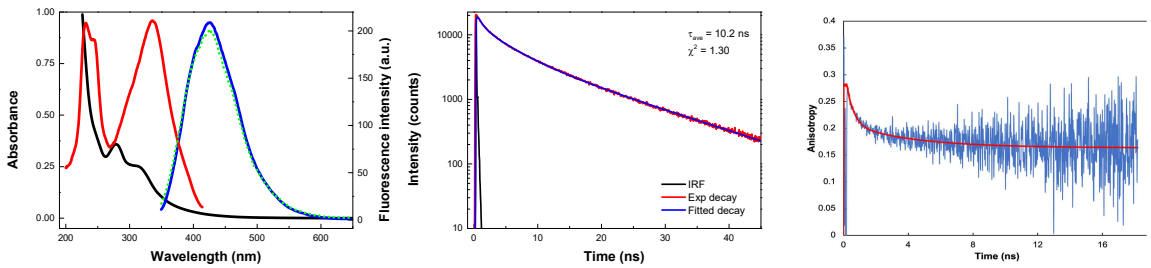

Figure 2 – (a) Ground-state absorption (black), excitation (red; monitored at 431 nm) and steady-state emission (blue; λ_{exc} =340 nm) spectra of an aqueous dispersion of CDs (0.1 mg/mL); (b) Time-resolved intensity decay of CDs (λ_{exc} = 340 nm; λ_{em} = 430 nm); (c) Time-resolved anisotropy decay of CDs in PVA.

Acknowledgements

We are grateful to Fundação para a Ciência e a Tecnologia/Ministério da Ciência, Tecnologia e Ensino Superior (FCT/MCTES) for financial support (CQ-VR projects (UIDB/00616/2022 and UIDP/00616/2022, and iBB projects UIDB/04565/2020 and UIDP/04565/2020 and i4HB project LA/P/0140/2020). D. A. S. thanks FCT for the doctoral grant SFRH/BD/143369/2019. We are also thankful to Dr. Aleksander A. Fedorov, Prof. Ana M. B. Rego, Dr. Ana M. Ferraria and Prof. Luis F. V. Ferreira for their contributions on the structural analysis of CDs.

References

[1] International Olive Council, 2020/2021. https://www.internationaloliveoil.org/2020-21-crop-year-production-down-consumption-up/

[2] DA. Sousa, AI. Costa, MR. Alexandre, JV. Prata, *Sci. Total Environ.* **2019**, *647*, 1097-105.

Efficient Amino-Sulfhydryl Stapling on Peptides and Proteins Using Bifunctional NHS-Activated Acrylamides

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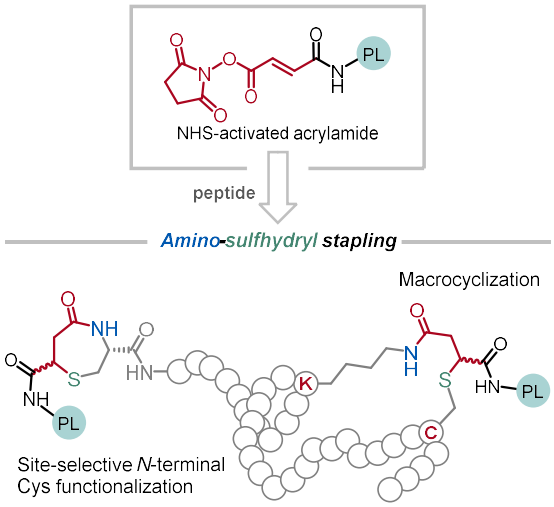
The quest for novel aqueous chemical strategies that allow chemo-, regio- and site-selective modifications of native biomolecules beought about major insights into basic biology and enabled the development of functional bioconjugates with unprecedented properties.[1] To deliver on these promises, bioconjugation strategies must allow easy access to well-defined constructs under biocompatible conditions that include low to room temperatures, mild stirring and aqueous buffered solvent at near physiological pH.

Herein, novel activated Michael acceptor has been extensively investigated for the selective modification o *N*-terminal cysteines through *N*-Hydroxysuccinimide (NHS)-activation of acrylamides that enable a subsequent intramolecular amidation. In particular, NHS-activated acrylamides exhibited remarkable selectivity and versatility for amino-sulfhydryl stapling not only in *N*-terminal cysteines (k_2 = 1.54 ± 0.18 x 103 $M^{-1}s^{-1}$) but also for the cross-linking of a cysteine to a nearby lysine residue under fine-tuned reaction conditions. The great control displayed by these reagents and the observed compatibility with other bioconjugation handles further allowed the dual site-selective functionalization of unprotected peptides. . This strategy was successfully applied to the late-stage functionalization of peptides and proteins with a PEG unit, fluorescent probe, and cytotoxic agent. The level of molecular control offered by NHS-activated acrylamides is expected to promote the amino-sulfhydryl stapling technology as a powerful strategy to design functional bioconjugates.[2]



Acknowledgements

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Maria J. S. A. Silva acknowledges financial support from SFRH/BD/132710/2017 and Bolsa excecional CRM:0026151.

References

[1] L. Xu, S. L. Kuan, T. Weil, *Angew. Chem. Int. Ed.* **2021**, *60*, 13757.

[2] Maria J. S. A. Silva, Hélio Faustino, Jaime A. S. Coelho, Maria V. Pinto, Adelaide Fernandes, Ismael Compañón, Francisco Corzana, Gilles Gasser, Pedro M. P. Gois, *Angew. Chem. Int. Ed.* **2021**, *60*, 10850.

Design of novel PKC modulators for breast cancer therapy based on molecular docking studies

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Cancer is one of the main causes of death worldwide. Many studies have been focusing on the development of more effective anticancer drugs. Protein Kinases (PKCs) have wide-ranging effects in cancer development, with PKC α, δ, ε, and ζ deserving particular attention in breast cancer research [1]. Interesting bioactive compounds have been discovered in *Plectranthus* genus (Lamiaceae) and, among them, some royleanones have been isolated and have revealed promising anticancer activity. 7α-Acetoxy-6β-hydroxyroyleanone (**Roy**, **Figure 1**), has been obtained from *P. grandidentatus* and exhibited promising cytotoxic activity; moreover, it represents an interesting starting material to be used in drug development [2].

In this study we aimed to improve **Roy** cytotoxicity through the ability to modulate PKC isoforms for breast cancer therapy. Hence, a library of new theoretical 12-OH **Roy** ester derivatives was studied exploiting molecular docking on PKC α, δ, ε, and ζ isoforms (**Figure 1**). Molecular docking was also used as a screening tool to assess the most promising derivatives suitable for PKC modulation (α, δ, ε, and ζ) to be further synthetized, using **Roy** as the starting material.

Several theoretical derivatives were predicted to fit the binding pocket with similar interactions and strength as the recognized PKC modulators.

Based on this, compounds **1** to **8** (**Figure 1**) were selected and prepared from **Roy** with overall good yields. New hemi-synthetic derivatives **1** to **8** are currently in *in vitro* evaluation as PKC modulators, to confirm the molecular docking outcomes.

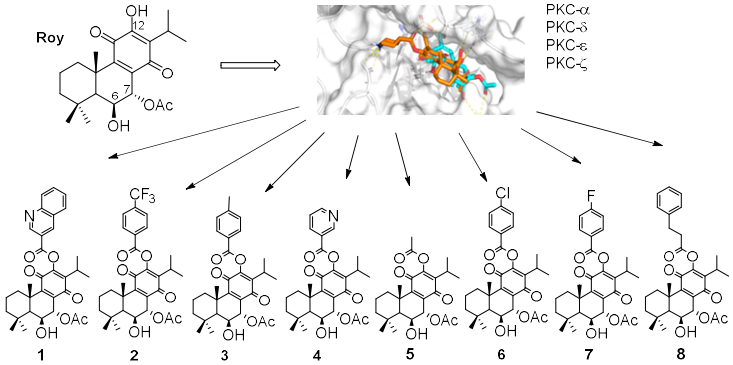

Figure 1 - New royleanone derivatives **1** to **8**, based on molecular docking screening.

Acknowledgements

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References

[1] V. M. S. Isca, M. Sencanski; N. Filipovic, D. J. V. A. Dos Santos, A. Č. Gašparović, L. Saraíva, C. A. M. Afonso, P., Rijo, A.T. García-Sosa, *Int. J. Mol. Sci.* 21 (2020) 3671. [2] C. E. S. Bernardes, C. Garcia, F. Pereira, J. Mota, P. C. Pereira, M.-J. Cebola, C. P. Reis, I. Correia, M. F. M. da Piedade, M. E. M. da Piedade, P. Rijo, *Mol. Pharm*. 5 (2018) 1412–1419.

Exploring the interactions between selected ligands and (3+1) PARP G-quadruplex

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PARP1 is a nuclear enzyme involved in DNA repair processes. Since its inhibition causes sensitization to DNA damaging chemotherapy (the so-called "synthetic lethality"), several inhibitors have been recently developed and exploited for clinical use. [1] However, the emergence of resistance to PARP1 inhibitors increased the interest towards alternative approaches able to interfere with PARP1 activity. In particular, within the promoter region of PARP1 a characteristic, non-canonical G-quadruplex-forming sequence was identified. [2] A strong correlation between G-quadruplex stabilization in gene promoters and transcriptional regulations has been proposed for several oncogenes. [3] Since no PARP promoter modulators have been described so far, the interaction with a small collection of G4 binders was investigated, taking into account the particular hybrid topology of PARP1 G4. Six structurally diverse compounds, extensively studied and known for showing great affinity towards canonical G4, were selected, and NMR, CD, and fluorescence titration studies were carried out. The results from the physico-chemical analyses, confirmed by molecular modelling, demonstrated that the structural requirements for an optimal interaction between the ligand and this peculiar G4 portion are quite strict. Overall, the studied compounds can be considered as a starting point for the identification of the key features necessary for a selective interaction with the PARP promoter G4.

References

[1] Murai, J. et al. Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. *Cancer Research* 72 (2012) 5588–5599

[2] Chambers, V.S. et al. Sequencing of DNA G-Quadruplex Structures in the Human Genome. *Nature Biotechnology* 33 (2015) 877–881

[3] Rhodes, D. et al. G-Quadruplexes and Their Regulatory Roles in Biology. *Nucleic Acids Research* 43 (2015) 8627–8637

Dengue virus capsid protein interactions with nucleic acids

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Dengue virus (DENV) and Zika virus (ZIKV) are mosquito-borne flaviviruses, sharing structural features. The nucleocapsid core of the mature virion is formed by the 11 kb viral (+) single-stranded RNA condensed with multiple copies of the capsid (C) protein. This is an essential protein, conserved among flaviviruses, which is involved in key steps of the viral life cycle, namely encapsidation and viral assembly. One key step, essential for viral replication, requires DENV C specific binding to intracellular lipid droplets (LDs), an interaction that was already fully characterized. In addition to the interaction with LDs, it was also demonstrated by us that DENV C interacts specifically with host very low-density lipoproteins (VLDL) and with viral RNA. The latter was hypothesized to occur through electrostatics. The previous findings led to the development of pep14-23, a patented peptide based on the region comprising amino acids 14 to 23 of DENV C, which is able to inhibit DENV C binding to LDs and VLDL. Then, to characterize DENV and ZIKV C binding to viral RNA, through biophysical approaches, we started examining locations within the viral RNA to which the protein has higher affinity, with specific RNA sequences being identified. Circular dichroism data show that some analogous single-stranded DNA sequences used as proxies of selected RNA sequences do indeed interact specifically with DENV C, causing changes in the protein secondary structure. Other biophysical approaches, such as dynamic light scattering, fluorescence and nuclear magnetic resonance spectroscopies will also be applied to better characterize this phenomenon, including the locations within DENV C to which the viral RNA is prone to bind. This data may allow developing inhibitors against the essential interaction of DENV C with viral RNA. The methodology used for DENV might be applied to other related flaviviruses (such as ZIKV), as well as other human viral pathogens.

Acknowledgements

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Reduction of carcinogenic PAHs in smoked fish

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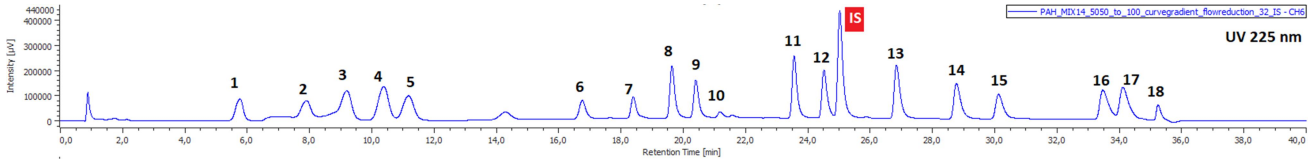
During project SmokLean (MAR2020, Cand.16-01-03-FMP-0025-IST), a strategy to capture carcinogenic Polycyclic Aromatic Hydrocarbons (PAHs), in wood smoke, before contact with food, was developed. A disposable polyurethane foam with <30Kg/m^3 density was optimized to capture PAHs in wood smoke. Two stacked 1'' foam plates (25x25cm) were inserted into a special drawer to be inserted into the food smoking apparatus.

Foam plates exposed to smoke were divided into 4 contiguous layers, which were further reduced to 5 grams of powder. The powder of each layer was Soxhlet extracted with 550 mL of acetonitrile for 6h. The extracts obtained were concentrated until they could be quantitatively evaluated by an HPLC-PDA procedure, duly calibrated, quality controlled, and with reproducibility and detection/quantitation limits studied using Horowitz's trumpets. The internal standard (IS) used, was the butyl ester of pyrene-butyric acid, synthesized and purified in-house.

Ten grams of each fish sample, exposed to smoke for 2h/30ºC, with and without capture of PAHs, were added to IS, and extracted with a standard QuEChERS method, using 1 mL of acetonitrile per gram of sample. The extracts were quantitatively evaluated by the above mentioned HPLC-PDA procedure.

Results of the quantitation were tabled for benzo-a-pyrene (#15, alone), and for a group known in the EU legislation as PAH4 {benz[a]anthracene (#11), chrysene (#12), benzo[b]fluoranthene (#13) and benzo[a]pyrene (#15)}, from a list of 18 PAHs analysed. These four compounds, contained in food, are the ones subject to EU legislation limits.



The results show that each foam plate can retain approximately 2000 micrograms of PAHs per gram of plate (40 000micrograms/20 g), or 500 micrograms of PAHs per gram of each of the four 5 grams-layer collected from the smoke entrance until the exit (10 000 micrograms per layer). Two foam plates used in each assay, smoked for 2h/30ºC, can retain PAHs, enough to saturate the first plate and adsorb 25% of the maximum capacity in the second plate (50 000 micrograms in total).

The smoked fish was evaluated for taste by a human panel. No difference in taste was observed between fish smoked with or without filter (n=4). Bacteriological study of both types of fish samples also did not reveal any statistically significant differences. However, a statistically significant reduction of 46% in carcinogenic PAH4 was observed when samples smoked with filter were compared with those smoked without filter.

Acknowledgements: are due to Professor Maria João Fraqueza (FMV-ULisboa) and Doctor Maria Leonor Nunes (previously at IPIMAR) for conducting the food smoking experiments and evaluating the food quality.

Enzymatic Kinetic Resolution in Flow of Bicyclic-Aziridines

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The demand for enantiomerically pure compounds in the pharmaceutical industry increases the complexity of the synthetic routes. Among the methodologies to obtain enantiopure compounds, lipase mediated kinetic resolution offers a green process, with a well-established route, distinct advantages of high activity, selectivity, and mild operating conditions. [1]

α-Hydroxycyclopenteno-aziridines (bicyclic-aziridines) are an intermediary to achieve molecules with biological properties such as functionalized aminocyclopentitols (*e.g.,* peramivir, ticagrelor, neplanocin A and trehazolin).[2] The bicyclic-aziridines are obtained in a racemic mixture through a photochemical transformation of pyridinium salts, for which we developed a flow reactor for gram-scale preparation. [3] These bicyclic-aziridines have a free secondary alcohol in their structure, allowing for an enzymatic kinetic resolution, which could be achieved by using Novozym 435, an immobilized lipase, CAL B. The obtention of enantiopure bicyclic-aziridines unlocks synthetic routes to complex chiral structures.

We herein disclose the enzymatic kinetic resolution of two bicyclic-aziridines: allyl bicyclic-aziridine and butyl bicyclic-aziridine, from early batch studies to flow (Figure 1 (B,D) and (C, E)).

We successfully obtained with short residence times (*S*)-allyl bicyclic-aziridine 98% enantiomeric excess (*ee*) and 46% isolated yield (Figure 1(C)), as well the obtention of (*R*)-butyl bicyclic-aziridine acetate in 95% *ee* and 20% isolated yield (Figure 1(B)).

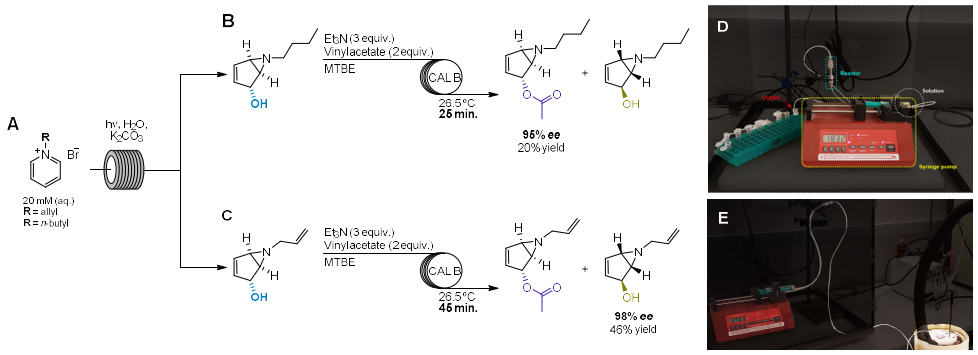

Figure 1. Obtention of enantiomeric pure bicyclic-aziridines: (A) Photochemical transformation of pyridinium salts in flow; Enzymatic kinetic resolution of (B) butyl-bicyclic -aziridine and (C) allyl-bicyclic -aziridine. Flow setup of enzymatic kinetic resolution (D) and (E).

Acknowledgements

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References

[1] Z.S. Seddigi, M.S. Malik, S.A. Ahmed, A.O. Babalghith, A. Kamal, *Coord. Chem. Rev.,* **348** 54 (2017).

[2] a) U. Košak, M. Hrast, D. Knez, N. Maraš, M. Črnugelj, S. Gobec, *Tetrahedron Lett.* **56** 529 (2015). b) J. Zou, P.S. Mariano, *Photoch. Photobio. Sci.* **7** 393 (2008). c) R. Ash, R. M. Barrer, C.G. Pope, *Proc. R. Soc. London, Ser. A*, **271** 19 (1963).

[3] a) L. Kaplan, J.W. Pavlik, K.E. Wilzbach, *J. Am. Chem. Soc.* **94** 3283 (1972). b) F. Siopa, J.P.M. António, C.A.M. Afonso*, Org. Process Res. Dev.* **22** 551 (2018). c) M.A.G. Fortunato, C.-P. Ly, F. Siopa, C.A.M. Afonso, *Methods Protoc.* **2** 67 (2019).

Direct electrochemical oxidation of abietanes

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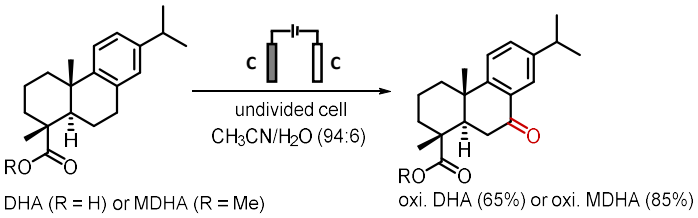
Colophony, a natural resin obtained from coniferous trees, is constituted by a group of diterpenes known as abietanes, which, along with its derivatives, has been found to have a wide variety of interesting biological activities, including the antimicrobial, antiviral, antitumoral, and anti-inflammatory activities. Constituents of this resin have a wide range of industrial applications, including synthetic rubbers, adhesives and fragrances. [1,2]

The benzylic oxidation of dehydroabietic acid, an abietane from colophony, and its methyl ester derivative, has been reported using oxidative protocols, such as using Jones reagent [3], Swern oxidation [4] or either using Chromium trioxide in stoichiometric [5] or catalytic quantities. [6] However, these protocols fail in the context of sustainability for several reasons, such as the use of toxic reagents and stoichiometric amounts.

The electrochemistry equipment used in this work were an ElectraSyn 2.0 system by IKA.

Herein, we report an electrochemical method for the benzylic oxidation of dehydroabietic acid, an alternative greener protocol for the formation of the benzylic ketone in very good yields using modern electrochemical methods. (Scheme 1). Moreover, this method can be applied to the corresponding methyl ester derivative. [7-9]



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

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References: [1] M.A. González, et al. Eur J Med Chem. 44(6), 2009, 2468–2472.
[2] G. Eksi, et al. Elsevier Inc., 2020, 313–345 p.
[3] E. Alvarez-Manzaneda, et al. Tetrahedron. 63, 2007, 11204.
[4] R.J. Rafferty, et al. Angew. Chem. Int. Ed. 53, 2014, 220.
[5] S.M.C.S. Monteiro, et al. New J. Chem. 25, 2001, 1091.
[6] Z. Zhou, et al. J. Gen. Chem. 89, 2019, 819.
[7] L. Meng, et al. Chem. - A Eur. J. 19, 2013, 5542.
[8] H. Wang, et al. Sci. Adv. 6, 2020, eaaz0590.

POSTER PRESENTATIONS

ENERGY & ENVIRONMENT

Application of bar adsorptive microextraction to monitor benzodiazepines in water matrices

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The Report of the International Narcotics Control Board for 2020 highlights the highest rates of benzodiazepines consumption in European countries. Benzodiazepines are pharmaceuticals widely prescribed as anxiolytics, anti-epileptics, hypnotics, muscle relaxants as well as sedatives. Moreover, according to the *Instituto Nacional da Farmácia e do Medicamento* (INFARMED), from 2011 to 2015, Portugal was the European country's greatest consumer of anxiolytics and sedatives in the Organization for Economic Cooperation and Development and benzodiazepines being among them. It is considered as a controversial pharmaceutical as patients can become addicted after consuming them, as well as being responsible for long term symptoms such as faints or cognitive disturbance. These psychotropic substances can be found in trace levels (ng L^{-1}) in surface water and wastewater because they are not completely removed from the wastewater treatment plants and let them to become emerging contaminants [1].

To monitor levels of such emerging contaminants, a novel sample preparation approach, bar adsorptive microextraction (BAμE) is proposed, complying with the green analytical chemistry principles, is user-friendly and cost-effective [2]. The methodology developed, BAμE in combination with high performance liquid chromatography-diode array detection (HPLC-DAD) was optimized, validated and applied to monitor six benzodiazepines (bromazepam, clobazam, clonazepam, diazepam, flunitrazepam and lorazepam) in water matrices (Figure 1). Under optimized experimental conditions limits of detection (LOD) and quantification (LOQ) of 0.3 and 1 μg L^{-1} were achieved, respectively. The analytical methodology also demonstrates good linearity ($r^2 \geq 0.9939$) in the range from 2 to 100 μg L^{-1} and recovery yields between 64% and 90%.

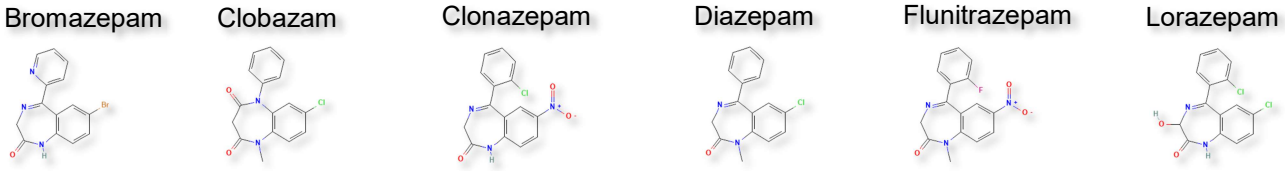

Figure 1. Chemical structures of the target Benzodiazepines.

Acknowledgements

Centro de Química Estrutural is a Research Unit funded by Fundação para a Ciência e a Tecnologia through projects UIDB/00100/2020 and UIDP/00100/2020. Institute of Molecular Sciences is an Associate Laboratory funded by FCT through project LA/P/0056/2020.

References

[1] International Narcotics Control Board, Psychotropic Substances 2021, United Nations, 2021.

[2] Ahmad, S., Nogueira, J., Talanta. 199 (2019) 195–202.

Detection of Benzophenones in Environmental Matrices by Bar Adsorptive Microextraction

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The occurrence of pharmaceuticals and personal care products in environmental matrices has been a topic of high interest in the scientific community since many are emerging environmental contaminants. These compounds can resist treatment in Wastewater Treatment Plants and be later detected in the environment. A good example of this group of substances are benzophenones, which are additives used in cosmetics, pharmaceuticals, and personal care products as ultraviolet filters. These filters can be found in environmental matrices such as wastewater, lakes, rivers, and coastal areas at low concentration levels (µg/L) [1,2].

The aim of this study was to monitor 8 benzophenones in environmental matrices through the development, optimization, and validation of bar adsorptive microextraction [3], followed by analysis using high-performance liquid chromatography with a diode array detector (BAµE/HPLC-DAD).

For the optimized experimental parameters, recoveries between 60 and 85% were obtained, with limits of detection and quantification between 0.1 and 1.0 µg/L and between 0.33 and 1.33 µg/L, respectively. The method precision as relative standard deviation was lower than 14%.

The proposed methodology proved to be an alternative strategy for the analysis of benzophenones in environmental matrices, presenting as main advantages the use of small amounts of sample and solvent, easy handling, simplicity, and excellent analytical performance.

Acknowledgements

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References

[1] S. D. Richardson and T. A. Ternes, Anal. Chem., 94 (2022) 382–416.

[2] C. Almeida, A. Stepkowska, A. Alegre, and J. M. F. Nogueira, J. Chromatogr. A, 1311 (2013) 1–10.

[3] N. R. Neng, A. R. M. Silva, and J. M. F. Nogueira, J. Chromatogr. A, 1217 (2010) 7303–7310.

Dye-sensitized solar cells based on porphyrin-ionic liquids for improved performance

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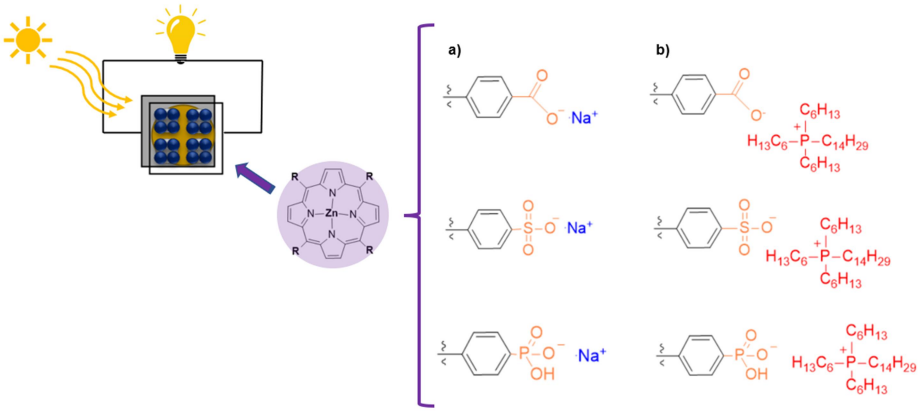

Over the past few years, the environmental impact of fossil fuels has become a significant concern, with alternative energy sources being proposed by many researchers.[1] One of the most exciting and abundant options is solar energy, which can be captured and converted into electric power using photovoltaic (PV) cells.[2] Dye-Sensitized Solar Cells (DSSC) are the third generation of PV cells, which differ from silicon PV devices by incorporating dyes, which can be structurally modified for improved light-harvesting properties.[3] Among the different types of photosensitizers that have been used in DSSC, porphyrins have an absorption spectrum that covers a broad region of the visible and near-infrared spectra and a long lifetime due to their excellent thermal, chemical, and photo-stabilities.[4,5] Recently, it has been found that dyes in the form of ionic liquids increase performance on the DSSC devices.[6] Therefore, we envisioned the construction of DSSC using Zn(II) porphyrin-ionic liquid derivatives as dyes, with multi-carboxylic, phosphonic, and sulfonic acid salts with sodium and $[P_{6,6,6,14}]^+$ as counter-ions. The DSSC's construction and efficiencies will be presented and discussed.

Acknowledgments

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References

[1] Owusu, P.A., Asumadu-Sarkodie, S., A review of renewable energy sources, sustainability issues and climate change mitigation, Cogent Engineering, 2016, 3, 1167990;

[2] N. L. Panwar, S.C. Kaushik, and S. Kothari, Role of renewable energy sources in environmental protection: A review, Renewable Sustainable Energy Rev., 2011, 15, 1513–1524;

[3] M. K. Nazeeruddin, E. Baranoff and M. Grätzel, Dye-sensitized solar cells: A brief overview, Sol. Energy, 2011, 85, 1172–1178.

[4] A. Hagfeldt, G. Boschloo, L. Sun, L. Kloo, and H. Pettersson, Dye-Sensitized Solar Cells. Chem. Rev., 2010, 110, 6595–6663.

[5] A. Hagfeldt, and M. Grätzel, Molecular photovoltaics. Acc. Chem. Res., 2000, 33, 269–277.

[6] A. L. Pinto, A. J. Parola, J. P. Leal, I. B. Coutinho, and C. C. L. Pereira, Dye-sensitized solar cells using fluorone-based ionic liquids with improved cell efficiency. Sustain. Energy Fuels, 2019, 3, 3510–3517.

Heterometallic Hexanuclear Co/Fe Complex as a Pre-Catalyst in the Homogeneous Oxidation of C–H Bonds with *m*-CPBA

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Catalytic oxidation of sp^3 C–H bonds is a key process in modern chemistry [1, 2]. Oxidations of C–H bonds with *m*-chloroperoxybenzoic acid (*m*-CPBA) catalysed by transition metal complexes are known to proceed through several routes, from the non-selective free radical to selective concerted and metal-mediated ones. However, there is a lack of understanding of the *m*-CPBA oxidative behaviour, reaction mechanisms and factors that trigger its activity.

We have studied the catalytic reaction of the stereospecific oxidation of saturated hydrocarbons using *m*-CPBA as an oxidant, the $[Co^{III}_4Fe^{III}_2O(Sae)_8]$ complex (Fig. 1) [3, 4] as a pre-catalyst and nitric acid as a promoter (where H_2Sae = salicylidene-2-ethanolamine). The combination of a protic promoter with the cobalt-based catalyst is essential for the pronounced catalytic effect and unusual stereoselectivity. The catalytic system hydroxylates tertiary sp^3 C–H bonds with retention of stereoconfiguration up to 99%, achieving exceptionally high TONs (up to 1.4×10^4) and reaction rates (TOFs up to 2 s^{-1}) [3]. The typical catalyst loading is 1000 ppm, but the system can efficiently work even at ppm loadings.

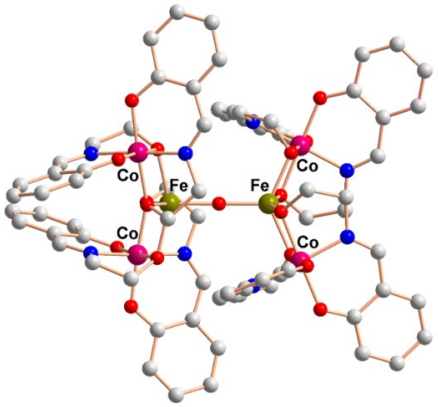

Fig. 1. Molecular structure of $[Co^{III}_4Fe^{III}_2O(Sae)_8]$.

Acknowledgements

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References

[1] D.S. Nesterov, O.V. Nesterova, A.J.L. Pombeiro, Coord. Chem. Rev. 355 (2018) 199-222.

[2] A.J.L. Pombeiro, M.F.C. Guedes da Silva (Eds.), Alkane Functionalization, Wiley, 2019.

[3] O.V. Nesterova, M.L. Kuznetsov, A.J.L. Pombeiro, G.B. Shul'pin, D.S. Nesterov, Catal. Sci. Technol. 12 (2022) 282–299.

[4] D.S. Nesterov, E.N. Chygorin, V.N. Kokozay, V.V. Bon, R. Boča, Y.N. Kozlov, L.S. Shul'pina, J. Jezierska, A. Ozarowski, A.J.L. Pombeiro, G.B. Shul'pin, Inorg. Chem. 51 (2012) 9110-9122.

Chemical engineered extracts of Portuguese biorenewable resources to the synthesis of diverse natural products hybrids towards new bioactive entities

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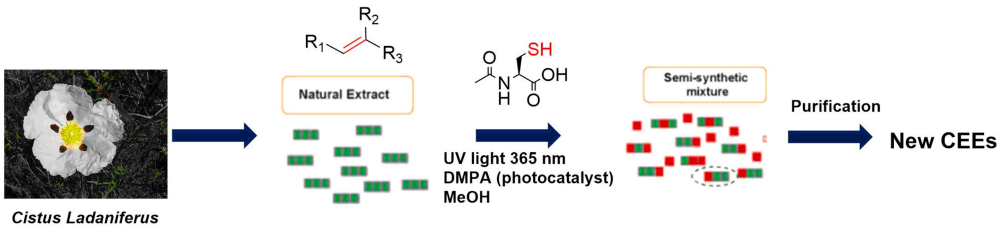
Natural products with biologically active pharmacophores are biologically validated starting points for the development of new drugs. Between 1981 and 2019, natural products (NPs) and their derivatives represented 24% of all newly approved drugs. Being NPs derivatives 81% of all newly approved NPs-based drugs [1]. *Cistus ladaniferus* is an aromatic plant from Mediterranean climates that exist in high quantity in Portugal. *Cistus ladaniferus* essential oils have shown antimicrobial and antitumoral biological activities[2]. An interesting methodology to access NPs derivatives is the preparation of chemically engineered extracts (CEEs). This approach focuses on the transformation of selected *chemical* functionalities, highly common in natural products extracts, into new *chemical* entities[3].

This work aims to develop a new and efficient methodology to prepare CEEs from *Cistus ladaniferus*. To this end, light-mediated thiol-ene reaction, was applied to natural extracts of *Cistus ladaniferus*, to took advantage of alkene functional groups and form thioether-CEEs **(Scheme 1).** The optimization of the reaction conditions was executed using limonene as model substrate. The optimized reaction conditions (Thiol, DMPA, MeOH under 365 nm UV light in a FEP tube) were applied to the natural extract of *Cistus ladaniferus,* however further optimization was needed. For the purification and identification of new CEEs two approaches are used: (i) Acid/base workups, purification by silica column and ^{1}H-NMR and MS analysis; (ii) Acid/base workups, isolation through preparative HPLC and ^{1}H-NMR and MS analysis. Due to the great diversity of alkene functions present in the natural extract and the low amount of each one, mass spectrometry techniques, such as LR-ESI-MS, UPLC/ESI-HR-MS, and UPLC/ESI-MS/MS were performed to identify and isolate, the new CEEs. Until now we can assure the presence of thioether-CEEs obtained through alkene-thiol coupling, characterized by retention time in LC, mass to charge ratio in MS[1], and pattern of fragmentation in MS[2].



Scheme 1: Global work strategy

Acknowledgements: Support for this work was provided by the European Union's Horizon 2020 research and innovation programme under grant agreement No 951996.

References:

[1] Lautié E., Russo O., Ducrot P., Boutin J. A., Unraveling Plant Natural Chemical Diversity for Drug Discovery Purposes, Front. Pharmacol, 2020, 11, 397

[2] Stępień AE., Cytotoxic and anti-cancer activity of the Cistus species of herbal plants, Eur J Clin Exp Med. 2017, 15(2),165– 168

[3] López SN, Ramallo IA., Sierra MG., Zacchino SA., Furlan RL., Chemically engineered extracts as an alternative source of bioactive natural product-like compounds, Proc Natl Acad Sci U S A. 2007, 104(2), 441-444

Strategy of HypnosAir - Understanding the impact of air quality on sleep quality considering an integrated human exposure approach

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Air quality is considered to be one of the main factors that influence human health and the well-being of citizens. This awareness results from the research developed in the last two decades, initially focused on the levels of human exposure to pollutants in outdoor environments and, later, in indoor environments. This change occurred because it was found that, in developed countries, people spend around 90% of their time indoors. Thus, in order to assess the real human exposure, it is crucial to consider an integrated approach of all micro-environments in which people are during 24 hours.

Since people spend a third of their lives sleeping and that sleep is essential to the well-being, performance and health of individuals, sleeping environments have started to gather the attention of the scientific community in recent years to assess exposure levels and how they can affect the quality of sleep - this is the question that remains unanswered until now. In addition, this micro-environment is poorly characterized, leading to inaccurate assessment of the integrated daily exposure of individuals. Most studies focus on comfort parameters (temperature and humidity) or single pollutants, such as carbon dioxide (CO_2). The characterization of indoor air quality (IAQ) during sleep faces several challenges that make it difficult to achieve (such as the noise interference of monitoring equipment in the sleep of individuals) and, therefore, it is essential to implement monitoring strategies that overcome them.

Some of the pilot studies that attempted to fully assess IAQ during sleep were carried out by the HypnosAir team and concluded that several pollutants (particulate matter (PM), CO_2, formaldehyde and volatile organic compounds) exceed the limit values of national legislation and guideline values of World Health Organization [1]. Taking into account the known negative impact that PM has on human health, this pollutant is of particular relevance to understand the impact of exposure during sleep on the quality of sleep and health of individuals.

HypnosAir aims to fill this gap in the current knowledge by carrying out a comprehensive study, based on the latest technologies, to understand which environmental factors may influence sleep quality and to assess the real contribution of the sleeping environment to the daily integrated human exposure. Ultimately, HypnosAir intends to define how it is possible to improve the quality of sleep by improving the quality of the air that people breathe during all day.

The scientific questions that HypnosAir intends to answer are:

1) Which is the contribution of the exposure to pollutants while sleeping to the daily exposure of an individual?

2) Which air pollutants have a negative impact on sleep quality and to what extent?

3) How different is particulate matter during sleep and in other indoor and outdoor environments, in terms of composition and toxicity?

4) Which are the best strategies to improve sleep quality of citizens considering the exposure in sleeping environments and other environments where people are during the day?

To successfully implement HypnosAir, a multidisciplinary team was created bringing together experts from different areas (environment, sleep and medicine).

Acknowledgements

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References

[1] Ramos J., Belo J., Silva D., Diogo C., Almeida S.M., Canha N. (2022) Influence of indoor air quality on sleep quality of university students in Lisbon. Atmospheric Pollution Research 13(2), 101301. DOI: 10.1016/j.apr.2021.101301

Photocatalytic transformations of quinic acid

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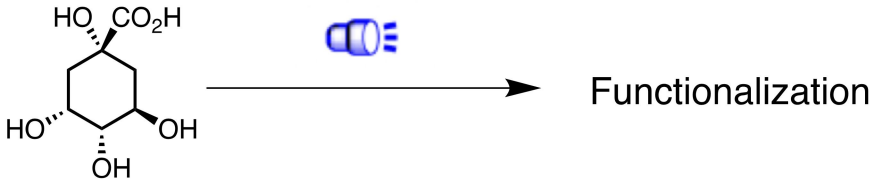
Quinic acid (QA) is a widely occurring metabolite in plants and microorganisms[1]. The synthesis of Oseltamivir (Tamiflu)[2], Bactobolin A[3] and Actinobolin[4] are probably the most distinct applications of QA in total synthesis. Exploration of stereoselective metal-free deoxygenation is a recent example of QA's synthetic value5. Additionaly, the O,O-silyl group migration on a QA-derived cyclitol gives suitable intermediate for the synthesis of vitamin D receptor modulator (VS-105)6. Photoredox catalysis is a known sustainable alternative to the use of less environmentally friendly superstoichiometric oxidants and reductants. Ruthenium and iridium complexes, in combination with visible light, are efficient photocatalysts (PC's) when powerful oxidants or reductants are needed, however, their toxicity and scarcity are a drawback for large scale and commodity chemicals synthesis. Easily accessible organic dyes represent a good alternative to metal-based PC's[7]. 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.



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References

1. Arceo, E.; Ellman, J. A.; Bergman, R. G., A direct, biomass-based synthesis of benzoic acid: formic acid-mediated deoxygenation of the glucose-derived materials quinic acid and shikimic acid. *ChemSusChem* **2010,** *3* (7), 811-3.
2. Abrecht, S.; Federspiel, M. C.; Estermann, H.; Fischer, R.; Karpf, M.; Mair, H.-J.; Oberhauser, T.; Rimmler, G.; Trussardi, R.; Zutter, U. J. C. I. J. f. C., The synthetic-technical development of oseltamivir phosphate Tamiflu™: A race against time. *Chimia* **2007,** *61* (3), 93-99.
3. Vojáčková, P.; Michalska, L.; Nečas, M.; Shcherbakov, D.; Böttger, E. C.; Šponer, J. i.; Šponer, J. E.; Švenda, J. J. J. o. t. A. C. S., Stereocontrolled synthesis of (−)-Bactobolin A. *Journal of the American Chemical Society* **2020,** *142* (16), 7306-7311.
4. Tharra PR, Mikhaylov AA, Švejkar J, Gysin M, Hobbie SN, Švenda J. Short Synthesis of (+)-Actinobolin: Simple Entry to Complex Small-Molecule Inhibitors of Protein Synthesis. Angew Chem Int Ed Engl. 2022 Apr 19;61(17):e202116520.
5. Holmstedt, S.; George, L.; Koivuporras, A.; Valkonen, A.; Candeias, N. R., Deoxygenative Divergent Synthesis: En Route to Quinic Acid Chirons. *J Organic Letters* **2020,** *22* (21), 8370-8375.
6. Holmstedt, S.; Efimov, A.; Candeias, N. R., O, O-Silyl Group Migrations in Quinic Acid Derivatives: An Opportunity for Divergent Synthesis. *J Organic Letters* **2021,** *23* (8), 3083-3087.
7. Gualandi, A.; Nenov, A.; Marchini, M.; Rodeghiero, G.; Conti, I.; Paltanin, E.; Balletti, M.; Ceroni, P.; Garavelli, M.; Cozzi, P. G., Tailored Coumarin Dyes for Photoredox Catalysis: Calculation, Synthesis, and Electronic Properties. *J ChemCatChem* **2021,** *13* (3), 981-989.

Synthesis, Crystal Structures and Phenoxazinone Synthase-like Catalytic Activity of Copper(II) Complexes with Aminoalcohol Ligands

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Mono- and polynuclear copper complexes attract special attention since they can be used as objects of studies in different scientific areas, including biochemistry, magnetochemistry and catalysis. Following our ongoing interest in the preparation of homo- and heterometallic complexes with N,O-donor ligands [1, 2] we have explored the synthetic systems containing simultaneously aminoalcohol ligand (2-benzylaminoethanol (HBae) or 2-butylaminoethanol (HBuae)) and carboxylic acid (cinnamic (Hca), valeric (Hva), propionic (Hpa) or 2-ethylbutyric acid (Heba)).

The reactions of copper(II) salts with aminoalcohol and carboxylic acid in non-aqueous solutions lead to the formation of the complexes $[Cu(ca)_2(HBae)_2]$ (**1**), $[Cu(va)_2(HBae)_2]$ (**2**), $[Cu_4(va)_4(Bae)_4]\cdot H_2O$ (**3**) [3], $[Cu_4(pa)_4(Bae)_4]\cdot H_2O$ (**4**) and $[Cu_4(eba)_4(Buae)_4]\cdot H_2O$ (**5**) (Fig. 1). Crystallographic analysis shows that **1** and **2** have mononuclear crystal structures, where the complex molecules are H-bonded forming extended supramolecular chains. The compounds **3**–**5** reveal cubane-like configuration based on the $\{Cu_4(\mu_3\text{-}O)_4\}$ core. The strong hydrogen bonding in **3**–**5** is responsible for the joining of the neighbouring tetranuclear molecules forming supramolecular 1D polymers. All obtained compounds exhibit phenoxazinone synthase-like catalytic activity towards the aerobic oxidative coupling of *o*-aminophenol to phenoxazinone chromophore.

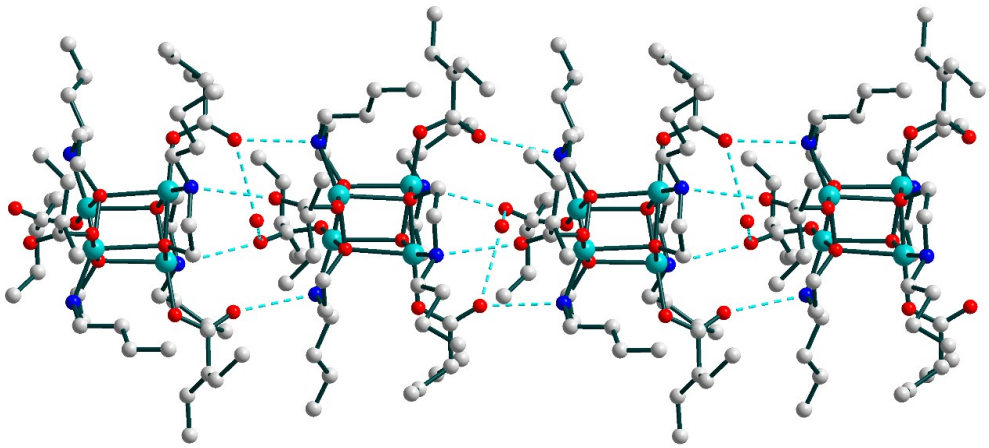

Fig. 1. Fragment of the supramolecular chain in **5**. Colour scheme: Cu, cyan; O, red; N, blue; C, grey.

Acknowledgements

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References

[1] D.S. Nesterov, O.V. Nesterova, A.J.L. Pombeiro, Coord. Chem. Rev. 355 (2018) 199-222.

[2] D.S. Nesterov, O.V. Nesterova, V.N. Kokozay, A.J.L. Pombeiro, Eur. J. Inorg. Chem. 27 (2014) 4496-4517.

[3] O.V. Nesterova, O.E. Bondarenko, A.J.L. Pombeiro, D.S. Nesterov, Dalton Trans. 49 (2020) 4710-4724.

Innovative headspace bar adsorptive microextraction approach for *on-site* monitoring of VOCs emitted by Portuguese tree species

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Nowadays, climate change persists to increase the incidence of heat waves and periods of drought, which contributes to the development of intense forest fires. The major consequences of extreme wildfires in lives, nature and infrastructures increases the significance of understanding the different sources of sudden changes in the fire's behavior. Studies have suggested that volatile organic compounds (VOCs) emitted from trees can accumulate under vegetation and, in certain atmospheric conditions might be more reactive, accelerating the fire growth [1,2]. In the last decades, modern sample preparation techniques such as solid phase microextraction have shown effectiveness for trace analysis of VOCs through headspace (HS) sampling mode. More recently, bar adsorptive microextraction (BAμE), a novel static-based microextraction technique, was proposed for trace analysis of target compounds of different polarity, showing effective results in various applications due to the high selectivity of the different sorbent coatings used (e.g., polymers and activated carbons) [3].

The present work aimed the development, optimization, validation, and application of a HS-BAμE methodology followed by gas chromatography coupled to mass spectrometry (GC-MS) analysis for monitoring VOCs emitted by the leaves of *E. globulus* Labill. and *P. pinaster* Aiton trees from the Sintra range. For five case study VOCs (α-pinene, β-pinene, myrcene, limonene and 1,8-cineole) the analytical approach achieved under optimized experimental conditions limits of detection and quantification of 25 and 83 ng, respectively, while showing remarkable linearity ($r^2 \geq 0.9966$) between 0.1 to 0.5 μg. Furthermore, the on-site application of the HS-BAμE/GC-MS methodology it was possible to detect four VOCs in the air nearby *E. globulus* Labill. (α-pinene, β-pinene, limonene and 1,7-cineole) and one near *P. pinaster* Aiton (α-pinene), in the range comprised between 0.102 ± 0.002 and 0.311 ± 0.008 μg, showing to be a promising alternative for monitoring VOCs on site in a forest environment, given its high simplicity and easy manipulation.

Acknowledgements

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References

[1] Abram, N. J; Henley, B. J.; Gupta, A. S.; Lippmann, T. J. R.; Clarke, H.; Dowdy, A. J.; Sharples, J. J.; Nolan, R. H.; Zhang, T.; Wooster, M. J.; Wurtzel, J. B.; Meissner, K. J.; Pitman, A. J.; Ukkola, A. M.; Murphy, B. P.; Tapper, N. J.; Boer, M. M.; *Commun. Earth Environ.* **2021**, 2, 1-17.

[2] Chatelon, F. J.; Sauvagnargues, S.; Dusserre, G.; Balbi, J. H.; *O. J. For*. **2014**, 4, 547-557.

[3] Nogueira, J. M. F.; *Anal. Chim. Acta* **2012**, 757, 1-10.

Homogeneous electroreduction of CO2: Fe(III) salphen as catalysts

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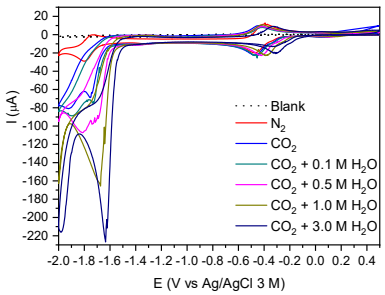
CO2 plays a crucial role in the carbon cycle, which keeps the Earth's temperature stable. The expansion of the human population and the energy demand, increased Earth's CO2 concentration unbalancing the carbon cycle, affecting our planet's energy balance. This led to the urgency of finding efficient pathways of carbon utilisation and recycling to form valuable products.

Molecular activation is crucial in chemical and biological systems, where CO2 is one important player. Thus, researchers and industries had a deep interest in creating catalysts that, by electro- and photoreduction, can convert CO2 either into liquid fuel precursors (CO and H2) or directly to liquid fuels (methanol and/or methane).

The electroconversion of CO2 can be made in homogeneous and heterogeneous media. The former has the advantage of modulating the catalytic active sites to improve selectivity.

The Fe(III) complexes are known for being good catalysts and the synthesis with salphen (N,N'-bis(salicyldene)-1,2-phenylenediamine) ligands is easy and with high yields. Therefore, the synthesis and characterisation of a mononuclear Fe(III) saphen complex is reported. Cyclic voltammetry, spectroelectrochemical and electrocatalyst studies of the complex are also investigated to be used as catalysts.



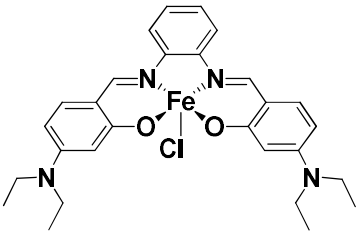


Figure 1. Cyclic voltammograms of complex (1 mM) in CH3CN under N2 or CO2 saturated solutions. Addition of different amounts of H2O to the CO2 saturated solutions.

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References

[1] A. W. Nichols, S. Chatterjee, M. Sabat, and C. W. Machan, Inorg. Chem. 2018, 57, 2111−2121.

[2] R. Bonetto, R. Altieri M. Tagliapietra, A. Barbon, M. Bonchio, M. Robert, A. Sartorel, ChemSusChem 2020, 13, 4111–4120.

[3] R. Bonetto, D. Civettini, F. Crisanti, A. Sartorel, Energies 2021, 14, 5723.

Ionic liquids as catalysts for bio-oil production

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This work aims to analyse the effect of ionic liquids and organic solvents on the liquefaction of biomass to produce bio-oil. It also intends to compare the bio-oils obtained from the conversion of different biomasses, namely, pine wood chips and *acacia saligna*.

Compared with organic solvents, ionic liquids are considered cleaner solvents due to their certain peculiar properties, such as good thermal stability and unique solvation ability. Therefore, it is intended to create an environment-friendly reaction medium with these liquids.

The biomass batch liquefaction assessments were carried out in two approaches: conventional and microwave heating. In the former, an oil bath or heating mantle provides the heating source, requiring a longer reaction time. On the other hand, when microwave radiation is used as an energy source, the conversion rate is sped up, leading to shorter residence times.

Results and discussion of the performance of different ionic liquids, as well as molecular organic solvents, will be presented, along with the characterisation of the biomass, solvents, and bio-oils.

Acknowledgements:

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References

[1] Rosson, E.; Sgarbossa, P.; Mozzon, M.; Venturino, F.; Bogialli, S.; Glisenti, A.; Talon, A.; Moretti, E.; Carturan, S.M.; Tamburini, S.; Famengo, A.; da Costa Ribeiro, A.P.; Benhabiles, S.; Kamel, R.; Zorzi, F.; Bertani, R. Processes 2021, 9, 1637

[2] Cristino, A.F.; Logan, D.; Bordado, J.C.; Galhano dos Santos, R. Processes 2021, 9, 1214.

[3] Consorti, C. S.; de Souza, R. F.; Dupont, J.; Suarez, P. A. Z.; Líquidos iônicos contendo o cátion dialquilimidazólio: estrutura, propriedades físico-químicas e comportamento em solução. Química Nova 2001, 24, 830

Copper (II) catalysed aminal synthesis in aqueous media and its remarkable applications

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Aminals are the condensation product of aldehydes and secondary amines. Structurally similar to acetals, these compounds have been used as intermediates, chiral auxiliaries and protection groups in reactions and in the biology field.[1]

The most common methodology for the formation of aminals involves the condensation of aldehydes with amines in ethanol or toluene under high temperatures using dehydrating agents to remove the water in the reaction, shifting the equilibrium to the product.[2] However, performing the reaction in aqueous media instead of organic solvents is an environmentally competitive process for the preparation of aminals.

This work reports on the formation of aminals, from aromatic aldehydes and furfural derivatives with different secondary amines in water under mild conditions **(Figure 1a)**. This is followed by the stability studies of different aminals and their use as protection group for aldehydes. Applying this approach together with the advantages of a continuous flow system allowed us to develop a new, simple and rapid methodology for selective removal of genotoxic aldehydes from APIs (Active Pharmaceutical Ingredient). Our method uses the diamine scavenging resin in a continuous flow system, generating the aminal within the microreactor efficiently **(Figure 1b)**.[3]

The described aminal compounds were prepared with a more sustainable methodology allowing the use of these interesting molecules as protection group and presenting a noteworthy role on the removal of genotoxic impurities of the APIs.

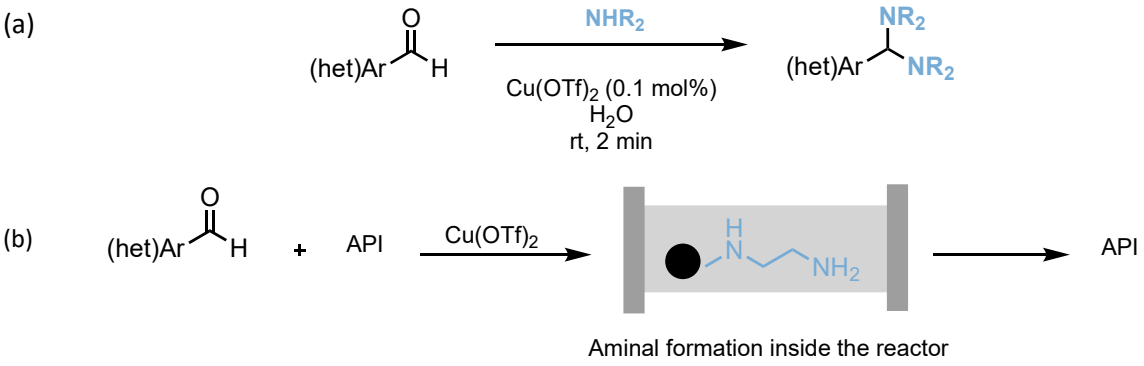

Figure 1. (a) Preparation of aminals from aromatic aldehydes and furfural derivatives with different secondary amines in water under mild conditions; (b) A new strategy for selective removal of genotoxic aldehydes from APIs.

Acknowledgements

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References

[1] A. Alexakis, N. Lensen, P. Mangeney, Tetrahedron Letters, 32 (1991) 1171-1174.

[2] M. A. Ramirez, G. Ortiz, G. Levin, McCormack, W. M. M. Blanco, I. A. Perillo, A. Salerno, Tetrahedron Letters, 55 (2014) 4774-4776.

[3] J. G. Pereira, J. P. M. António, R. Mendonça, R. F. A. Gomes, C. A. M. Afonso, Green Chemistry, 22 (2020) 7484-7490.

Thermochemical Liquefaction of Burnt Pine Heartwood

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Energy is an important factor for sustaining economic growth and maintaining a high standard of living. The high costs and environmental impacts of fossil fuels have been a major impact in the search for sustainable sourcing, and research is being developed in this area [1].

Biomass is one of the important and major renewable fuel sources. Biomass is considered carbon neutral since its carbon is recycled from the atmosphere [2]. Biomass energy has many advantages such as its renewable nature, carbon neutral ability, low sulphur emission during combustion and storage. Biomass is a resource for producing new liquid fuels, syngas, hydrogen, solid fuels and valuable fuels. The liquefaction of lignocellulosic residues of biomass is a well-known concept recently. research process [3].

Liquefaction of renewable bio-resources has attracted attention due to the global need for new technologies, where environmental impact is reduced, and long-term sustainability is increasing. The use of biomass-derived chemicals to synthesize materials traditionally made from petroleum-based ones can reduce the current dependence on fossil resources and environmental problems associated with their exploitation and add value to agroforestry by-products [4].

Wildfires in Portugal each year sometimes kill and injure large. According to the official report of the Portuguese authorities nine firing points were reported and the largest ones were registered as “Pedrógão Grande” (28,914 ha) and “Góis” (17,521 ha) fires [5].

In this study, bio-oil production was performed by thermochemical liquefaction. Burnt pine heartwood as biomass, the standard chemical 2-Ethylhexanol as solvent and p-Toluenesulfonic acid was used as catalyst, and the solvent for washing was acetone. Optimal results showed a bio-oil yield of 86.03 % and HHV of 36.41 MJ/kg. This study is to evaluate the thermochemical liquefaction of burnt pine heartwood and validate woody wastes, especially for recovering and preventing some of the values lost during wildfires, in order to produce bio-oil with a good yield.

Acknowledgements

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Authors acknowledge financial support CLEANFOREST I&D project (ref. ª PCIF/GVB/0167/2018) project.

References

[1] World Bioenergy Association. GLOBAL BIOENERGY STATISTICS 2021 World Bioenergy Association. (2021).

[2] Ren, S. et al. The effects of torrefaction on compositions of bio-oil and syngas from biomass pyrolysis by microwave heating. Bioresource Technology 135, 659–664 (2013).

[3] Galhano, R. et al. Natural polymeric water-based adhesive from cork liquefaction. Industrial Crops and Products 84, 314–319 (2016).

[4] Maxime, A. et al. Production of biomaterials from cork: Liquefaction in polyhydric alcohols at moderate temperatures. Industrial Crops and Products 54, 296–301 (2014).

[5] Couto, F.T., Iakunin, M., Salgado, R., Pinto, P., Viegas, T., Pinty, J-P., Lightning modelling for the research of forest fire ignition in Portugal, Atmospheric Research, 104993, 242 (2020).

Modeling solvent effects on solution enthalpies of 1-butyl-3-methylimidazolium tetrafluoroborate

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Solvent effects on solution enthalpies at infinite dilution ($\Delta_{sol}H^{\infty}$) of the ionic liquid (IL) 1-butyl-3-methylimidazolium tetrafluoroborate – [BMIm]BF_4 – were previously studied using a quantitative structure-property relationship (QSPR) methodology. Results indicated the need to use a more appropriate QSPR model to reach a deeper understanding of the thermochemical process. [1]

Recently, we have proposed a *new* model equation to evaluate solvent effects on physicochemical processes, the *m*KAT equation, which dissects solute-solvent interactions into four independent contributions: polarizability (*DI*), dipolarity (*Dip*), HBD acidity (α) and HBA basicity (β). [2]

In the present work, we use the *m*KAT equation, together with a quantifying parameter (*C*) related to solvent-solvent interactions, to study the referred $\Delta_{sol}H^{\infty}$ values reported for 15 solvents. The use of the *m*KAT+*C* equation shows that: *i)* a suitable 3-parameter model (R^2 = 0.88) is attained (Eq. 1) with no reported outliers (an improvement over our previous work [1]); *ii)* the *C* parameter (which measures the energy required to form a cavity in the solvent) is statistically relevant and, as expected, contributes endothermically to the dissolution process; *iii)* concurrently, both the solvent's polarizability and dipolarity exhibit an exothermic contribution; *iv*) most interestingly, the gas-phase estimate (which should correspond to the vaporization enthalpy ($\Delta_{vap}H$) of the IL), shows a value ($118_{\pm19}$) quite consistent with reported $\Delta_{vap}H$ for [BMIm]BF_4 ($131_{\pm5}$ kJ mol^{-1}). [3]

$$\Delta_{sol}H^{\infty}/\text{ kJ mol}^{-1} = 118_{\pm19} - 80_{\pm20}DI - 96_{\pm13}Dip + 33_{\pm6}C \qquad \text{Eq. 1}$$

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References

[1] M. Reis, R. Elvas-Leitão, F. Martins, J. Chem. Eng. Data 55 (2010) 616–620.

[2] L. Moreira, R. Elvas-Leitão, F. Martins; J. Mol. Liquids 362 (2022) 119656.

[3] R. Liang, M-R Yang, Q-X Zhou, Acta Phys.-Chim. Sin. 26 (2010) 1468-1472.


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Preliminary Assessment of the Stability of a Tramadol Hydrochloride-Celecoxib Co-crystal by Differential Scanning Calorimetry

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Co-crystals have, in recent years, been explored as a novel way to improve the properties of active pharmaceutical ingredients (API), such as solubility and dissolution rate, or as an alternative to multimodal therapies, in which two or more APIs are present in the same drug. In most cases bicomponent materials are used.

A critical aspect, within this context, is the accurate assessment of the stability of the co-crystal relative to its decomposition in the precursors, given the impact of this process in the properties and shelf life of a drug [1].

In this work the stability of a recently reported co-crystal consisting of tramadol hydrochloride (THC) and celecoxib (CEL), Figure 1, in a 1:1 molecular ratio (THC:CEL) [2], has been preliminarily assessed. The assessment was based on the determination of the standard molar enthalpy of the dissociation reaction, $\Delta_r H^\circ_m(1)$:

$$\text{THC:CEL (cr)} \rightarrow \text{THC (cr)} + \text{CEL (cr)} \qquad (1)$$

which reflects the differences in lattice enthalpy between the co-crystal and its precursors. The result $\Delta_r H^\circ_m(1)$ = 23.6±7.8 kJ·mol^{-1} was obtained by comparing the enthalpy of fusion of THC:CEL(cr) with that of a THC(cr)+CEL(cr) physical mixture, measured by differential scanning calorimetry (DSC). The fact that a significantly endothermic $\Delta_r H^\circ_m(1)$ value was found suggests that the THC:CEL co-crystal is quite stable and unlikely to dissociate into the THC and CEL precursors.

These two API are frequently used in multimodal therapies for pain relief, due to their complementary action, and this novel compound is already in clinical trials.

(a) (b)

Figure 1. Molecular structures of (a) tramadol hydrochloride (THC) and (b) celecoxib (CEL).

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References

[1] I. O. Feliciano, D. P. Silva, M. F: M. Piedade, C. E. S. Bernardes, M. E. Minas da Piedade, Molecules 26 (2021) 571417.

[2] C. Almansa, R. Mercè, N. Tesson, J. Farran, J. Tomàs, C. R. Plata-Salamán, Cryst. Growth Des. 17 (2017) 1884-1892

The Polymorphism of Caffeine from an Energetic Point of View

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Polymorphism, the ability of a substance to form materials with distinct molecular packings, is an important field of research with applications in various areas, as it allows changing the physical properties of a substance (e.g., stability, color, melting temperature, and solubility) without its chemical modification. Understanding and predicting the ability of a compound to exhibit this phenomenon is, therefore, key in the development of new materials in fields as different as explosives, paints, and electronics [1]. For this, an important aspect to be evaluated is the lattice energy differences between different phases, which can be obtained, for example, from enthalpies of sublimation.

With this in mind, this work describes the revaluation of the enthalpy of sublimation of the anhydrous polymorphs of caffeine (figure 1) which show significant discrepancies in the literature [2]. The experiments were performed by Calvet microcalorimetry using samples characterized by powder X-ray diffraction and differential scanning calorimetry.

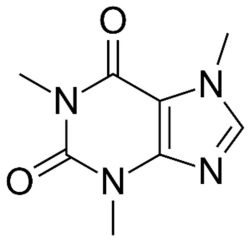

Figure 1. Molecular structure of caffeine.

Acknowledgments

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References

[1] Cruz-Cabeza, A.J.; Feeder, N.; Davey, R.J.; Commun. Chem. 3 (2020) 10-13.

[2] Acree, W.; Chickos, J.S.; J. Phys. Chem. Ref. Data. 45 (2016) 033101.

Solubility Control of Compounds by Multicomponent Crystals Formation

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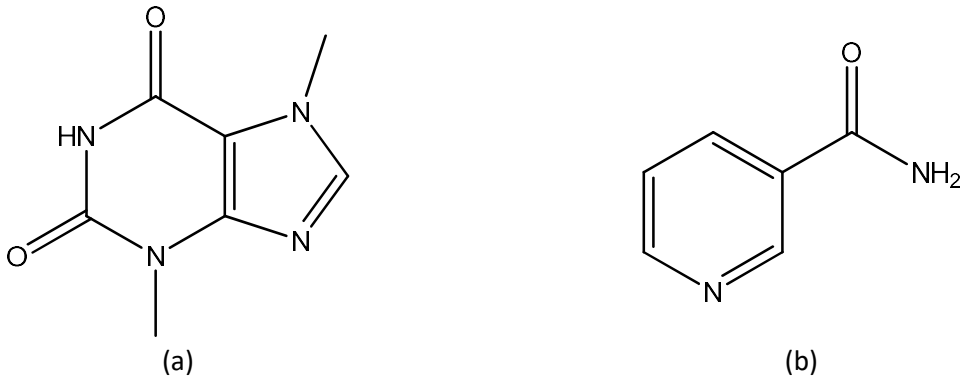
One of the main concerns related to the production of active pharmaceutical ingredients (API) is that around 70% of the promising substances may fail due to unsuitable physical properties, such as their solubility. [1] To address this question, the production of multicomponent crystals (crystals containing two or more molecules in their crystalline lattice) has become one of the most promising strategies to adjust the solubility of APIs without compromising their therapeutic action. [2]

This work describes the use of multicomponent crystals to adjust the solubility of theobromine and nicotinamide (Fig. 1). The synthesis of these compounds was performed by mechanochemistry, mixing the compounds with hydroxybenzoic acids and dicarboxylic acids respectively. These compounds were characterized by differential scanning calorimetry and powder X-ray diffraction. Finally, the solubilities were evaluated and compared with that of the pure compounds.



(a) (b)

Fig. 1. Chemical Structure of (a) Theobromine and (b) Nicotinamide

Acknowledgments

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References

[1] Cerreia Vioglio, P., Chierotti, M. R. & Gobetto, R. Pharmaceutical aspects of salt and cocrystal forms of APIs and characterization challenges. Adv. Drug Deliv.Rev. 117 (2017) 86–110.

[2] Morissette, S. L. et al. High-throughput crystallization: Polymorphs, salts, co-crystals and solvates of pharmaceutical solids. Adv. Drug Deliv. Rev. 56 (2004) 275–300.

Cathodic electrodeposition of Fe-MOF-74 and derivatives

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Purines play a major role in medical applications since their concentration levels translate into a useful diagnostic tool for some clinical disorders: gout, cardiovascular diseases, Lesch–Nyhan syndrome, or type 2 diabetes.[1] Therefore, the scientific community has been developing rapid, sensitive, and selective methods for the detection of these compounds. From all, metal-organic frameworks are a distinguished subclass of nanomaterials that take advantage of host-guest chemistry, potentially behaving as a sensor.[2] In this work, our group reports the synthesis of new ligands (Figure 1), characterised by nuclear magnetic resonance (NMR) and Fourier-transform infrared spectroscopy (FTIR). These will be applied to the electrochemical fabrication of Fe-MOF-74 films and derivatives thereof, characterised by FTIR, scanning electron microscopy (SEM), particle-induced X-ray emission (PIXE) and Rutherford backscattering spectrometry (RBS).

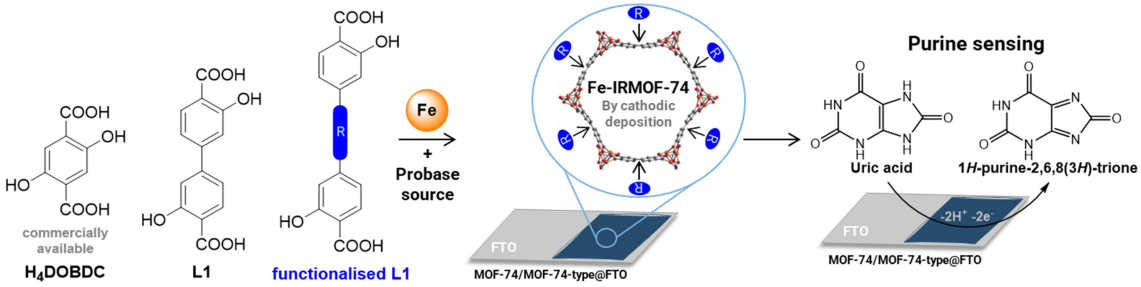

Figure 1. Fe-MOF-74 thin films and derivatives.

Acknowledgements

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References

[1] N. Lavanya, C. Sekar, R. Murugan, G. Ravi, Mater. Sci. Eng. C. 65 (2016) 278.

[2] I. Strauss, A. Mundstock, M. Treger et al., ACS Appl. Mater. Interfaces. 11 (2019) 14175.

Exploring antimicrobial biossurfactants for the development of hydrogel formulations

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Introduction: Nowadays, healthcare-associated infections are one of the most common complications faced in a healthcare setting. Moreover, bacterial resistance to most available antibacterial drugs is increasing and making previously easily treatable serious infections a major healthcare problem [1]. Thus, the demand for antimicrobial alternatives not prone to resistance development is rapidly increasing [2]. In the herein presented work, chitosan hydrogels impregnated with antimicrobial biosurfactant active agents, not prone to resistance development, produced by yeast were developed as antibacterial coatings for medical devices. This work aims to reduce healthcare-associated infections related to invasive procedures.

Methods: The active agent used in the antibacterial chitosan (Chi) hydrogel formulations were sophorolipids produced by *S. bombicola* CBS 6009 [3]. Hydrogel formulations with different Chi concentrations that ranged from 1% to 3% (w/v) were prepared and impregnated with sophorolipids. Firstly, the viscosity of these solutions was assessed using a rotatory viscosimeter (Brookfield Ametek, DVE) and later the antibiofilm activity was tested against *S. aureus* and quantified by crystal violet method.

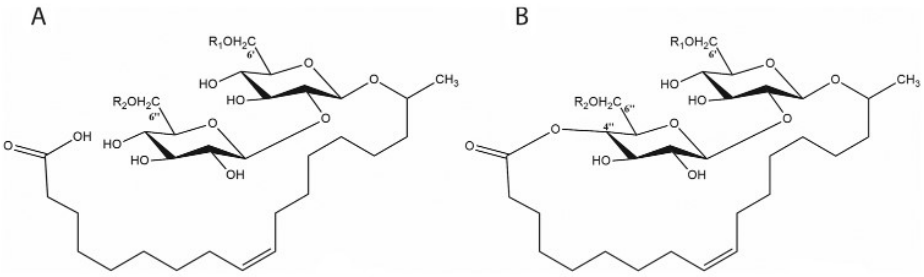

Fig 1. Sophorolipids in acidic (A) and lactonic form (B).

Results: The production the formulation's active agents by *S. bombicola* yielded 1.52 g of sophorolipids after 144 hours. Among the plain chitosan solutions tested, the 2%, 2.5% and 3% (w/v) chitosan solutions demonstrated an adequate antibiofilm activity against *S. aureus* after 24 hours. This antibiofilm activity was also showed to increase with the raise of chitosan concentration. The incorporation of sophorolipids produced by *S. bombicola* were shown to improve the antibiofilm activity of the formulations when at a concentration of 3 mg/mL. The 2% (w/v) chitosan solution was shown to be too fluid to be used for medical devices by the viscosity assessment whilst the 3% (w/v) chitosan solution was shown to be too viscous.

Conclusions: Chitosan hydrogel impregnated with sophorolipids shows a potential to be used in the development of antibacterial coatings intended for the improvement of the antimicrobial properties of biomaterials.

Acknowledgements

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References

[1] European Centre for Disease Prevention and Control (ECDC), 2014. Annual epidemiological report. Antimicrobial resistance and healthcare-associated infections 2014. ECDC, Stockholm, p22.

[2] Simões NG, Bettencourt AF, Monge N, Ribeiro IAC. Novel Antibacterial Agents: An Emergent Need to Win the Battle Against Infections. Mini Rev Med Chem. 2017;17(14):1364-1376. doi: 10.2174/1389557516666160907151454. PMID: 27629996.

[3] Mendes RM, Francisco AP, Carvalho FA, Dardouri M, Costa B, Bettencourt AF, Costa J, Gonçalves L, Costa F, Ribeiro IAC. Fighting S. aureus catheter-related infections with sophorolipids: Electing an antiadhesive strategy or a release one? Colloids Surf B Biointerfaces. 2021 Dec;208:112057. doi: 10.1016/j.colsurfb.2021.112057. Epub 2021 Aug 23. PMID: 34464911.

New Hybrid Photoactive Materials Based on Glycoporphyrins

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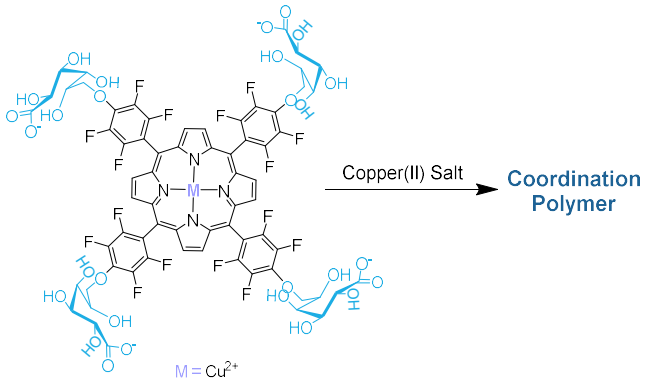
As the presence of organic contaminants derived from pharmaceuticals in wastewater is currently recognized as a serious environmental issue, the development of new strategies for water treatment has gained a tremendous scientific interest.[1] Photoremediation of wastewater arises as a promising and cost-effective technology since it only requires a photosensitizer (PS) and sunlight.[2] The outstanding photophysical and photochemical properties of porphyrins, and their derivatives, have been widely reviewed in the biomedical field, namely as PS in Photodynamic Therapy.[3]



Nevertheless, new applications involving these organic dyes have emerged in recent years, such as photocatalysis.[4] In this perspective, this work aims at designing heterogenous photocatalysts based on coordination polymers built from porphyrins bearing carbohydrate moieties and Cu(II) ions. The synthesis of new glycoporphyrin ligands is described alongside with attempts to isolate these hybrid materials.

Acknowledgements

Support for this work was provided by CQE (UIDB/00100/2020 and PTDC/QUI-QIN/29778/2017) and CICECO (UIDB/50011/2020 & UIDP/50011/2020) research units, through national funds and where applicable co-financed by FEDER, within the PT2020 Partnership Agreement. SB thanks FCT for a PhD scholarship (SFRH/BD/140098/2018). The research contract of FF (REF-168-89-ARH/2018) is funded by national funds (OE), through FCT, in the scope of the framework contract foreseen in nos. 4, 5 and 6 of article 23 of the Decree-Law 57/2016, of 29 August, changed by Law 57/2017, of 19 July.

References

[1] Sushil , K. et al., Chemical Reviews, 107 (2007), 2319-2364.
[2] Alves, E. et al., Journal of Photochemistry and Photobiology, 22 (2015), 34-57.
[3] Kou, J. et al., Oncotarget, 8 (2017), 81591–81603.
[4] a) Costa e Silva, R. et al., Beilstein Journal of Organic Chemistry, 16 (2020), 917-955; b) Fernández, L. et al., Dyes and Pigments 142 (2020), 535-543.

Probing aggregation interactions of $OHC_6H_4C(O)R$ (R = H, CH_3, CH_2CH_3) compounds in ethanol through solution density measurements

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Crystallization from solution is one of the most important processes used to obtain highly pure solid products. [1,2] However, knowledge of the early stages of crystallization from solution (pre-nucleation and nucleation stages [3]) is scarce, frequently leading to manufacture problems related with polymorphism (the possibility of existence of different crystalline forms of a molecule with different packing architectures). An open question, within this scope, is how solute – solute and solute - solvent interactions determine the aggregation processes in solution, which underlie nucleation processes proceeding through evaporative crystallization.

In this work, solution density measurements were used to investigate the aggregation/solvation of 4'-hydroxybenzaldehyde (HBA), 4'-hydroxyacetophenone (HAP) and 4'-hydroxypropiophenone (HPP) (Figure 1) in ethanol.

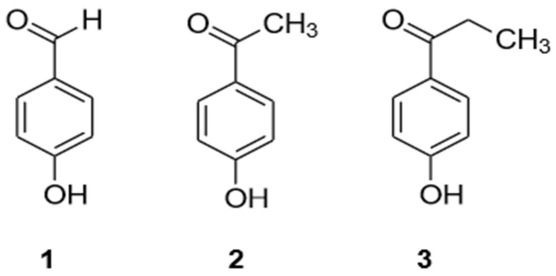

Figure 1. Molecular structures of 4'-hydroxybenzaldehyde (1), 4'-hydroxyacetophenone (2) and 4'-hydroxypropiophenone (3).

In the very dilute region, HBA and HPP apparent molar volumes decrease for increasing solute concentrations, while an opposite trend was observed for HAP solutions, trendlines approaching constant values at higher concentrations, where solute-solute interactions prevail.

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References

[1] C. E. S. Bernardes, M. L. S. Matos Lopes, J. R. Ascenso, M. E. Minas da Piedade, Cryst.Growth Des. 14 (2014) 5436–5441.

[2] J. W. Mullin, Crystallization, fourth ed., Butterworth: Oxford, 2001.

[3] D. Erdemir, A. Y. Lee, A. S. Myerso, Acc. Chem. Res, 42 (2009), 621-629.

Synthesis of iron-based coordination polymers and discrete molecules for application as spin-labile materials

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The study of magnetic systems able to combine their spin lability with the effect of optical rotation is named molecular dichroism, an area of great interest in magnetism. Molecules possessing this effect show promise as a magnetochiral molecular sensors, since they can model unpolarized and polarized light beams, due to the combined effect of optical rotation and its magnetic properties [1].

The synthesis and characterization of bidentate and tridentate ligands (Figure 1) and, also, of the resulting Fe(II) and Fe(III) complexes is presented here. While the Schiff-base ligand preferably forms Fe(III) complexes, the other two are more likely to form coordination Fe(II) polymers [2,3].

Acknowledgements

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P.N.M. acknowledges FTC for financial support (CEECIND/00509/2017).

References

[1] M. Atzori et. al., Sci. Adv., 2021, 7(17), 1-8.

[2] Y. Garcia et. al., J. Am. Chem. Soc., 2011, 133, 15850-15853.

[3] A. Vicente et. al., Dalton Trans., 2018, 47, 7013

Photodegradation of 17β-estradiol by Zirconium-Porphyrin MOF

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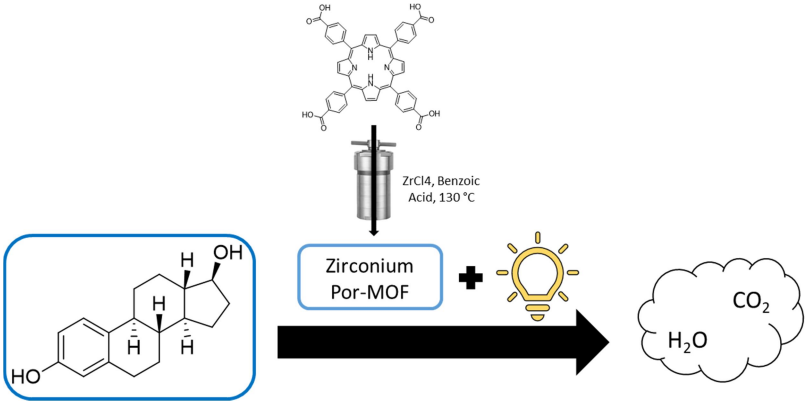
There is a wide range of pharmaceuticals used to treat many medical conditions. Though being a positive aspect of modern society when it comes to healthcare, it poses nevertheless a serious environmental problem as an increasing volume of pharmaceutical compounds are being detected as contaminants in wastewaters and, concomitantly, in water reserves.[1,2] It is imperative to develop and implement effective and efficient ways to treat water by removing or, at least, transforming this type of pollutants into more environmentally benign species. Advanced Oxidation Processes (AOPs) have shown to be an interesting solution to rapidly oxidize these organic pollutants to less hazardous products[3], and porphyrin-based Metal-Organic Frameworks (Por-MOF) were found to be effective as catalysts for this purpose.[4,5] In this context, we prepared a zirconium MOF based on the tetrakis(4-carboxyphenyl)porphyrin (**H_2TPP(COOH)$_4$**) and tested its photocatalytic activity in the degradation of 17β-estradiol. Our main results will be presented.



Acknowledgements

We wish to thank FCT for the financial support to CQE (UIDB/00100/2020 and PTDC/QUI-QIN/29778/2017) and CICECO (UIDB/50011/2020 & UIDP/50011/2020) research units, through national funds and where applicable co-financed by FEDER, within the PT2020 Partnership Agreement. The research contract of FF (REF-168-89-ARH/2018) is funded by national funds (OE), through FCT, in the scope of the framework contract foreseen in nos. 4, 5 and 6 of article 23 of the Decree-Law 57/2016, of 29 August, changed by Law 57/2017, of 19 July.

References

[1] A. L. Boreen, W. A. Arnold, K. McNeill, *Aquatic Sciences*, **2003**, 65, 320-341.

[2] M. Mon *et. al*, *J. Mater. Chem. A*, **2018**, 6, 4912.

[3] Y. Xu, *et. al*, *J. Mater. Chem. A*, **2017**, 5, 12001.

[4] P. Silva, *et. al*, Chem. Soc. Rev., **2015**, 44, 6774.

[5] C. F. Pereira, *et. al*, *Molecules,* **2016**, 21,1348.

Development of acid chars for bar adsorptive microextraction technique

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The present work aimed to develop and characterize acid chars as potential adsorptive phases for bar adsorptive microextraction technique (BAμE), followed by high performance liquid chromatography with diode array detection to monitor trace levels of nine pharmaceutical compounds and hormones in water matrices. Both polar and nonpolar compounds were selected as model compounds, such as, 17-α-ethinylestradiol, clofibric acid, mefenamic acid, carbamazepine, diclofenac, estrone, gemfibrozil, triclosan and sulfamethoxazole, to represent different therapeutic classes. The acid chars were prepared by H_2SO_4-mediated carbonization of sisal using two different concentrations, 9 M and 13.5 M. To study the potential of acid chars as BAμE phase, the effect of different organic solvents to clean the acid chars and the influence of the matrix pH were performed. For benchmarking the two lab-made acid chars were tested along with a commercial powdered activated carbon. The carbon materials (acid chars and commercial activated carbon) were characterized by N_2 adsorption isotherms and by the pH at the point of zero charge. The results obtained showed that, despite having incipient porosity, the acid chars managed to obtain a response for all analytes under study and in some cases, the recoveries efficiencies overcame those attained with the commercial activated carbon used as control. Therefore, this work showed that acid chars have potential as adsorbents for samples enrichment.

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References

[1] S.M. Ahmad, A.S. Mestre, N.R. Neng, C.O. Ania, A.P. Carvalho, J.M.F. Nogueira, ACS Appl. Bio Mater. 3 (2020) 2078–2091.

Life & Health

Development of New DprE1 Inhibitors Against *Mycobacterium tuberculosis*

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Tuberculosis (TB) is an airborne disease caused by **Mycobacterium tuberculosis** (MTB) that usually affects the lungs and remains one of the deadliest infectious diseases worldwide. The development of new antitubercular drugs is essential, especially due to the prevalence of drug-resistant tuberculosis [1]. A new promising target is decaprenylphosphoryl-β-d-ribose-2'-oxidase (**DprE1**), an essential enzyme for cell wall synthesis, and several new inhibitors have been described. [2] One of the first classes described were **dinitrobenzamines** (DNBs), described as **covalent inhibitors** of dprE1 by activation of a nitro moiety and formation of a covalent bond to the residue cys387. [3]

Previous work in our group has led to compounds with very good antitubercular activities, that potentially act on dprE1, and, in order to explore structural diversity for this type of derivatives, new derivatives are here proposed, making use of alkyl linkers with some structural features described in the literature, such as terminal cyclic or aromatic groups.

Here, the challenging synthesis of such derivatives, as well as the preliminary studies of their chemical and biological stability and their antitubercular activity will be presented and discussed.

Acknowledgements

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References

[1] World Health Organization Global Tuberculosis Report; 2021; ISBN 9789240037021.

[2] Piton, J. et al. 2017. Structural studies of Mycobacterium tuberculosis DprE1 interacting with its inhibitors. *Drug Discovery Today*. 22, 3 (2017), 526–533.

[3] Wang, A. et al. 2018. Design, synthesis and antimycobacterial activity of 3,5-dinitrobenzamide derivatives containing fused ring moieties. Bioorganic and Medicinal Chemistry Letters. 28, 17 (2018), 2945–2948.

Evaluation of the morphological and functional properties of erythrocytes in amyotrophic lateral sclerosis patients

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Amyotrophic Lateral Sclerosis (ALS) is a devastating and fatal neurodegenerative disorder, involving progressive degeneration of motor neurons in spinal cord, brainstem, and motor cortex.[1] Respiratory dysfunction is the major determinant of functional impairment and death in ALS.[1] Hypoxia derives from respiratory muscles weakness, but its role in precipitating further neuronal damage or skeletal muscle dysfunction is unclear.[2] Venous thromboembolism (VTE) is commonly reported in ALS, in general associated to immobility, ageing and progressive respiratory failure[3], but other risk factors have not been thoroughly explored. VTE is a medical condition responsible for the formation of blood clots in veins. This can derive from abnormalities in the erythrocyte membrane (e.g., changes in elasticity), which depend (among other factors) on its lipid content, such as in phosphatidylcholine or sphingolipids[3]. In inflammatory conditions, γ' fibrinogen (an *in vivo* variant of fibrinogen) has its relative percentage increased in the total plasma fibrinogen and is closely correlated with other markers of inflammation.[4]

The main purpose of our study was to evaluate changes in morphological, biomechanical, and biophysical properties of erythrocytes from ALS patients. We also evaluated changes on γ' fibrinogen plasma levels as a possible biomarker of ALS.

Human blood samples from ALS patients (n=32) were analysed and compared with healthy donors (n=33) and non-healthy donors with other neurological diseases (n=9) in order to evaluate the changes in morphology and surface elasticity of erythrocytes. Samples were examined by atomic force microscopy (AFM), zeta-potential analysis and quantification of γ' fibrinogen in plasma levels.

Results have shown that erythrocytes from ALS patients and from non-healthy donors are stiffer than for healthy controls (853.2 ± 747.2 Pa *vs.* 242.4 ± 306.6 Pa, $p<0.001$, and 974.7 ± 526.4 Pa *vs.* 242.4 ± 306.6 Pa, $p<0.007$, respectively). Additionally, zeta-potential analysis showed that the membranes of erythrocytes from ALS patients are less negatively charged than for the healthy control group, in the presence of higher concentrations of fibrinogen, when compared to the healthy control group ($p=0.01$ at 1.0 mg/ml fibrinogen and $p=0.03$ at 2.0 mg/ml fibrinogen). Regarding erythrocyte membrane roughness, results showed that the membrane of the erythrocytes from ALS patients is smoother than for healthy controls (surface roughness 1.96 ± 0.34 nm *vs.* 2.37 ± 0.54 nm, $p=0.004$). In addition, ALS patients presented higher plasma concentrations of γ' fibrinogen than healthy controls (58.8 ± 12.63 mg/dL *vs.* 41.99 ± 9.85 mg/dL, $p<0.001$).

Using AFM together with other biophysical techniques, our results indicate that erythrocytes from ALS patients present electrostatic, biomechanical, and morphologic changes on their surface. These findings could contribute to dissect the complex interplay between respiratory function, progression rate, lipid profile and survival in ALS. Furthermore, γ' fibrinogen plasma levels represented a possible novel biomarker in ALS research.

Acknowledgments

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1. Nelson, A. Amyotrophic lateral sclerosis. Preoperative Assess. Manag. Third Ed. 231–232 (2018).
2. Gladman, M., DeHaan, M., Pinto, H., Geerts, W. & Zinman, L. Venous thromboembolism in amyotrophic lateral sclerosis: A prospective study. Neurology 82, 1674–1677 (2014).
3. Warschawski, D. E. *et al.* Choosing membrane mimetics for NMR structural studies of transmembrane proteins. Biochim. Biophys. Acta - Biomembr. 1808, 1957–1974 (2011).
4. Pronto-Laborinho, A. C.; Lopes, C. S. *et al.* γ' Fibrinogen as a Predictor of Survival in Amyotrophic Lateral Sclerosis. *Front. Cardiovasc.Med.*, *8*, 715842 (2021).

Derivatization of weak acids: a synthesis pathway towards new potential antitubercular drugs

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First and second-line TB drugs are less effective against multidrug-resistant (MDR-TB), extensively drug-resistant (XDR-TB) strains and HIV co-infection. In 2020 The World Health Organization (WHO) recorded 1.5 million fatalities caused by TB, where 14% were HIV co-infected patients [1].
The development of new antitubercular drugs is critical to treating drug-resistant TB strains.
Trans cinnamic and salicylic acids are weak acids that have anti-mycobacterial activity. For specific acids, ester prodrugs are more active and can be activated by esterases to liberate the acids[2]. Cinnamic and salicylic acid derivatives containing nitro substituents in the aromatic ring were synthesized, and their activity was compared against non-nitro containing compounds.
Cinnamic and salicylic esters were synthesized via two different methodologies: 1) Fischer esterification between the corresponding acids and desired alcohols (butanol; hexanol; octanol; decanol; dodecanol) using a catalytic amount of sulfuric acid; 2) addition of thionyl chloride to the weak acid to create the corresponding acyl chloride; followed by nucleophilic addition of the corresponding alcohol to the chloride, in the presence of 4-dimethylaminopyridine (DMAP) and triethylamine; or potassium carbonate. Cinnamic and salicylic amides were synthesized through the same nucleophilic addition methodology, with their corresponding amines. Minimum inhibitory and minimum bactericidal concentrations for the compounds against *M. tuberculosis* were obtained. Results will be discussed.

Acknowledgements:

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[1] 'Tuberculosis (TB)', Oct. 14, 2021. https://www.who.int/news-room/fact-sheets/detail/tuberculosis (accessed May 19, 2022).

[2] D. Pires *et al.*, 'Esters of Pyrazinoic Acid Are Active against Pyrazinamide-Resistant Strains of Mycobacterium tuberculosis and Other Naturally Resistant Mycobacteria In Vitro and Ex Vivo within Macrophages', *Antimicrob Agents Chemother*, vol. 59, no. 12, pp. 7693–7699, Dec. 2015, doi: 10.1128/AAC.00936-15.

Exploring two-photon activable caging groups for glioblastoma prodrug development

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Glioblastoma (GBM) is the most common, aggressive, and lethal type of primary brain tumour, with an extremely low survival rate[1]. Despite recent progress made possible by a better understanding of the disease, GBM prognosis remains grim, defining a high societal challenge[2,3]. This project aims to improve the therapeutic tolerability and prognosis for glioblastoma patients by developing prodrugs which release an appropriate antitumor drug in a controlled manner upon near-infrared (NIR) light irradiation. The hypothesis behind this work is that antitumor drugs, appropriately modified with a two-photon-activable protecting group, can be precisely delivered to the glioblastoma cells upon NIR light irradiation, avoiding off-site effects and improving efficacy.

In this work, several derivatives of the o-hydroxycinnamate photocaging group (fluorescent upon drug release) were synthesized, including one with doxorubicin (Figure 1). In the future work, derivatives of another photocaging group, the *o*-nitrobiphenylpropyl, will be synthesized and conjugated with anticancer drugs.

The synthesized prodrugs will be evaluated for their photochemical properties and against cancer cell lines for their activity. The outcome of this project will expand the field, possibly leading to breakthroughs in the development of light-activated cancer therapeutics.

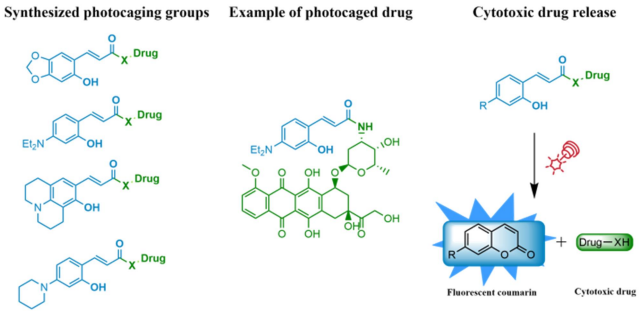

Figure 3 - Overview of the developed work

Acknowledgements

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References

[1] Tan, A. C. et al., CA: A Cancer Journal for Clinicians 70 (2020), 299–312.

[2] Liu, E. K. et al., Current Neurology and Neuroscience Reports 20 (2020), 1042-6.

[3] Davis, M. E., Clinical Journal of Oncology Nursing 20 (2016), 1–8.

Novel bio-based nanoplatforms for cancer phototherapy

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Cancer is one of the leading health problems worldwide due to its mortality. In addition to conventional cancer therapies (surgery, radio-, chemo- and immune-therapies), other non-invasive therapies, with high precision and less side effects, have been studied in the last few decades such as photodynamic therapy (PDT) and photothermal therapy (PTT) [1,2]. The derivatization of the photoactive compound (photosensitizer, PS) with biomolecules such as carbohydrates allows a targeted delivery strategy by recognition of uniquely expressed or overexpressed receptors on tumor cells, thus, increasing the selectivity of the treatment [3]. The combination of PS derivatives with photothermal agents (i.e., Au nanoparticles) allows to simultaneously perform PDT (through formation 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].

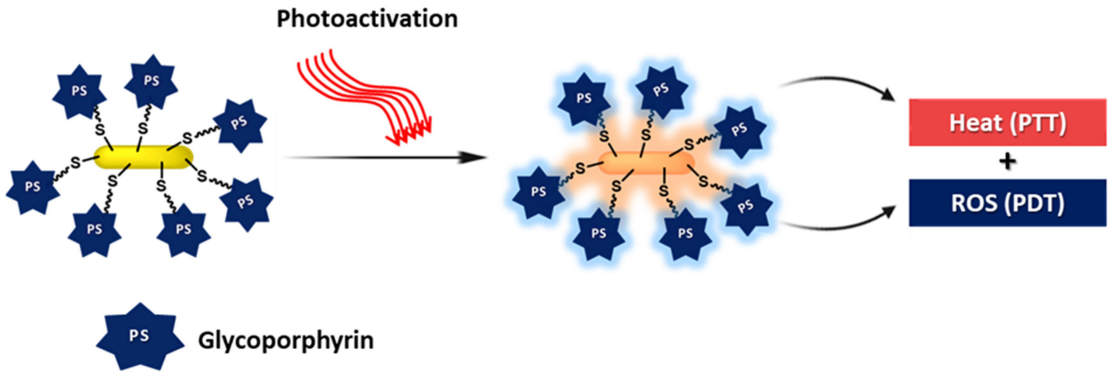

Figure 1. (Nano)formulation of bio-based AuNRs with glycoporphyrins

Acknowledgements

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References

[1] Bogoeva, V.; Siksjø, M.; Sæterbø, K. G.; Bernt, T.; Bjørkøy, A.; Lindgren, M.; Gederaas, O. A. *Photodiagnosis Photodyn. Ther.* **2016**, *14*, 9–17.

[2] Szliszka, E.; Czuba, Z. P.; Kawczyk-Krupka, A.; Sieron-Stoltny, K.; Sieron, A.; Krol, W. *Med. Sci. Monit.* **2012**, *18* (1), BR47–BR53.

[3] Gao, S.-L.; Kong, C.-Z.; Zhang, Z.; Li, Z.-L.; Bi, J.-B.; Liu, X.-K. *Oncol. Rep.* **2017**, *38* (4), 1967–1976.

[4] Chen, J.; Fan, T.; Xie, Z.; Zeng, Q.; Xue, P.; Zheng, T.; Chen, Y.; Luo, X.; Zhang, H. *Biomaterials* **2020**, *237*, 119827.

[5] Gai, S.; Yang, G.; Yang, P.; He, F.; Lin, J.; Jin, D.; Xing, B. *Nano Today* **2018**, *19*, 146–187.

Synthesis of novel asymmetric and symmetric 1,3-diaryltriazenes

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Triazenes are azocompounds characterized by the presence of 3 consecutive nitrogen atoms. It is a class of compounds that has been studied for about 150 years showing different applications, namely, as protecting group in natural product synthesis, as linker when incorporated into polymers and used in the synthesis of oligomers and novel heterocycles [1]. Nevertheless, their most prominent and studied feature is their cytotoxic activity towards several classes of tumour cells. [2]

The herein present work aimed to synthetize a small library of 1,3-diaryltriazenes to further test their potential antimicrobial activity. Their general structure is shown in figure 1.

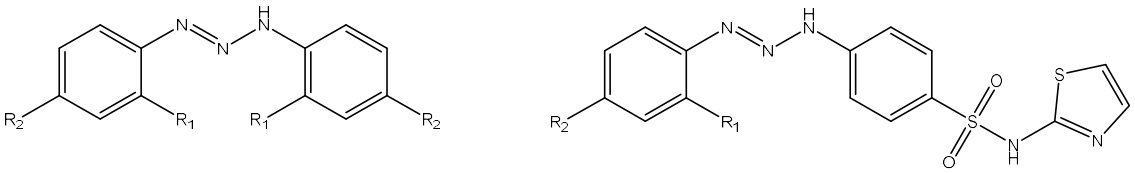

Fig.1-General structure of 1,3-diaryltriazenes synthetized

This work involved the synthesis of eight distinct 1,3-diaryltriazenes. Different substituted anilines were submitted to diazotization to form their correspondent diazonium salt. Depending on the starting aniline, two different reactions were used for the diazotization procedure. While one of the reactions was carried out in an organic solvent using tert-butyl nitrite as the nitrite source, the other was carried out in an aqueous medium using sodium nitrite as the nitrite source. Two of the new 1,3-diaryltriazenes were symmetrical and were created by reacting the anilinediazonium salt with the respective aniline, while the other six were asymmetric and created by reacting various anilinediazonium salts with sulfathiazole. Different techniques were used to purify symmetrical and asymmetrical 1,3-diaryl triazenes, and the resulting compounds had yields between 12% – 35%.

The 1,3-diaryltriazenes were characterized by proton NMR and FTIR ATR and are currently being subjected to biological activity assessment.

Further work is under development to assess the synthesized compounds antimicrobial activity and elucidate on their suitability for biomaterials antimicrobial properties improvement.

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References

[1]- Mendes E, Perry MJ, Francisco AP. (2011), “The synthetic utility of triazenes in heterocyclic synthesis In: Heterocyclic Targets in Advanced Organic Synthesis, chapter 6, pp125-144, (Maria do Carmo Carreiras and José-Marco Contelles, ed.), Ed. Research Signpost, Trivandrum, Kerala, India ISBN 978-81-308-0431-6

[2]- Francisco AP, Mendes E, Santos AR, Perry MJ. (2019) “Anticancer triazenes: from bioprecursors to hybrid molecules”, Curr Pharm Des 25, 1623, doi: 10.2174/1381612825666190617155749

Phytochemical and bioactivity study of the acetonic extract and fractions of *Plectranthus hadiensis*

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Natural products are an important source of bioactive lead molecules. The genus *Plectranthus* belongs to the Lamiaceae family and is known to be rich in abietane-type diterpenes which possess relevant biological activities. Specifically, *P. hadiensis* (Forssk.) Schweinf. *ex* Sprenger has been documented for its use against different tumors. Therefore, the aim of this work was to perform a bio-guided isolation of compounds from the acetonic extract from *P. hadiensis* stems. Additionally, *in vitro* antioxidant, antimicrobial activities and general toxicity have been evaluated.

The ultrasound-assisted extraction of *P. hadiensis* stems using acetone afforded six fractions. In a preliminary biological activity screening, fractions III and V showed the highest antioxidant and antimicrobial activities, whereas none of the fractions showed general toxicity, according to the *Artemia salina* assay. Several abietane-type diterpenes were identified and quantified, such as 7α-acetoxy-6β-hidroxyroyleanone (Roy) and 6β,7β-dihydroxyroyleanone (DiRoy), which agrees with the HPLC-DAD profile of the extract and fractions co-injected with authentic samples; moreover, the stem extracts of the current study were compared with previously studied extracts from the leaves, highlighting significative differences in terms of content of Roy, as confirmed both by HPLC-DAD and TLC analyses. In particular, a high amount of Roy was detected in the leaves, while the stems resulted to be richer in DiRoy.

Overall, the antioxidant and antimicrobial activities of fractions III and V could be ascribed to the high presence of Roy, in agreement with previous works from our group about extracts containing the same molecule [1]. Furthermore, studies about the cytotoxicity profile of the obtained fractions are currently ongoing.

Acknowledgements

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E.M.D-M acknowledges financial support from predoctoral FPU 2019 fellowship from University of Alcalá.

References

[1] Domínguez-Martín, E.M.; Magalhães, M.; Díaz-Lanza, A.M.; Marques, M.P.; Princiotto, S.; Gómez, A.M.; Efferth, T.; Cabral, C.; Rijo, P. Molecules. 27 (2022), 3813.

Synthesis of VHL HOMO-PROTAC and RIPK2 PROTAC, based on 2,2'-pyridine moieties as a linker

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The Proteolysis Targeting Chimera (PROTAC) is a heterobifunctional molecule comprising an E3 ligase ligand fused to a protein-ligand (POI), separated by a linker. The PROTAC's primary objective is the target degradation using the Ubiquitin-Proteasome System (UPS) enzymatic machinery, an essential proteolytic system of intracellular proteins. For POI degradation, the UPS system adds, by E3 ligase action, a ubiquitin tag to the native protein structure, which is recognised by proteasome 26S, where degradation happens. The PROTAC molecule enhances the POI ubiquitin tag labelling, resulting in selective and specific protein degradation, which has pharmacology attractive [1].

In this project, we synthesised two different PROTACs: a VHL HOMO-PROTAC and RIPK2 PROTAC. The difference between them is the target. In HOMO-PROTAC the target is an E3 ligase, where there is a self-degradation. The progression of some diseases like cancer could be a result, of an E3 ligase overexpression [2]. In RIPK2 PROTAC the target is a Receptor-Interacting serine/threonine-Protein Kinase 2 (RIPK2) protein, which is responsible for an inflammatory response of the immune system, having consequences inflammatory bowel diseases and cancer [3]. These two PROTAC have in common a 2,2'-bipyridine scaffold as a linker. These structures give stability and flexibility to PROTAC. Moreover, the 2,2'-bipyridine scaffolds are frequently used as organic ligands in ruthenium(II) complexes, giving the possibility to form an inorganic hexavalent PROTAC, being more potent and efficient on target degradation [4].

Key-words: VHL HOMO-PROTAC; RIPK2 PROTAC; 2,2'-piridine moieties; Ruthenium(II) complex hexavalent PROTAC.

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Fundação para a Ciência e Tecnologia (PTDC/MED-QUI/31468/2017)

References

[1] – Nalawansha DA, Crews CM., Vol. 27, Cell Chemical Biology. Elsevier Ltd; 2020.

[2] – Chen Y, Jin J. Acta Biochimica et Biophysica Sinica. 2020 Jul 10;52(7):776–90.

[3]- Honjo H, Watanabe T, Kamata K, Minaga K, Kudo M. Vol. 12, Frontiers in Pharmacology.

[4] – Soliman N, Gasser G, Thomas CM. Advanced Materials. 2020 Nov 19;32(47):2003294.

Development of sustainable and active cellulose-based food packaging films

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Introduction: Numerous outbreaks of foodborne diseases caused by pathogens have been associated with biofilm formation. To control this problem and guarantee food quality and safety, food packaging is often used. The packaging industry is among industries that highly depend on plastic and under this scope there is an urgent need to find novel environmentally friendly alternatives [1]. Thus, biological-based polymers packaging has recently emerged as a substitute for conventional plastic. Cellulose and its derivatives are among alternative biopolymers used in the food packaging industry due to their unique characteristics. Cellulose acetate (CA) is one of them that may be highlighted for being non-toxic and degradable and presenting stable hydrolytic capabilities. Moreover, CA films can be functionalized, for the improvement of their antioxidant and antimicrobial properties [2]. Aim: This work is focused on the development of a functionalized cellulose-based film with cranberry extract intended for active food packaging aiming to increase food shelf life and prevent biofilm formation. Methods: A extract was first obtained from cranberries. Antioxidant activity of the extracts was tested (e.g., Folin-Ciocalteu's, DPPH methods) as well as their antimicrobial properties through the determination of the Minimum Inhibitory Concentration (e.g. microdilution method), and antibiofilm activity (e.g. crystal violet assay). Next, CA films incorporated with active extracts were developed by the solvent casting method. Their properties were evaluated through several analyses (e.g. light transmission, Scanning Electron Microscopy, and FTIR-ATR). Results: Cranberry extracts proved to be suitable for presenting antioxidant and antimicrobial activity. They presented a high total phenolic content, 256.8±23.5mg/Gallic acid equivalents/g extract, a half-maximal inhibitory concentration at 0.21mg/mL, and a MIC at 3.125mg/mL against S. aureus, and an MBIC at 3.125mg/mL, showing also antibiofilm properties. After films optimization, extracts were incorporated. The films showed a reduction in the light transmission and an increase in opacity, due to the films' red color. They also showed a lower contact angle, meaning that the films raised their hydrophilicity. Conclusion: The cellulose-based films with cranberry extract seem promising for sustainable and active food packaging. Thus, this approach shows potential towards the enhancement of food products' safety and quality.

Acknowledgements

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References

[1] Severo C, Anjos I, Souza VGL, Canejo JP, Bronze MR, Fernando AL, et al. Development of cranberry extract films for the enhancement of food packaging antimicrobial properties. Food Packaging and Shelf Life. 2021 Jun 1; 28:100646.

[2] Rajeswari A, Jackcina E, Christy S, Swathi E, Pius A. Fabrication of improved cellulose acetate-based biodegradable films for food packaging applications. Environmental Chemistry and Ecotoxicology. 2020; 2:107–14.

Synthesis of novel potentially bioactive D-glucuronamide-based nucleoside and nucleotide analogs containing 1,2,3-triazole units

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Synthetic nucleosides, nucleotides and their analogs or mimetics have occupied an important place in medicinal chemistry, with several compounds in clinical use to treat various types of cancers and viral infections [1]. These groups of molecules are prompted to interfere with nucleos(t)ide-dependent biological events that are crucial for the progress of various diseases [1]. The antimicrobial potential of synthetic and natural nucleos(t)ides has also been well documented [2]. Major issues associated with their clinical use include their low bioavailability and the emergence of chemotherapeutic resistance [1a]. The design and synthesis of novel bioactive nucleoside/nucleotide-like structures that may overcome these limitations, potentiate alternative mechanisms of action and open new therapeutic opportunities is of significant interest.

In this context, we report herein on the synthesis of a variety of nucleoside, nucleotide and sugar diphosphate analogs/mimetics constructed on D-glucuronamide templates, which are rather unusual glycosyl units in nucleoside chemistry, and comprising a 1,2,3-triazole moiety. The triazole unit was envisaged as a surrogate of a nucleobase or as a potential neutral and rather stable surrogate of a phosphate group when combined with other moieties such as phosphonate or amide to establish new potential neutral diphosphate group mimetics. The synthetic methodologies used azido pyranoses and D-glucofuranuronolactone as precursors and employed key steps such as azide-alkyne 1,3-dipolar cycloaddition, *N*-glycosylation, or Arbuzov reaction.

Some compounds were subjected to antibacterial evaluation, from which one showed potent effect against the Gram-positive bacterial pathogen *Streptococcus pneumoniae*, with an activity higher than that of a standard antibiotic, thus tuning it a promising lead molecule for further investigations.

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References:

[1] a) L. P. Jordheim, D. Durantel, F. Zoulim, C. Dumontet, *Nat. Rev. Drug. Discov.* **2013**, *12*, 447-464. b) J. Shelton, X. Lu, J. A. Hollenbaugh, J. H. Cho, F. Amblard, R. F. Schinazi, *Chem. Rev.* **2016**, *116*, 14379-14455.
[2] a) M. Serpi, V. Ferrari, F. Pertusati, *J. Med. Chem.* **2016**, *59*, 10343-10382. b) J. M. Thomson, I. L. Lamont, *Front. Microbiol.* **2019**, *10*, 952.

Effect of an ultra-thin hydroxyapatite surface treatment on bacterial adhesion

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The ability of different bacterial strains to colonize medical devices is among the most critical features associated with implant-related infections [1,2]. Due to the widespread use of antibiotics as a prophylactic measure, the number of bacteria with antibiotic resistance is increasing, making the treatment of severe infections even more difficult. Among other infection-prevention possibilities, there is an urgent need for new effective strategies that decrease the adherence of bacteria to implants and, consequently, the frequency of implant-associated infections [3,4]. Although the mechanisms by which bacteria adhere to surfaces are not fully understood, there is evidence that the initial adhesion process is intimately associated with the properties of the implants surface [5-8]. Here, we studied the effect of an ultra-thin hydroxyapatite surface treatment (HAp) on the bacterial cell attachment to an anodized titanium surface (Ti6Al4V) representative of those used for implants in trauma care. Atomic force microscopy (AFM)-based force spectroscopy was used to assess bacterial adhesion at the single-cell level of *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Staphylococcus epidermidis* to the surface of uncoated titanium and of samples modified with HAp. Single bacterial probes were used to measure the interaction forces between a single bacterium and the surface of the samples. To better understand the initial adhesion process, interaction forces were measured with increasing bacterium-surface contact times, up to 150 s. AFM results clearly show that the HAp surface treatment decreased the probability of bacterial binding for all the bacterial strains tested. A decrease of 7% to 35% of the frequency of binding events was observed at all contact times tested. Moreover, even when a bacterial binding occurred, the force and the energy needed to overcome the adhesion and detach the bacterium from the surface of the samples was lower than the observed for the untreated samples. The HAp surface treatment induced a decrease of, at least, 51% and 41% of the force and the energy, respectively, of the bacteria-surface interaction. With this methodology, we were able to quantitatively demonstrate the decrease of the interaction forces involved in the initial adhesion process between bacteria and implant surface. The obtained results provide valuable insight on the mechanisms of bacterial cell adhesion to implant surfaces.

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References

[1] Arciola CR, Campoccia D, Montanaro L. Nat Rev Microbiol. (2018) 16,397-409.
[2] Ribeiro SM, Felício MR, Boas EV, Gonçalves S, *et al*. Pharmacol Ther. (2016) 160,133-144.
[3] Amin Yavari S, Castenmiller SM, Strijp JAG, Croes M. Adv Mater. (2020) 32,e2002962.
[4] Hall-Stoodley L, Costerton JW, Stoodley P. Nat Rev Microbiol. (2004) 2,95-108.
[5] Gittens RA, Scheideler L, Rupp F, *et al*. Acta Biomater. (2014) 10,2907-2918.
[6] Su Y, Cockerill I, Zheng Y, Tang L, Qin Y-X, Zhu D. Bioact Mater. (2019) 4,196-206.
[7] Wang M, Tang T. J Orthop Translat. (2019) 17, 42–54.
[8] Yuan Y, Hays MP, Hardwidge PR, Kim J. RSC Adv. (2017) 7, 14254-14261.

COMPUTER-ASSISTED DESIGN OF INDOLOISOQUINOLINES AS POTENTIAL NEW ANTICANCER DRUGS

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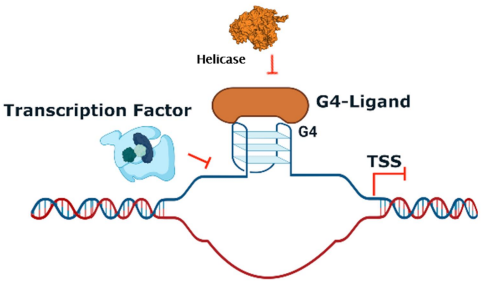
Cancer is a societal burden demanding innovative approaches. G-quadruplexes (G4) are a noncanonical higher-order structure formed in guanine rich DNA or RNA sequences, which are involved in relevant biological functions and are often overrepresented in cancer cells. They can promote genomic instability in DNA replication and modulate transcription and translation. These structures are found in promoter regions of many cancer-related genes such as *c-MYC*, which plays an important role in cellular regulatory processes, as well as in cancer development and progression [1]. G4's have transient structural arrangements and can be unfolded by helicases, like DHX36 [2]. The stabilization of G4s by small organic molecules has shown promising results as an anticancer drug target [3] but it still possesses some obstacles, such as the lack of selectivity towards specific G4s. To overcome that, in this project, we propose to design, synthesize and evaluate indoloisoquinoline derivatives as potential inhibitors of the interaction between *c-MYC*:G4 and its negative regulator, the helicase DHX36 [2]. The indoloisoquinoline scaffold was combined with a library of purchasable fragments to create a final database of 2208 compound derivatives. This dataset was then used in a computational Molecular Docking screening campaign targeting the recently resolved structure of *c-MYC*:G4 in complex with DHX36 [2], to identify the most promising inhibitors. These compounds will be synthesized and evaluated, using *in vitro* assays, for binding and selectivity to the *c-MYC*:G4. The obtained results will be integrated into additional structure:function evaluations, and guide new computational predictions, synthesis, and functional validation.



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Israa Aljnadi acknowledges Global Platform for Syrian Students and ULisboa for a PhD scholarship.

References

[1] me, aim, bb, vbl, pa Pharmaceuticals. 15 (2022) 300.

[2] cms, tr, dna, mp, bs, ms, fra, Nature. 558 (2018) 465-469.

[3] me, bb, aim, pa. Bioorg Med Chem Lett. 72 (2022) 128862.

In silico approaches to the identification of small molecules for immuno-oncology therapy

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Introduction: Immunotherapy is a key pillar in cancer therapy. Although cancer immunotherapy has advanced, there are still few multi-target techniques capable of keeping the immune system under control in cancer patients. However, various animal models show that tumors can activate a variety of immunosuppressive mechanisms. The inhibition of the PD-1/PD-L1 immunosuppressive pathway and TGF-β signaling demonstrates a synergistic effect of dual-blockade due to enhanced T cell infiltration into tumor center and anti-tumor immune response. The primary goal of our research project is the discovery of multi-targeting small compounds with the ability to block PD-1/PD-L1 interaction and TGF-β signaling, with a particular emphasis on inhibitors of PD-L1 and TGF-β receptor I (TGF-βRI). These small molecules could have the capacity to cross cellular membranes, could interact with the intracellular ATP-binding site of TGF-βRI, with the nuclear targets and with the PD-L1 contained in tumor-secreted exosomes.

Materials and Methods: Using PDB data and diverse molecular docking packages, a thorough investigation of crystallographic structures, benchmarking studies, and ligand-target interaction profiles was carried out for PD-L1 and TGF-βRI. To apply filters for virtual screening models, in silico approaches were investigated. These included the score cut-off of docking studies, basic interactions between target and ligand, excluding PAINS, and physicochemical features. Based on this computer-aided drug design work, 60 ChemBridge's compounds were tested experimentally with the PD-1/PD-L1 HTRF® binding assay kit (Cisbio Assays, Codolet, France).

Results: Four compounds with different scaffolds which can disrupt the interaction between PD-1/PD-L1 were found by HTRF® scouting (IC50=6-20 µM).

Conclusions: In the future we will screen the 60 ChemBridge's compounds as potential TGF-βRI inhibitors. Then, a multi-target design will be taken into account.

Keywords: Immunotherapy; Computer-Aided Drug Design; Multi-target; PD-L1; TGF-βRI

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References

[1] Dong H. et al. Cham: Springer International Publishing, 2018;

[2] Zitvogel L. et al. Cham: Springer International Publishing, 2018;

[3] Acúrcio R. C. et al. Med. Chem. Commun., 10 (2019) 1810-1818.

Generation of a small library of tetracyclo-quinolizidine alkaloid derivatives for targeting resistant cancer cells

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Cancer is a leading cause of death worldwide. Multidrug drug resistance (MDR), a complex and multifactorial phenomenon, remains the major impediment to the successful chemotherapy of cancer. Therefore, there is an urgent need of new anticancer compounds and new strategies for overcoming MDR [1].

Aiming at finding new plant-derived compounds for tackling cancer drug resistance, in this work several derivatives of a natural bioactive tetracyclo-quinolizidine alkaloid, found in *Sophora* species, were prepared by 1,4-addition to the β-carbon of an α-β-carbonyl system. Moreover, some derivatives were also prepared by reaction of the carbonyl group with different hydrazines. The structures of the new derivatives were characterized mainly by NMR experiments.

With this strategy, we expect to obtain a library of novel derivatives that will be evaluated in further studies as MDR reversers, namely as ABC transporters inhibitors.

References

[1] M. Kartal-Yandim, A. Adan-Gokbulut, Y. Baran, Crit. Rev. Biotechnol. 8551 (2015) 1–11.

Acknowledgements

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Action of cationic photosensitisers against *Escherichia coli*

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The interaction between light, a photosensitiser and dioxygen (O_2) has been widely used in various biomedical areas, including to treat bacterial infections [1]. The photodynamic inactivation of microorganism (PDI) as main focus the search for more promising PSs that can quickly and effectively kill microorganisms [2]. One of the PSs class developed for PDI in recent years is the asymmetric cationic porphyrins, as they have shown high inactivation efficiency towards multiresistant microorganisms. In this communication, we present the synthesis, characterisation, and biological tests on bioluminescent *E. coli* of new asymmetric cationic porphyrin-cyclodextrin bioconjugates[3].

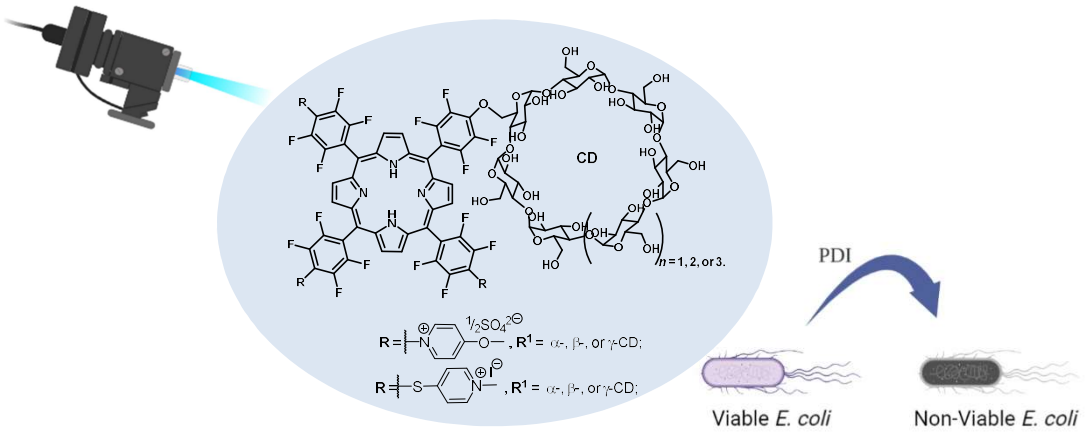

Figure 1. Structure of cationic porphyrin-cyclodextrin and an illustrative scheme of *E. coli* before and after PDI approach.

Acknowledgements

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References

[1] Ribeiro, C.P.S.; Lourenço, L.M.O. *Journal of Photochemistry and Photobiology C: Photochemistry Reviews* **2021**, 48, 100422.

[2] Ribeiro, C.P.S.; Gamelas, S.R.D.; Faustino, M.A.F.; Gomes, A.T.P.C.; Tomé, J.P.C.; Almeida, A.; Lourenço, L.M.O. *Photodiagnosis and photodynamic therapy*, **2020**, 31, 101788.

[3] Ribeiro, C.P.S.; Faustino, M.A.F.; Almeida, A.; Lourenço, L.M.O. *Microorganisms*, **2022**, 10, 718.

Synthesis and applications of new bisquinolizidine derivatives from bio renewable resources

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Bisquinolizidine alkaloids, such as (+)-lupanine, are found in several plants of the subfamily *Faboideae* including the genus *Lupinus*. These molecules are characterized by a common chiral bispidine core and possess a variety of biological activities, from antiarrhythmic and oxytocic properties to a partial agonist of the nicotinic acetylcholine receptor [1,2]. Our group have been developing methods for the sustainable isolation of these alkaloids [3]. Currently, our research interests include developing methodologies for the functionalization of bisquinolizidine alkaloids for medicinal chemistry applications. In this work, we present two synthetic strategies: a) synthesis of 17-substituted lupanine derivatives through the nucleophilic addition of Grignard reagents to the iminium ion derived from lupanine (Figure 1a); and b) synthesis of ammonium salts through N-alkylation reactions (Figure 1b). Finally, we present preliminary results of the biological activity of these bisquinolizidine derivatives.

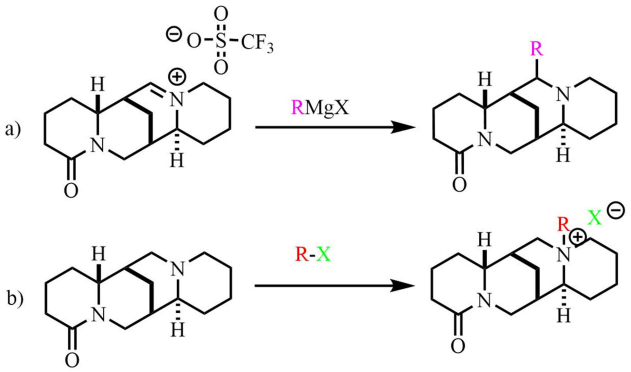

Figure 4 - Reaction scheme of the addition of Grignard reagents (a) and alkylation reactions (b).

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References

[1] T. Aniszewski, Biology of Alkaloids, 2nd Ed., Elsevier, 2015.

[2] V. S. Gawali, S. Simeonov, M. Drescher, T. Knott, O. Scheel, J. Kudolo, H. Kählig, U. Hochenegg, A. Roller, H. Todt, N. Maulide, ChemMedChem. 12 (2017) 1819-1822.

[3] N. Maulide, B. Peng, C. A. M. Afonso, R. F. M. Frade, Process for preparing enantiopure Lupanine and Sparteine, 2014, EP2808326A1.

Preparation of oxygenated metabolites of agrochemical active ingredients

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The development of plant protection products requires the safety profile analysis of active ingredients (AIs). This includes toxicity determination of AI metabolites. A very common phase-one metabolism reaction is C-oxygenation, catalyzed by cytochrome P450 enzymes[1,2]. Thus, the synthesis of oxygenated AI metabolites is of great importance to agrochemical producing companies, namely ASCENZA Agro[3], for safety evaluation purposes.

Herein, we describe the synthesis of hydroxylated aromatic metabolites of several AIs, using methods described by Tobias Ritter and co-workers[4] (**Figure 5**). This method allows the late-stage oxygenation of the aromatic positions, by generating mesylate derivatives with bis(methanesulfonyl) peroxide as an oxidant, followed by conversion to the corresponding phenols.

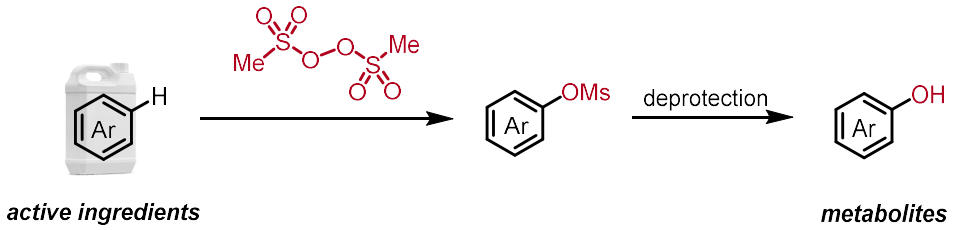

Figure 5. Synthetic route for the late-stage aromatic and benzylic oxygenation of AIs.

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References

[1] Reichl, F.-X.; Schwenk, M. *Regulatory Toxicology*, 2nd ed.; Reichl, F.-X., Schwenk, M., Eds.; Springer Nature Switzerland AG: Cham, Switzerland, **2021**.
[2] Guengerich, F. P. *Chem. Res. Toxicol. 14* (6), **2001,** 611–650.
[3] https://www.ascenza.pt/.
[4] Börgel, J.; Tanwar, L.; Berger, F.; Ritter, T. *J. Am. Chem. Soc. 140* (47), **2018**, 16026–16031.

β-Carboline indole alkaloid derivatives. Evaluation of their antiproliferative activity and ability as ABC transporter inhibitors

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Multidrug resistance (MDR) of cancer cells is one of the most pressing health issues of our days. The resistance of tumour cells to anticancer drugs can arise due to a multiplicity of factors, including the overexpression of ABC transporter proteins. Thus, the development ABC transporter inhibitors is considered among the most realistic approaches for overcoming MDR.

Aiming at finding new MDR reversers, a natural β-carboline indole alkaloid was derivatized. Twenty new urea derivatives were prepared by reaction with different aliphatic and aromatic isocyanates. Their structures were assigned by NMR data, including 2D NMR (HMQC and HMBC).

Firstly, the in vitro antiproliferative activity of selected compounds was evaluated on a panel of sensitive and resistant cancer cell lines. The IC50 values for each compound were determined by the 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenylthetrazolium bromide (MTT) viability assay. As a next step, the ability of the compounds to act as inhibitors for the ABC transporters P-gp and BCRP was investigated by flow cytometry.

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A Computational Approach to Combat Multiple Myeloma: Exploring EZH2-Proteasome Dual-Targeting Drug Discovery

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Enhancer of zeste homolog 2 (EZH2) is a histone methyltransferase with potential therapeutic applications in human cancer. EZH2 is frequently upregulated in cancer, and its overexpression has been found in solid tumors such as prostate cancer and multiple myeloma (MM), where it also plays a role in drug resistance development. Patients with MM have had no cure until recently, with the vast majority having developed resistance and/or relapse after first-line therapy with new medicines. Another key target in MM is the proteasome, which was revolutionized by the first proteasome inhibitor, bortezomib, roughly 15 years ago. Even though the FDA has approved multiple combination therapy combining proteasome inhibitors with other drugs, drug resistance remains a significant issue. To address this issue, researchers are increasingly interested in developing a multi-target medication that can block multiple targets or pathways at the same time. The simultaneous targeting of EZH2 and proteasome the 20S is a promising new technique because of a common route that suppresses EZH2 activity when the proteasome is inhibited. Here, we devised a cutting-edge computational strategy to identify and characterize combined EZH2 and 20S proteasome inhibitors as a possible therapeutic option for MM. To do so, known ligands for each protein were employed in docking studies against both proteins. Machine learning models were also used to investigate the characteristics that make a ligand active in each target. Finally, molecular dynamics simulations were performed with the top candidates identified by molecular docking experiments. These results will be presented and discussed.

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References

[1] Filipe Estrada, 2020, “Discovery and optimization of a multi-target strategy for proteasome inhibition: Development of models to predict its physical and pharmacological properties.”, MSc thesis, Faculty of Pharmacy, University of Lisbon, Lisbon

[2] Estrada, F.G.A.; Miccoli, S.; Aniceto, N.; García-Sosa, A.T.; Guedes, R.C. Exploring EZH2-Proteasome Dual-Targeting Drug Discovery through a Computational Strategy to Fight Multiple Myeloma. Molecules 2021, 26, 5574. https://doi.org/10.3390/molecules26185574

Sustainable development of trehalolipids using a cell-based approach towards anticancer activity

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Nowadays, glycolipids (GLs) biosurfactants are getting more and more attention due to their potential in such diverse fields as bioremediation, oil recovery, cosmetics, pharmaceutical and biomedical, among others. They show unique properties, like biological activities, as antimicrobial and antiviral, growth inhibition and differentiation-inducing activities against human leukemia cells, as gene delivery carriers with increased gene transfection in mammalian cells in gene therapy of cancer. GLys are amphiphilic components, composed of a hydrophilic polar sugar head group and a hydrophilic apolar lipid moiety. They are usually produced extracellularly on living surfaces by microbial sources. One of these GLs belongs to the trehalose families. Important properties of these compounds include mild production conditions, lower toxicity, higher biodegradatibility, environmental and biocompatibility.

The goal of this work was the optimization of the sustainable production and the downstream processing of trehalolipids (TLS), in a cost-effective mode.

In this work trehalolipids were produced by *Rhodotorula sp*, using a microscale approach. The trehalolipids production was followed by HPLC-MS. Medium composition regarding carbohydrate and fatty acid sources, initial concentration of nutrients, stoichiometric ratio of carbon / nitrogen and fermentation time were studied. A quality by design approach was used as part of the optimization process. Among the inorganic salts tested, ammonium salts were preferred nitrogen sources for SL production. The kinetics of *Rhodotorula sp* growth at the different media used and the respective TLS production will be presented. Extraction of the trehalolipids was carried out and they were characterized by conductivity and tensiometry. Biological activity of trehalolipids was evaluated.

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Andrographolide derivatives with antiproliferative activity against resistant cancer cells

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Cancer is the second most common cause of mortality and morbidity worldwide. Despite the advances in cancer treatment, drug resistance remains a challenging task for medicinal chemists. Aiming at developing new compounds for overcoming drug resistance, a set of derivatives of andrographolide, a major constituent of Andrographis species (Acanthaceae), was prepared. Twenty-one new triazoles were obtained by introducing an azide group into the acetylated derivative of andrographolide and subsequent reaction with alkynes. The compounds were elucidated mainly by NMR, including bidimensional (COSY, HMBC, HSQC) experiments. The antiproliferative activity of some of these compounds was evaluated against a panel of human cancer cell lines from pancreas (Panc-1), breast (MCF7, MDA-MB-468), and ovarian (IGROV-1). The compounds were found to be cytotoxic, displaying IC_{50} values < 10 µM. They were also evaluated against a non-malignant fibroblast cell line (HFF-1) and some of the derivatives were found to be slightly selective.

Acknowledgements

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Design and development of novel heterobifunctional degraders targeting AKT protein kinase

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Akt is a serine-threonine kinase belonging to the Phosphatidylinositol-3-kinase signalling pathway which plays a key role in regulating fundamental physiological processes such as cell proliferation and survival, apoptosis and angiogenesis. The aberrant activation and overexpression of such kinase has been detected in various types of malignancies and, in particular, it has been associated with the proliferation and survival of cancer cells. Given its major role in tumorigenesis and resistance to anticancer treatments, Akt represent a valid therapeutic target for treating and preventing cancer and numerous efforts have been made in order to design agents capable to modulate the activity of this critical protein. Accordingly, a wide variety of Akt inhibitors, including ATP-competitive and allosteric inhibitors have been developed. However, despite many of them are associated with nanomolar potency and are currently in different stages of clinical development, they showed poor selectivity and clinical efficacy.[1-3] Additionally, Akt has been showed to be provided with kinase-independent functions which cannot be silenced with conventional inhibition approaches, thus leading to urgent need of new therapeutic strategies capable to entirely modulate the Akt protein activity.[2] A promising alternative exploits targeted protein degradation by using Proteolysis Targeting Chimeras (PROTACs), heterobifunctional molecules consisting of a target binder and an E3 ligase-recruiting ligand tethered by a linker able to promote target degradation via hijacking the endogenous ubiquitin proteasome system. PROTAC technology has contributed to a paradigmatic shift in drug discovery revealing remarkable advantages compared to the conventional inhibition approach and demonstrating great potential both as a therapeutic and as a biological probe. Numerous PROTAC degraders have been designed against a broad spectrum of clinically relevant targets allowing to significantly extend the druggability space with its unique mechanism of action.[2, 3] The rationale of this work is that a targeted degradation-based approach could represent a valid alternative to achieve a more efficient and lasting Akt inactivation. In particular, the present work is aimed at the rational design and characterization of a library of novel Akt-targeting PROTACs based on the potent Akt allosteric inhibitor Miransertib which is currently under clinical investigation for the treatment of solid tumours and Proteus syndrome.[1]

Acknowledgements

Support for this work was provided by Fundação para a Ciência e a Tecnologia. The author acknowledges financial support from grant 2021.05358.BD

References

[1] Lazaro, G. et al. 2020, 48(3), 933-943;

[2] Yu, X. et al. 2021, 64(24), 18054-18081;

[3] Yu, X. et al. 2022, 65(4), 3644-3666.

Design of a new gemini lipoaminoacid with lipase sol-gel bioimmobilizates towards gene delivery

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Lipoaminoacids (LAA) are an important group of biosurfactants, formed by a polar hydrophilic part (amino acid) and a hydrophobic tail (lipid). The gemini LAA structures allow the formation of a supramolecular complex with bioactive molecules, like DNA, which provides them with good transfection efficiency. Lipoamino acids (LAA) are biocompatible and biodegradable biosurfactants, a promising alternative to viral vectors in gene delivery.

Lipases are naturally involved in lipid and protein metabolism, so they are an alternative to the chemical production of LAA, offering an eco-friendly biosynthetic process option. This work aimed to design the production of novel cystine derived gemini through a bioconversion system using immobilized lipase. The lipase Porcine Pancreatic Lipase (PPL) was used, immobilized in sol-gel lenses. L-cystine dihydrochloride and dodecylamine were used as substrates for the bioreaction. The production of LAA was evaluated by TLC, and colorimetric reaction with eosin. The identification and quantification was carried out by HPLC-MS/MS. A new medium was developed where dodecylamine was melted and added to the cystine and to the biocatalyst, building a system of mainly undissolved substrates, leading to 5 mg/mL of LAA. For the first time the gemini derived cystine lipoaminoacid was produced, identified and quantified in in both co-solvent and solvent-free media, with the lipases PPL. The self-assembly behaviour of LAA solutions, in absence or presence of DNA, was studied by conductivity and fluorescence regarding the application as transfection agents.

References

Carvalho, P.M., Guedes, R.C., Bronze, M.R., Faustino, C.M.C., Ribeiro, M.H.L. Design of a new gemini lipoaminoacid with immobilized lipases based on an eco-friendly biosynthetic process. *Catalysts*, 2021, 11(2), pp. 1–27, 164

Faustino, C., Martins, T., Duarte, N., Ribeiro, M.H. Self-Assembly of Lipoaminoacids-DNA Based on Thermodynamic and Aggregation Properties*Journal of Surfactants and Detergents*, 2020, 23(3), pp. 581–593

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Finding new potential inhibitors of PBP2a from methicillin resistant *Staphylococcus aureus*

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is a worldwide concern that requires new management approaches. MRSA is a major cause of nosocomial infections, with a high mortality rate due to multi-resistance to β-lactams. MRSA resistance is related to the acquisition of a PBP2a-coding *mecA* gene; the mecA protein has low affinity to β-lactams, preventing their antibiotic action. *S. aureus* PBP2a adopts a closed conformation, inaccessible for β-lactams, due to changes at a serine nucleophile in the active site and to the presence of a loop protecting the active site from inhibitors. Conformational changes of this loop are regulated allosterically. Thus, there is a pressing need for innovative antibiotics to control resistance in these strains.

In this work, a structure-based computational molecular docking screening approach was employed, using the X-ray structures of the closed and open PBP2a conformations (PDB ID 1vqq and 3zg0, respectively). Different ring-sized lactams, fluorenone, flavone and quinazolinone derivatives were tested as possible inhibitors for both catalytic and allosteric sites. Known specific inhibitors were also tested. Molecular dynamics simulations were deployed to understand whether binding of natural substrate and most promising hit compounds can induce protein conformational changes.

The PBP2a known inhibitor, L-695256, displayed the best results, with binding affinities of -6.2 kcal.mol^{-1} for the allosteric site in the native PBP2a and -9.4 kcal.mol^{-1} for active site of acylated PBP2a protein (PDB:3zg0). Promising hit compounds tested in this work presented significant improvements in affinity for both catalytic sites, for instance, -8.1 kcal.mol^{-1} for the allosteric site in the native PBP2a (PDB:1vqq) and -12.1 kcal.mol^{-1} for active site of acylated PBP2a protein (PDB:3zg0). Hit compounds maintained the expected interactions to the protein has known inhibitors. These obtained lower binding energies for these interesting scaffolds present significant improvements in affinity for both sites. Moreover, binding of one of the most promising hit compounds to the allosteric site induce protein conformational change and subsequently to a more accessible catalytic residue.

These results indicate that tested compounds are promising hits targeting PBP2a protein from MRSA, contributing towards their potential use to overcome β-lactam resistance. Currently, more molecular dynamics simulations are being deployed to understand whether the binding of other hit compounds to the allosteric site can induce protein conformational change, contributing to a more accessible active site.

Acknowledgements

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biobank|CQE: a powerful tool for medicinal chemistry

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Biobanks are crucial tools for translational research. The biobank|CQE has been created to support the development and testing of new molecules with possible health benefits, and as a repository of human and non-human samples relevant to the Centre's research.

Currently, the biobank|CQE gathers a collection of human specimens, ranging from blood samples and isolated blood cells, to preserved tissues and subcellular fractions, as well as animal tissues.

Human samples have been used to develop cellular models in order to study the effects of commercial drugs on the activity of immune cells. This approach relies on the isolation of immune cells from healthy donors, exposure of those cells to specific drugs and the identification of altered pathways resorting to MS-based techniques.

As the biobank|CQE also collects samples from medicated donors, the previously identified altered pathways are also being identified in blood samples of such donors and correlated with their medication. This double-edge approach allows for the quick and simple identification of possible drug-side effects that can be used in drug repurposing approaches.

On the other hand, the resources of the biobank|CQE allow the rapid screening of numerous molecules to probe their toxicity or biological activity, in different cellular targets.

An overview of the different resources and their application to study molecules as possible new drugs will be given.

Acknowledgements

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Magnetic and imprinted cross-linked enzyme aggregates of rhamnopyranosidase in microbioreactors towards neuroprotective bioactive compounds

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Magnetic and imprinted cross-linked enzyme aggregates (mCLEAs) have emerged as interesting biocatalyst design for purification and immobilization of enzymes. The CLEAs technology present many advantages, as it is simple and amenable to rapid optimization, leading to low costs and short time to-market processes.
The group of polyphenols has an important therapeutic value, with emphasis on anti-oxidant and anti-inflammatory actions, and recent studies point to considerable neuroprotective effects in different pathologies, including neurodegenerative diseases. One of the problems associated with these compounds is their reduced availability on the market, since they are obtained from the extraction of plants. This group includes flavonoids such as naringin, hesperidin or rutin, which naturally occur in fruits. Some studies have shown that the biological activity is dependent on the (de) glycosylation of the molecules. The *α*-rhamnopyranosidase (Rhnase) catalyzes the hydrolysis of a broad spectrum of natural sugars, including polyphenolic compounds. The major sources of this enzyme production are filamentous fungi and yeasts. Rnase is an enzyme commercially attractive, due to is potentially useful in food and pharmaceutical industries.
The main goal of this work was the development of a viable and economic process for the production and purification of rhamnopyranosidase (Rhnase) from the filamentous fungi - *Aspergillus niger* and *Beauveria* and *Pichia pastoris*, using a microscale approach in batch and fedbatch mode. The strains were inoculated onto PDA media. Several parameters were evaluated in the production of Rhnase with optimum activity: type of fungus, growth time, presence of inducers (rhamnose, naringin, sucrose), use of specific substrates to test α-L-rhamnosidase and β-D-glucosidase activity (p-NPR, p-NPG) and nonspecific substrates (rutin, naringin, hesperidin, among others). The enzyme was concentrated and purified using different conditions and was immobilized onto magnetic particles in cross-link enzyme aggregates (CLEAS). Afterwards the biocatalyst was used in a microreactor in batch and fedbatch mode, at different flow rates with evaluation of volumetric productivity. The biosynthetic compounds target the microglial cells as their therapeutic target, playing their neuroprotective role.

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The Boron Hot-Spot Methodology: Peptide Functionalization

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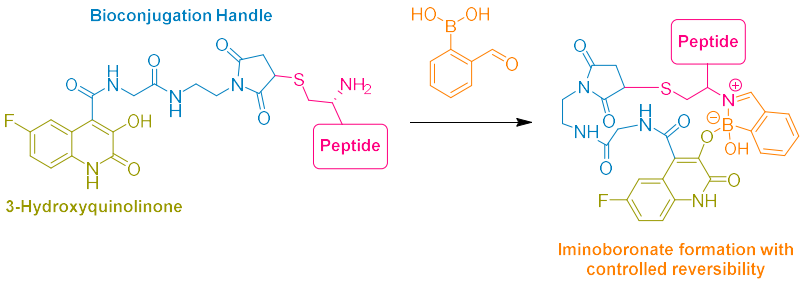
Bioconjugation strategies allow the combination of biomolecules and a variety of payloads with different properties. Recently, several bioconjugates reached the market as therapeutics with high-specific targeting capacity. [1] While most of these strategies relies on the formation of stable constructs under complex physiological conditions, stimuli-responsive constructs are being developed to be applied in drug delivery and live-cell imaging. [1,2] Boronic acids (BA) can be explored as a molecular construction tool due to their ability to establish reversible covalent bonds with vicinal/nitrogen nucleophiles. [1,3]

Here, we developed a "boron hot-spot" (BHS) with the ability to be installed specifically on N-terminal cysteines (Cys) of peptides chains. The BHS is composed by a bioconjugation handle and a 3-hydroxyquinolinone heterocicle (3HQ) that stabilizes the formation of iminoboronates in the presence of the boronic acid. (Scheme 1). The incubation of the BHS-Cys with 2-formylbenzeneboronic acid (2-FBBA) in ammonium acetate solution (20 mM, pH 7.0) afforded the desired imine within 2h at 37 °C. Electrospray ionization mass spectrometry (ESI-MS) studies were performed, showing the compatibility of the BHS with different amino acid side chains and competing functionalities. Installed in more complex peptides (c-Ovalbumin and RGD), the BHS favors the N-terminal iminoboronate over the formation of in-chain iminoboronates. Exhibiting an N-terminal and an in-chain Cys residue, RGD was used to install two BHS, but only the N-terminal modification promoted the assembly with 2-FBBA. The resulting iminoboronates showed to be stable in ammonium acetate solution at pH 7 and 4.5 or in the presence of bovin serum albumin (BSA), although in the presence of glutathione they showed to be reversible.



Scheme 1. BHS Methodology

Acknowledgements

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References

[1] António, J. P. M.; Russo, R.; Carvalho, C. P.; Cal, P. M. S. D., Chem. Soc. Rev., 2019, 48, 3513.
[2] Koniev, O.; Wagner, A. Chem. Soc. Rev. 2015, 44 (15), 5495–5551.
[3] Boutureira, O.; Bernardes, G. J. L. Chem. Rev. 2015, 115 (5), 2174–2195

ERCCI-XPF complex small molecule inhibitors: A novel *In silico*-based drug discovery protocol

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Non-small cell lung cancer (NSCLC), the most common subtype among lung cancer cases, presents low survival rates due to late diagnosis and metastasis progression. Adjuvant platinum-based chemotherapy is usually the first-line therapeutic approach. The overall survival and resistance to cisplatin in NSCLC has been correlated with ERCC1 gene overexpression. ERCC1 forms a complex with XPF that has a determinant role in the Nucleotide Excision Repair pathway, being thus an attractive target in oncology. The purpose of this work was to develop a strategy aiming at identifying novel and more efficient ERCCI-XPF complex small molecule inhibitors by devising a computer-based drug design (CADD) protocol to potentiate cisplatin's efficacy and overcome resistance.

The CADD protocol aimed at the curation of the databases to screen, target selection and preparation, and optimization of the computational protocols needed (e.g. molecular docking, structure-based virtual screening, inhibitors fingerprints, and descriptors, among others) to identify potential hit compounds. Firstly, an exhaustive structural and physicochemical characterization of the ERCC1-XPF complex was performed. This analysis particularly focused on the potential binding site, and key features that could possibly disrupt the complex stability. A library of small molecule inhibitors with reported activity against the ERCCI-XPF complex was retrieved from ChEMBL and curated. The MOEv09.2020 was used to visualize and prepare the protein and the library (e.g. protonation, isomers, tautomers) to screen. Molecular docking and virtual screening were achieved using GOLD v2020.1 software, and the results were analyzed according to poses, binding affinities, and quantitative protein-ligand interaction fingerprints. The screening protocol incorporated the use of different filters to reduce the selection of pan-assay interfering compounds and increase the probability of identifying chemotypes with optimal drug-like properties. Our findings illustrate the importance of small-molecule key features for the inhibition of ERCCI-XPF endonuclease activity and provided important insights that allowed the discovery of potential inhibitors with new chemotypes.

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Exploring a new drug design strategy based on pocket similarity between druggable and undruggable proteins

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The pharmaceutical industry is currently facing a problem related to the overuse of the same therapeutic targets for disease treatments. To solve that problem, it's necessary to search for novel targets in the unexplored human genome, and the most efficient way of doing that is by using *in silico* methods. Over the years massive amounts of data related to both, proteins and small molecules with biological effects have been stored in databases, and currently, their entirety is only possible through computational strategies.

In this work, we propose a strategy to take advantage of the protein pockets' similarity and determine whether those with information pointing out to be improbable potential therapeutic targets might not be validated. For that, we treated the therapeutic targets from the ChEMBL database and filtered them into groups based on the work done by Oprea et al[1]. We created two groups for comparison between them: one consists of the proteins lacking chemical association with biologically active molecules or proteins that weren't explored yet for drug targeting and named them the Potential Target Candidates (PTC) group, and the other group denominated as Well-Knowns (WK) group consisting of proteins that have at least one registered interaction directly with a mechanism of action with an approved drug or targets that have no known mechanism of action with approved drugs but are known to easily bind small molecules with registered effect on diseases. We determined both groups' protein cavities through CAVIAR[2] (CAVity Identification and Rationalization) and using PocketMatch[3] ran a similarity search between the Potential Target Candidates' cavities and the binding pocket of each Well-Known target.

The similarity search revealed promising matching results between the two groups. The computational strategy developed and the results will be presented and discussed.

Acknowledgements

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References

[1] Oprea, T. I.; Bologa, C. G.; Brunak, S. et al., Nature 17(2018) 317-332

[2] Marchand J.-R., Pirard B., Ertl P. et al., Journal of Computer-Aided Molecular Design 6(2021) 737-750

[3] Yeteru K., Chandra N., BMC Bioinformatics 1(2001) 1-17

Development of Novel Ripk1 inhibitors Targeting Necroptosis Pathway

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Necroptosis is a form of programmed cellular death, alike apoptosis, although it also presents necrosis characteristics, such as membrane rupture, with externalization of cellular content leading to inflammation [1]. Overactivation of necroptosis is linked to worsening prognosis in various inflammation related pathologies [2]. Recent studies have shown potent inhibitors for this death mechanism [1]; however, none have been approved to be used therapeutically. The present research aims to develop necroptosis inhibitors specific for receptor binding serine threonine protein kinase 1 (RIPK1), based on a scaffold discovered in high throughput screening (Figure1) [3]. Synthesis is accomplished by a process of converging synthesis, allowing for derivatization of the model pharmacophore, including substitutions to the benzimidazole ring, as well as varying the heteroaromatic ring and its lateral group. Currently eight compounds have been synthesized and will be tested for their specificity for the target and inhibitory activity.

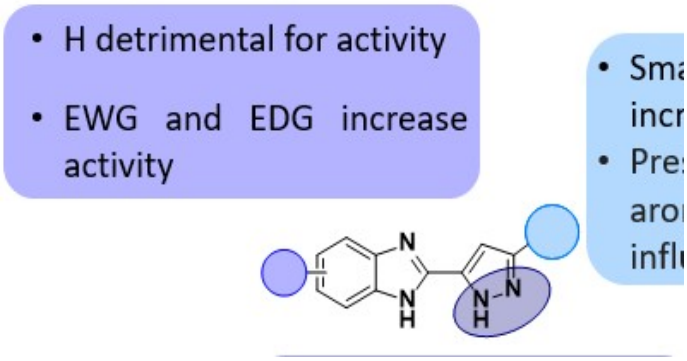

Figure 6 - Scaffold discovered in High Throughput Screening, illustrating the structure activity relation on the variable sites.

Acknowledgements

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References

[1] Zhuang C, Chen F. Small-Molecule Inhibitors of Necroptosis: Current Status and Perspectives. J Med Chem 2020; 63: 1490–1510.

[2] Liu X, Xie X, Ren Y, et al. The role of necroptosis in disease and treatment. MedComm 2021; 730–755.

[3] Brito, H.; Marques, V.; Afonso, M. B.; Brown, D. G.; Börjesson, U.; Selmi, N.; Smith, D. M.; Roberts, I. O.; Aniceto, N.; Guedes, R. C.; Moreira, R.; Rodrigues, C. M. P. Cell Death Discov. 2020.

Computer-aided drug design campaign in the search for new dual inhibitors for Multiple Myeloma

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Multiple myeloma in the United States (US) alone accounts 1.8% of all new cancer cases in 2020, with an estimated 32,270 new cases. In 2020 the number of deaths as a result of multiple myeloma (MM) are already 12,830, representing 2.1% of all cancer deaths. In the US, there were an estimated 140,779 people living with multiple myeloma, in 2017 [1]. Recent studies revealed that relapse of myeloma developed due to acquisition of resistance to proteasome inhibitors, owing to mutations of proteasome complex, upregulation of transporter channels, or cytochrome components, and induction of alternative compensatory pathways [2]. Proteasomes are large, multicatalytic protein complexes that cleave cellular proteins into peptides. Proteasome inhibitors are an important class of drugs for the treatment of multiple myeloma and mantle cell lymphoma, and they are being investigated for other diseases. The key nuclear export protein CRM1/XPO1 may represent a promising novel therapeutic target in human MM. Here we showed that chromosome region maintenance 1 (CRM1) is highly expressed in patients with MM, plasma cell leukemia cells and increased in patient cells resistant to bortezomib treatment [3]. In this work, we propose a multitarget approach in which we employ computational strategies to identify dual proteasome and CRM1 inhibitors that could overcome resistance in MM and other cancers. We created 3D-pharmacophore models, using MOE2020 software to support hit finding. Pharmacophore models were made for both proteasome and CRM1 targets. Molecular docking was performed in both models to predict possible dual inhibitors. The performance of all models was validated against robust databases and the most predictive models were optimized further by systematic modification of the chemical features. The results revealed valuable information about the key interactions and the 3D-geometries associated with proteasome and CRM1 dual inhibition activity.

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Fernandes P.M.P. acknowledges financial support from PD/BD/143158/2019.

References

[1] National Cancer Institute. SEER Cancer Stat Facts https://seer.cancer.gov/statfacts/html/mulmy.html.

[2] Soriano, G. P. et al., Leukemia 30 (2016) 2198–2207.

[3] Tai Y.T. *et al.*, Leukemia 28 (2014) 155-65.

P-glycoprotein inhibition from *Plectranthus* royleanone diterpenoids

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The development of multi-drug resistance (MDR), including the overexpression of membrane transport proteins like P-glycoprotein (P-gp), continues to be a major impediment to effective treatments in cancer therapy. With the global number of tumor cases increasing, the search for novel anti-cancer therapeutics is essential. Known for their medicinal properties, *Plectranthus* species are rich in diterpenes, such as the 7α-acetoxy-6β-hydroxyroyleanone (**Roy**), which has previously demonstrated cytotoxicity against various cancer cell lines, including NCI-H460 [1]. Based on molecular docking studies [2], 10 hemi-synthetic derivates of **Roy**, that displayed strong P-gp interactions *in silico,* were prepared. The antitumoral activity of the compounds **1**-**10** was tested against resistant human cancer cell lines NCI-H460/R and DLD1-TxR. Cell viability and cell death induction were assessed using MTT assay and by Annexin V/PI, respectively. The results showed that derivatives **2**, **3** and **4** have the most prominent selectivity (selectivity index, *SI* = 2.7, 2.3 and 2.6 times, respectively) towards cancer cells, compared to normal lung fibroblasts MRC5. Moreover, the same derivatives showed a reduction in P-gp activity in Rho123 accumulation assay and indicated P-gp inhibition in the DOX accumulation assay in resistant cell lines NCI-H460/R and DLD1-TxR. Overall, it was demonstrated that three abietane diterpenoid derivatives induced P-gp inhibition in MDR cancer cell lines, standing as novel selective compounds for the treatment of lung and colon cancer. Further investigations are ongoing for the preparation of new analogues starting from other biologically active diterpenoids, as potential hits for the synthesis of new P-gp modulators.

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References

[1] Garcia C, *et al*. *Current Pharmaceutical Des*. **2019**; 24(36):4207–36.
[2] Isca V, *et al*. *ACS Medicinal Chemistry Letters*. **2020**; 11 (5), 839-845.

DEVELOPMENT OF NOVEL NECROPTOSIS INHIBITORS: TARGETING RIPK1

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Necroptosis, a regulated form of necrosis, is the major mechanism of cellular death upon extracellular inflammatory signalling and is crucially dependent on the kinase activity of RIPK1 and its downstream mediators: RIPK3 and pseudokinase MLKL. Consequently, RIPK1 has emerged as a promising therapeutic target for the treatment of a wide range of human neurodegenerative, autoimmune, and inflammatory diseases.[1-3]

To address the scarcity of chemotypes targeting necroptosis and RIPK1, iMed.ULisboa recently developed a phenotypic high-throughput screening strategy to identify novel necroptosis inhibitors from a library of more than 250,000 compounds (AstraZeneca).[4] This collaborative effort led to the discovery of several new compounds active against RIPK1 and/or RIPK3, including a small set of compounds containing a 2,5-disubstituted thiazole scaffold (**Figure 1)**.

Taking into account the gathered knowledge, and following Computer-Aided Drug Design (CADD) investigations, we have synthetized a highly diversified library of thiazole-based analogues in order to identify the structural features that determine necroptotic activity and contribute to RIPK1's selectivity.

We now report the first insights on the structure-activity relationships (SAR) relevant for antinecroptotic activity, disclosing promising hit compounds with potencies (EC_{50} values) within the low micromolar range, in both murine and human cell lines. More so, the undergoing RIPK1 inhibition investigations will add crucial insights into the thiazole-based library's ability to modulate RIPK1 activity.

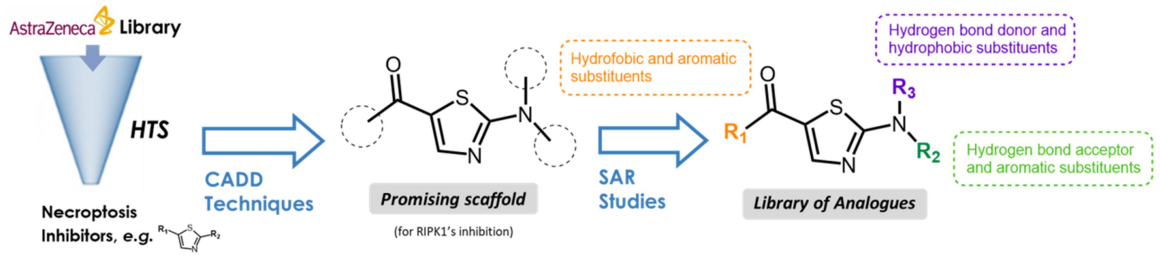

Figure 1. Overall strategy for probing the chemical space around the thiazole's core structure.

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References:

[1] Liu X, Xie X, Ren Y, et al. The Role of Necroptosis in Disease and Treatment. MedComm, (2021), 2, 730–755.
[2] Degterev, A.; Ofengeim, D.; Yuan, J. Targeting RIPK1 for the Treatment of Human Diseases. Proc. Natl. Acad. Sci. (2019), 116 (20), 9714-9722.
[3] Coornaert, I.; Hofmans, S.; Devisscher, L.; Augustyns, K.; Van Der Veken, P. . D. M.; G. R. Y.; Martinet, W. Novel Drug Discovery Strategies for Atherosclerosis That Target Necrosis and Necroptosis, (2018), 477-488.
[4] Brito, H.; Marques, V.; Afonso, M. B.; Brown, D. G.; Börjesson, U.; Selmi, N.; Smith, D. M.; Roberts, I. O.; Fitzek, M.; Aniceto, N.; et al. Phenotypic High-Throughput Screening Platform Identifies Novel Chemotypes for Necroptosis Inhibition. Cell Death Discov. (2020), 6 (1).

Azobenzene photoswitches to modulate VEGFR2 inhibition

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Angiogenesis is a highly controlled process in healthy adults but also plays a key role in tumor growth. VEGFR2 is a dynamic and crucial tyrosine kinase receptor involved in angiogenesis.[1] Thus, targeting VEGFR2 with selective inhibitors can be regarded as a promising anticancer therapy and a useful strategy to understand the dynamic behavior of this enzyme. Photopharmacology is a powerful tool to reduce side effects in cancer therapy since photoactive ligands are designed to interact with their targets only after light exposure.[2,3]

In the present study we aim to expand the toolbox of anti-angiogenic agents by developing new photoactivatable inhibitors based on known VEGFR2 inhibitors that can be exclusively activated *in situ* using light of biocompatible wavelength, suitable for cells and, ultimately, for living tissues. These transformations will generate configurational isomers with distinct geometries displaying differentiated behavior when interacting with the target. For this purpose, a new sorafenib derivative (Figure 1), with an azobenzene photoswitch incorporated into the structure of the known VEGFR2 inhibitor, was synthesized and characterised for its photochemistry. The new compound exhibits the desired photoswitching properties for the pursued applications (biocompatible light excitation, high switching efficiency, high *E-Z*/*Z-E* conversion, good fatigue resistance, and thermal stability of *Z*-isomer).

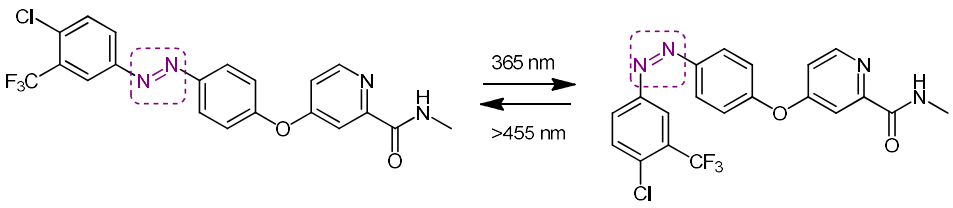

Figure 1: Photoswitchable sorafenib derivative.

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References:

[1] a) González, S. D.; Marion, N.; Nolan, S. P., *Chem. Rev.* **2009**, *109*, 3621. b) Hahn, F. E., *Angew. Chem. Int. Ed.* **2006**, *45*, 1348.

[2] Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V., *Chem. Soc. Rev.* **2011**, *40*, 5336.

[3] Velema, W. A.; Szymanski, W.; Feringa, B. L., *J. Am. Chem. Soc.* **2014**, *136*, 2178.

Development of new drugs to treat tuberculosis based on the dinitrobenzamide scaffold

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Despite the efforts made to stop the tuberculosis (TB) epidemic, it still remains one of the leading causes of death from an infectious disease [1]. In particular, the recent rise in multidrug resistant variants has left the scientific community worried, creating an urgent need for the discovery of new effective drugs against both drug-susceptive and drug-resistant TB. A promising new target for such compounds is DprE1. This epimerase is essential for the formation of a vital precursor of the arabinogalactan biosynthesis, one of the components of the mycobacterial cell wall. Numerous inhibitors of this target have been described, among them nitrobenzamides [2]. The literature available for nitrobenzamides potentially acting on DprE1 show a multitude of structural features, most of which can be classified in three parts: a nitroaromatic amide, a linker and a terminal group. It is believed that these inhibitors act on DprE1 through the formation of a covalent bond with Cys387. Previous work in the group has led to derivatives that showed promising activities against *Mycobacterium tuberculosis.* We are developing compounds based on the DNB scaffold that take in consideration these previous results in order to create more active inhibitors. To synthesize our library of compounds we started by joining the linker, by nucleophilic addition/elimination using an acid chloride, and then we joined the last aromatic moiety via Mitsunobu reaction. Compounds synthesized show relevant activity (MIC ranging from 30 to 150 nM), hence we are also developing a docking approach to try to confirm the mode of action of our inhibitors and to guide the synthesis of the next compounds.

Acknowledgements

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References

[1] World Health Organization Global Tuberculosis Report; 2021; ISBN 9789240037021.

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

Synthesis of Unnatural Conformationally Constrained Amino Acids by Cross-Dehydrogenative Coupling

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Metal-catalyzed cross-dehydrogenative coupling (CDC) has emerged in recent years as a powerful technique to make C–C bonds or C–X bonds (X = N, O, S, P) directly from two C–H bonds or a C–H and an X–H bond [1–3]. No prefunctionalization is required, only an oxidant to act as the terminal acceptor of the two hydrogen atoms. Coupled with homogeneous catalysis with earth abundant metals, e.g. Cu, Fe or Co, cheap and nontoxic, CDC provides environmentally friendly processes which are atom-, energy-, time- and cost-efficient. We have explored oxidative amination, i.e. C–N bond formation under oxidative conditions, as a means to obtain conformationally constrained amino acids functionalized with imides.

Since the imide group is also an important pharmacophore present in a large range of medicinally important molecules, e.g. antiepileptic, antineoplastic and anti-Parkinson drugs, amongst others (Scheme 1a), the new compounds are of interest for peptidomimetics, drug design and also for synthetic applications [4,5]. Scheme 1b highlights the method developed.

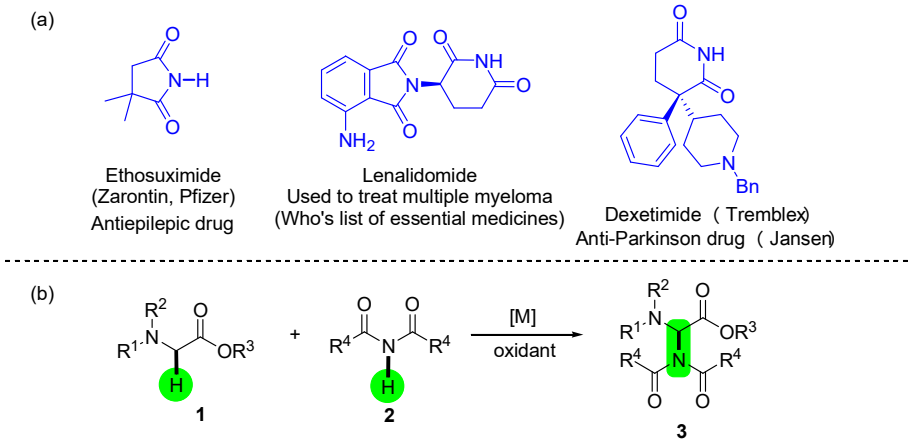

Figure 1. (a) Examples of pharmacologically important imides; (b) The method developed.

Acknowledgements

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References

[1] A. M. Faisca Phillips, A. J. L. Pombeiro, ChemCatChem 10 (2018) 3354.

[2] C.-Y. Huang, H. Kang, J. Li, C.-J. Li, J. Org. Chem. 84 (2019) 12705.

[3] A. M. Faisca Phillips, M. F. C. Guedes da Silva, A. J. L. Pombeiro, Catalysts 10 (2020) 529.

[4] M. A. T. Blaskovich, J. Med. Chem. 59 (2016) 10807−10836.

[5] J. J. Li, Imide-Containing Synthetic Drugs, in: F. A. Luzzio (Ed.), Imides, Medicinal, Agricultural, Synthetic Applications and Natural Products Chemistry, Developments in Organic Chemistry, Elsevier, Amsterdam, 2019, pp. 353-366.

Development of Novel Hybrid Compounds based on the Triazene Scaffold as a Strategy to Fight Metastatic Melanoma

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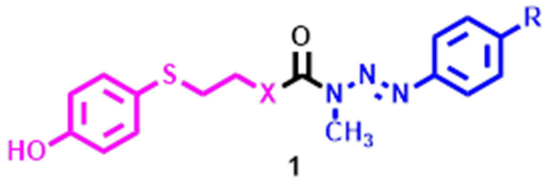
Metastatic melanoma is one of the most untreatable skin tumours, with all current therapeutic regimens showing low response levels and very limited survival rates (less than 10% after 10 years)[1]. Currently, different strategies such as immunotherapy, chemotherapy, and combination therapy are used to treat metastatic melanoma, however, most of them lack selectivity and demonstrated more toxicity rather than improved overall survival[2]. Therefore, new approaches to manage this deadly disease are highly urgent, not only to enhance the cure rate but also to extend clinical benefits to patients[1]. Molecular hybridization is one of the most promising medicinal chemistry strategies for developing novel molecular entities to overcome the limitations of current chemotherapeutic treatments. In this work, we synthesized a new series of hybrid molecules 1 (Figure 1) with two different pharmacophores: a DNA alkylator, the monomethyltriazene (blue), and a sulfur tyrosine analogue that specifically target malignant melanoma cells (pink). It is expected that hybrid compounds 1 will be active only in melanoma cells after tyrosinase activation an enzyme overexpressed in these tumour cells.



1

R= CN, Br, CH_3, $COCH_3$, CO_2Me, CO_2Et, $CONH_2$
X= O, S

Figure 1- General structure of hybrid compounds

The parent molecules were hybridized through a carbamate linker and the compounds were obtained with yields between 50% and 65%. The hybrids were characterized by ^{1}H NMR, ^{13}C NMR spectroscopy. Preliminary stability studies by HPLC were performed and showed half-lives ($t_{½}$) > 96h in phosphate buffer saline (PBS) and $t_{½}$ > 7h in human plasma. Subsequently, the hybrids will be evaluated as tyrosinase substrates and as cytotoxic agents in melanoma cancer cell lines.

Acknowledgements

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References

[1] Shailender B, Scott S. Tykodi, John A. Thompson, MD, Oncology. 23 (2009) 488-496.

[2] Francisco AP et al, Curr Pharm Des, 25 (2019) 1623-1642.

Development of nano-based drug delivery system to target infections

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Osteomyelitis treatment is highly challenging due to the need of high levels of antimicrobials employed by extended periods of time [1]. Innovative options of targeted and controlled drug delivery systems, presenting sustained antimicrobials release, high concentrations of drugs at the infected areas and low concentrations in the blood stream need to be considered [2]. In this context, the aim of the study was to develop a stabilized chitosan nanoparticulate (NPs) system loaded with minocycline, a tetracycline antibiotic with broad spectrum antimicrobial activity against osteomyelitis associated pathogens [1,2].

Stabilized NPs were prepared using the ionotropic gelation technique according to previously optimized method in our lab [1]. Nanoparticles were characterized in terms of particle size distribution and polydispersity index (PDI) by dynamic light scattering (DLS), as well as the surface charge by zeta potential. The drug loading (DL%) and encapsulation efficiency (EE%) of minocycline in the nanoparticulate system was evaluated. Minocycline quantification was estimated by spectrophotometry. Furthermore, NPs antimicrobial activity was assessed by the broth microdilution method against *Staphylococcus aureus* (ATCC® 25923TM) [2].

The stabilized NPs (blank and loaded with minocycline) presented particle size of 260-360 nm with a PDI of 0.300-0.400 and a zeta potential of +15-+20mV. NPs efficiently encapsulate minocycline (%EE = 17.3±2.2%) presenting a %DL of 1.7±0.2. Minocycline loaded NPs showed a minimum inhibitory concentration value of 16 μg mL^{-1}. Further studies are planned to further characterize minocycline loaded chitosan nanoparticles.

Acknowledgements

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References

[1] Martin, V., Ribeiro I.A.C., Alves M.M., Gonçalves L., Almeida A.J., Grenho L., Fernandes M.H., Santos C.F., Gomes P.S., Bettencourt A.F., Int. J. Pharm. 572 (2019), 118821.

[2] Matos, A.C., Marques, F., Pinto, R., Ribeiro, I.A., Gonçalves, M. L.M., Vaz, A., Ferreira, J. Almeida, A., Bettencourt, A.F., Int. J. Pharm. (2015), 200-8.

Methanolic extracts from *Plectranthus* spp. and their biological activity for dermocosmetic uses

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The search for natural products as active ingredients in cosmetics has gained increased interest among the scientific community in recent years. *Plectranthus* spp. is a well-known genus used in traditional medicine for skin conditions. It belongs to the Lamiaceae family and is distributed in tropical areas of the globe.

The aim of this work was to scientifically validate the use of these species for skin disorders and to probe potential applications in cosmetic formulations. Therefore, we assessed and evaluated the biological activity of the eight spp. of *Plectranthus* (*P. ambigerus*, *P. barbatus*, *P. cylindraceus*, *P. ecklonii*, *P. fruticosus*, *P. grandidentatus*, *P. hadiensis*, *P. madagascariensis*) cited as traditionally used for skin conditions.

All the species were collected and dried at room temperature, then ultrasound-assisted extractions were performed in presence of methanol as the solvent. Methanolic extracts (10% w/v) were screened to assay their potential bioactivity as antioxidants, antimicrobials and on skin-related enzymes, as well as their general toxicity. The results showed a very promising antioxidant activity, but only a moderate effect against bacteria; however, no relevant general toxicity was highlighted. Good tyrosinase inhibition was observed, together with an excellent inhibitory activity on collagenase, making the methanolic extract a promising raw material to be used for the development of dermocosmetic formulations, especially those with anti-ageing activity. More studies are ongoing to probe other relevant biological activities and to further ascertain the safety of the extracts.

Acknowledgements

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References

[1] D. Matias *et al.*, *Biomolecules*. **2019**;9(5):1-13. DOI:10.3390/biom9050179.

[2] E. Ntungwe *et al.*, *Pharmaceuticals*. **2021**;14(5):1-11. DOI:10.3390/ph14050402.

[3] J. Marçalo *et al.*, J. Enzyme Inhib. Med. Chem. **2021**; 36(1): 257-69. DOI:10.1080/14756366.2020.1862099.

Site-Selective Orthogonal Functionalisation of Peptides at N-terminal Cysteines with Multivalent NHS-Activated Acrylates

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Traditional chemotherapeutic drugs with strong cytotoxicity face long-standing problems regarding non-specific biodistribution and targeting in the body, poor water solubility and low therapeutic indices.[1] Due to their biological activity, many peptides and are known to be potent anticancer agents.[2] The chemoselectivity and mildness of the processes attained with peptide bioconjugation should successfully install modifications at pre-determined sites without disturbing the structure, function and activity of peptides. Site-selective chemical appendage of multiple functionalities on native peptide backbone methods, resulting in homogeneous conjugates, is a highly demanding and complex tool of modern chemical biology. Our research group started to study NHS-activated acrylic ester as suitable reagents for the selective stapling of amino-sulfhydryl groups.[3] After achieving wonderful results we've decided to broaden the research by designing novel NHS-activated acrylates that hold various payloads in a single bioconjugation handle and can site-selectively and orthogonally target the N-terminal cysteine of peptides. The bioconjugation generates a stable 1,4 thiazepan 5-one core and the attained bioconjugates were design to be further used for theranostics studies (figure 1).

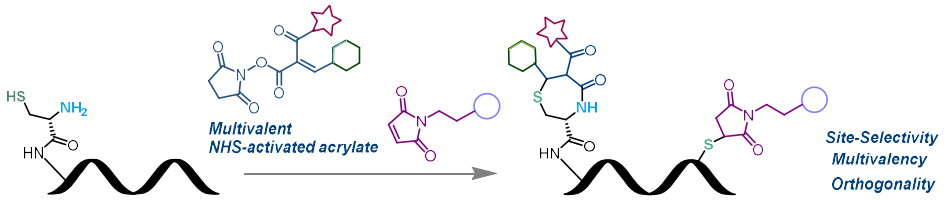

Figure 7: Multivalent NHS-activated acrylate for the site-selective and orthogonal multifunctionalisation of peptides.

Acknowledgements

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References

[1] J. Lu, F. Jiang, A. Lu, G. Zhang, Int. J. Mol. Sci. 17 (2016) 561.

[2] C. Li, P. Haratipour, R. Lingeman, J. Perry, L. Gu, R. Hickey, L. Malkas, Cells 10 (2021) 2908.

[3] M. Silva, J. Coelho, V. Pinto, A. Fernandess, I. Compañon, F. Corzana, G. Gasser, P. Góis, Angew. Chem. Int. Ed. 60 (2021) 10850-10857.

Pyrroloquinolones based hybrids for multitarget approach on tuberculosis

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Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis (Mtb). Currently, TB is the second main cause of death due to a single organism, only after the Covid-19 [1]. The global control of TB is highly challenged by the prolonged duration of the existing treatments, patient compliance and the development and spread of multidrug and extensively drug resistant TB [2]. Another challenge is that the available anti-TB drugs do not address the latent infections, that are prevalent in 90 % of infected people. If the immune system is compromised these latent forms can become active and contagious. Therefore, it is crucial the discovery of novel molecular structures and the development of new drugs to tackle drug resistant and latent Mtb [2].

Mtb's viability depends on the energy produced by its respiratory chain. Combination of compounds targeting different components of the electron transport chain (ETC) has been considered as an innovative and potentially successful approach to avoid the emergence of resistance [3].

Here we present the synthesis of a small library of pyrroloquinolones (PYQ). These compounds are developed to multitarget the ETC of Mtb, through the inhibition of cytochrome *bcc* while simultaneously releasing nitric oxide. To expand the library of PYQ, we diversify the linker between the PYQ core and the substituents at **R** position (**Fig. 1**). Biological evaluation against Mtb H37Rv strain as well as aqueous solubility determination will also be presented.

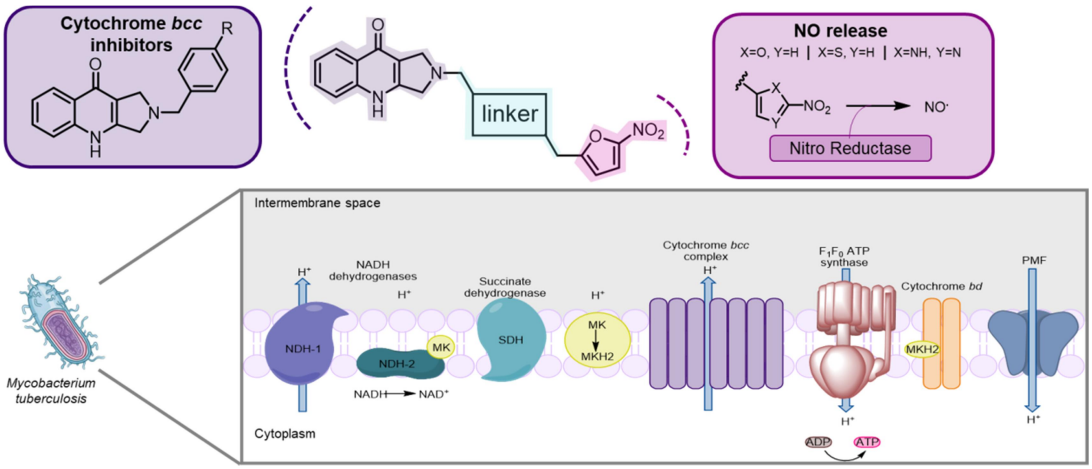

Fig. 1 - Anti-TB compounds multitargeting the electron transport chain of Mycobacterium tuberculosis.

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References

[1] World Health Organization, Global tuberculosis report 2021.
[2] Campaniço, A.; Harjivan, S. G.; Warner, D. F.; Moreira, R.; Lopes, F; Int. J. Mol. Sci. 2020, 21, 8854
[3] Beites, T.; O'Brien, K.; Tiwari, D.; et. al., Nat. Comm., 2019, 10, 1-12

Technology & Industry

Bar Adsorptive Microextraction (BAμE) devices vs. Solid-Phase Microextraction (SPME) LC Tips: Which are more effective for enriching local anesthetics from complex matrices?

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Green Analytical Chemistry (GAC) is a widely accepted mixture of a pragmatic point of view concerning the reduction of expenses and an ethical compromise with environmental sustainability [1]. In this context, the development of analytical strategies that allow a more eco-user-friendlier approach in monitoring substances of abuse in several matrices have accelerated in the last decades.

In this contribution, we propose the comparison of commercially available solid-phase microextraction (SPME) LC Tips against in-lab made bar adsorptive microextraction (BAμE) devices [2] for the selective enrichment of local anaesthetics (lidocaine, benzocaine, procaine and tetracaine) from aqueous phases. All devices were coated with C18 polymeric phase. After the extraction phase, the target compounds were desorbed into a suitable solvent (100 μL) followed by gas chromatography-mass spectrometry (GC-MS) analysis.

The results show that similar conditions are needed to maximize the recoveries using both types of microextraction devices. These include matrix pH (12.3), extraction temperature (25 °C), time (60 min) and agitation speed (1400 rpm). However, the BAμE devices, which are 100 to 200 times less expensive, presented 1.2 to 3 times higher extraction efficiencies and lower imprecision than the SPME LC Tips. These results show that using in-lab made devices compete very favourably against commercially available ones, without compromising analytical performance.

The optimized approach will be fully validated and applied to monitor these compounds in biological matrices.

Acknowledgements

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References

[1] De La Guardia, M.; Garrigues, RSC Green Chem. 2020, 2020-Janua, 1–18.

[2] Ahmad, S.M.; Gonçalves, O.C.; Oliveira, M.N.; Neng, N.R.; Nogueira, J.M.F. Molecules 2021, 26, 1–32.

Extraction of chitin contained in a new type of biomass

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The aim of this study is to extract the chitin contained in a new type of biomass - insect exuviae - to transform it into chitosan that possesses many characteristics with potential promising applications, while carrying out the experiments with the greener approach possible. Indeed, the biodiversity of the insects provides a wide range of expectations for the future and the potential applications[1].

In this work basic bioplastics have been made to assess the impact of different parameters such as the size of the particles, the temperature, and the addition of colorants regarding the resistance, the flexibility, and the viability. FTIR analysis and microscopic observations are made to compare the different results and to explain the different behaviors of each sample.

In addition, the influence of size in absorbed water content will be shown presented and discussed.

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References

[1] Ribeiro, A.P.C.; Matias, I.A.S.; Carabineiro, S.A.C.; Martins, L.M.D.R.S. , *Catalysts* 165 (2022), 285

Ionic liquids for the degradation of Dyes

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From the last few decades, environmental pollution is one of the major problems due to increased industrialization. Nowadays, its a serious problem of water pollution as it has led to the discharge of toxic and hazardous chemicals into the water bodies. Dyes are the main class of organic compounds that pollute the water. Hence, their effective removal is pivotal. Degradation using metal ions can lead to more problems. Due to low volatility, chemical stability, and chelating abilities of ionic liquids, the application of functionalized ionic liquids can effectively reduce the amount of these pollutants. In this work we will present some examples of ionic liquids action in the degradation of several dyes.

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References

[1] R. Zhao, X. Yu, D. Sun, L. Huang, F. Liang, Z. Liu ACS Applied Nano Materials 2 (2019) 2127-2132

Dry biomass on the degradation of Dyes

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In this work, we studied the effect of dry biomass extracted from vegetal and animal sources on the degradation of dyes. Waterbodies are affected by pollution produced by different industries such as paper mills, textiles, tanneries, and food, which use dyes [1] in their processes, which are difficult to be degraded using metal complexes because of their toxicity for the environment. Therefore, the removal of these dyes is extremely important to preserve human health and protect the environment. In this work, we study several biomasses and applied them to the degradation of several pigments

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References

[1] Argumedo-Delira, R.; Gómez-Martínez, M.J.; Uribe-Kaffure, R. Dyes. *Appl. Sci. 11 (*2021**)**, *11*, 448

ZnO prepared by lupins waste

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This work is about the synthesis of green catalysts for the degradation of the pigment methylene blue (MB). This coloured wastewater is produced by textile industries and is harmful to the environment but also to human health. This pollutant dye can persist for a long time in water and thus strategies to degrade it are necessary. In this work, we produced zinc oxide (ZnO)[1] in by economically and environmentally friendly approaches. The synthesis was based on lupin waste. Several physicochemical parameters such as size, morphology, and shape, of these synthesized particles have changed the catalyst activity influencing the efficiency in our reaction.

The aim of the study is to give a second life to the food leftovers by synthesizing zinc oxide from lupin's peel and its conservative water and apply it to the degradation of pollutants as MB.

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References

[1] M. Naseer, U. Aslam, B. Khalid, B.Chen , *Sci Rep* 10, 9055 (2020)

Copper foams for water pollutants

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Copper foams, which have been developed only in the past few years, provided specific surface areas and roughnesses that are important in catalysis. The foams are made by depositing a 3D copper structure [1] on a copper plate surface by applying a strong electric current. Bubbles from hydrogen evolution result in the dynamic hydrogen bubble template (DHBT) method that cause the copper to be deposited in sponge-like porous structure of various sizes. After depositing the copper foams on an electrode, these were used for pigment degradation to see their efficiency as catalysts.

Acknowledgements

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References

[1] F. Stergioudi, E. Kaprara, K. Simeonidis, D. Sagris, M. Mitrakas, G. Vourlias, N. Michailidis, Materials & Design 87 (2015), 287-294

Extraction of chitosan contained in a new type of biomass

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The objective of this study was to extract chitin from black soldier fly (BSF) larvae exuviae and to convert it into chitosan. In fact, insect biorefinery is considered a key technology in the 21st century due to the importance of the sustainable production of various bio-derived fine chemicals [1]. Extraction of chitin was performed by solubilization in acid and alkali solutions at room temperature, with the greener approach possible. Conversion of chitin to chitosan was performed through a deacetylation step by using NaOH. Different size of biomass was used and FTIR analysis and microscopic observations were made to compare the different results obtained.

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References

[1] Ribeiro, A.P.C.; Matias, I.A.S.; Carabineiro, S.A.C.; Martins, L.M.D.R.S., *Catalysts* 165 (2022), 285

Viscosity of the binary system 1-Pentanol+1-Butanol and Ethanol+1-Butanol at 0.1 MPa and Temperatures from 283.15 K to 353.15 K

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Viscosity is an important property for chemical and petroleum industries playing a key role in the transport of fluids and therefore in the design of processes. Alcohols have a wide range of industrial applications such as solvents, reactants synthesis of other compounds, additives to gasoline, and in cryogenic power generation systems.[1] In addition to these, some alcohols can replace fuel, and consequently there is an increased interest in its properties. However, a lack of data regarding alcohols mixture's viscosity at a wide range of temperatures and pressures exists. It is critical to have accurate data on the viscosities of these types of mixtures for technical applications in industry.[2]

The aim of this work is to measure the viscosity of two binary systems of alcohols (ethanol+butanol and pentanol+butanol) and the viscosity of the three pure alcohols (ethanol, butanol and pentanol). The viscosities were measured at 0.1 MPa and at 8 temperatures ranging from 283.15 K to 353.15 K. The viscosities measurements were done using a Julabo 18V viscometer thermostatic bath with a Julabo ME temperature controller. The viscometer was from SI Analytics (Type 538 10 type I).

Figure 1- Viscometer equipment.

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References

[1] Shan, Z., & Asfour, A.-F. A. (1998). Viscosities and densities of eight binary 1-alkanol systems at 308.15 and 313.15 K. In Fluid Phase Equilibria (Vol. 143).
[2] Faria, M. A. F., Martins, R. J., Cardoso, M. J. E. M., & Barcia, O. E. (2013). Density and viscosity of the binary systems ethanol + butan-1-ol, + pentan-1-ol, + heptan-1-ol, + octan-1-ol, nonan-1-ol, + decan-1-ol at 0.1 mpa and temperatures from 283.15 K to 313.15 K. Journal of Chemical and Engineering Data, 58(12), 3405–3419. https://doi.org/10.1021/je400630f

Tetrazoles 2002-2022: twenty years of a delightful research

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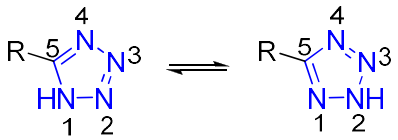
The chemistry of tetrazole and its derivatives remains a topic of intense research. The wide interest in this class of compounds stems mainly from their potential and important applications in major areas such as medicine, agriculture, automobile industry, imaging technology, coordination chemistry and as high energy materials. In drug design and development, 5-substituted tetrazoles are commonly used as a bioisosteric replacement for the carboxylic acid moiety and the 1,5-disubstituted tetrazole ring is known as an excellent mimic for the cis-amide bond. Tetrazoles are also interesting molecules from a structural point of view. Hydrogen atoms directly bound to the tetrazole ring are labile and may give rise to different tautomers (see Scheme 1. for an example of tautomerism of tetrazole derivatives), their relative populations depending on the chemical environment (see reference [1] for an excellent review paper on tetrazole chemistry).

In this communication, the author presents some of the most relevant results he has obtained in different topics of the chemistry of tetrazole derivatives achieved in the last twenty years, *viz.*: on homogeneous, heterogeneous and organo-catalysis, photochemistry, spectroscopy, criospectroscopy and molecular structure, organic synthesis, coordination chemistry and medicinal chemistry.[2-14]

Scheme 1. Tautomerism of Tetrazole Derivatives



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

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References

[1] C.G. Neochoritis, T. Zhao, A. Dömling, Chem. Rev. 119 (2019) 1970-2042.
[2] S.C.S. Bugalho, L. Lapinski, M.L.S. Cristiano, L.M.T. Frija, R. Fausto, Vib. Spectrosc. 30 (2002) 213-225.
[3] N.C.P. Araújo, A.F. Brigas, M.L.S. Cristiano, L.M.T. Frija, et al., J. Mol. Catal. A: Chem. 215 (2004) 113-120.
[4] L.M.T. Frija, M.L.S. Cristiano, E.M.O. Guimarães, et al., J. Mol. Catal. A: Chem. 242, (2005) 241-250.
[5] L.M.T. Frija, I.V. Khmelinskii, M.L.S. Cristiano, J. Org. Chem. 71 (2006) 3583-3591.
[6] L.M.T. Frija, I.D. Reva, A. Gómez-Zavaglia, et. al., Photochem. Photobiol. Sci. 6 (2007) 1170-1176.
[7] L.M.T. Frija, I.V. Khmelinskii, I.D. Reva, et al., Org. Biomol. Chem. 6 (2008) 1046-1055.
[8] L.M.T. Frija, A. Ismael, M.L.S. Cristiano, Molecules 15 (2010) 3757-3774.
[9] L.M.T. Frija, I. Reva, D.V. Coelho, et al., Org. Biomol. Chem. 9 (2011) 6040-6054.
[10] L.M.T. Frija, M.L.S. Cristiano, et al., J. Photochem. Photobiol. C: Photochem. Reviews 18 (2014) 71-90.
[11] L.M.T. Frija, E.C.B.A. Alegria, et al. J. Mol. Catal. A: Chem. 425 (2016) 283-290.
[12] L.M.T. Frija, M.L. Kuznetsov, B.G.M. Rocha, et al. Molecular Catalysis 442 (2017) 57-65.
[13] L.M.T. Frija, E. Ntungwe, P. Sitarek, et al. Pharmaceuticals 12 (2019) 167.
[14] L.M.T. Frija, B.G.M. Rocha, M.L. Kuznetsov, et al. Pure and Applied Chemistry 92 (2020) 151.

Catalytic performance of copper(II) C-scorpionate complexes for the oxidation of 1-phenylethanol

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In this study, the catalytic activity of previously synthesized copper(II) complexes bearing C-scorpionate ligand, hydrotris(pyrazol-1-yl)methane ($HCpz_3$),[1–4] was evaluated for the peroxidative oxidation of 1-phenylethanol using conventional heating and alternatives techniques, and following the principles of green chemistry. The interest in the oxidation of 1-phenylethanol arises from the importance of the oxidized product, acetophenone, which is widely used as feedstock for several valuable chemicals such as insecticides, pharmaceuticals, and resins. [5] The copper complexes $[CuSO_4(HCpz_3)]\bullet 5H_2O$ (1), $[Cu(HCpz_3)_2](NO_3)_2$ (2) and $[\{Cu(CH_3COO)_2\}_3(HCpz_3)_2]\bullet H_2O$ (3) were synthesized as reported [1,2] and were characterized by UV-Vis and cyclic voltammetry. The catalytic activity of the above copper complexes has been tested with *tert*-butyl hydroperoxide (*t*-TBHP), under mild conditions (temperature below 80 °C, green oxidant, solvent-free, or green solvents) and using alternative techniques such as ultrasonic irradiation, microwave, and ball-milling. The influence of various parameters, such as reaction time, type and amount of catalyst, and temperature, is also evaluated and discussed.

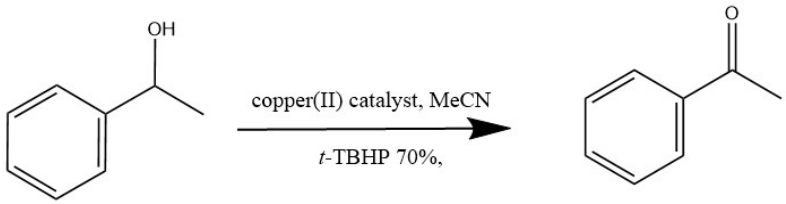

Figure 1 – Peroxidative oxidation of 1-phenylethanol in the presence of copper(II) complexes

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References

[1] M. Adediran Mesubi, F. Okwudilichukwu Anumba, Transit. Met. Chem. 1985 101 10 (1985) 5–8.

[2] D. Martini, M. Pellei, C. Pettinari, B.W. Skelton, A.H. White, Inorganica Chim. Acta 333 (2002) 72–82.

[3] L.M.D.R.S. Martins, Coord. Chem. Rev. 396 (2019) 89–102.

[4] H.M. Lapa, M.F.C. Guedes da Silva, A.J.L. Pombeiro, E.C.B.A. Alegria, L.M.D.R.S. Martins, Inorganica Chim. Acta 512 (2020) 119881.

[5] M.N. Kopylovich, A.P.C. Ribeiro, E.C.B.A. Alegria, N.M.R. Martins, L.M.D.R.S. Martins, A.J.L. Pombeiro, Adv. Organomet. Chem. 63 (2015) 91–174.

Fe3O4-based core/shell nanocomposites as heterogeneous catalysts for the peroxidative oxidation of 1-phenylethanol

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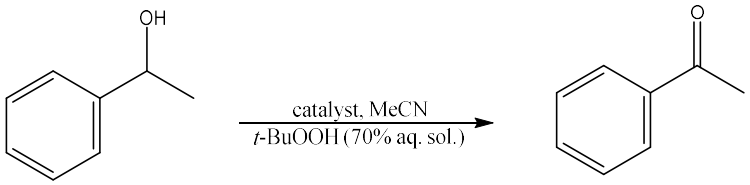
In this work, magnetite Fe_3O_4-based core/shell nanocomposites have been successfully synthesized using the layer-by-layer method (Fe_3O_4@CuMOF) and by a modified co-precipitation route, followed by facile hydrothermal treatment (Fe_3O_4@TiO_2) and applied as heterogeneous catalysts for the peroxidative oxidation of 1-phenylethanol with t-butyl hydroperoxide (70% aq. solution) as oxidant, and under for the conventional heating, to the respective ketone, acetophenone, with the ability of subsequent removal by means of an external magnetic field. Acetophenone is used as a flavouring agent in foods, fragrance in soaps and perfumes, and as a solvent. The influence of various parameters, such as, reaction time, type and amount of catalyst, temperature and presence of additives, is also evaluated.



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References

[1] Ke, F.; Qiu, L.-G.; Yuan, Y.-P.; Jiang, X.; Zhu, J.-F. *J. Mater. Chem.* 2012, *22*, 9497-9500.

[2] Matias, I.A.S.; Ribeiro, A.P.C.; Ferraria, A.M.; Rego, A.M.B.; Martins, L.M.D.R.S *Nanomaterials* 2020, *10*, 2111.

[3] Ullmann's Encyclopedia of Industrial Chemistry, Bohnet, M., Wiley-VCH, Weinheim, 2003.