LISBOA
UNIVERSIDADE DE LISBOA

COLÉGIO de QUÍMICA

# UL CHEMISTRY PhD MEETING

## 2nd Meeting of the CQUL (2ECQUL)

# Book of Abstracts

4-5 DECEMBER 2017

Reitoria da Universidade de Lisboa

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The Universidade de Lisboa (ULisboa) Chemistry PhD Meeting, an initiative of the recently created College of Chemistry of the Universidade de Lisboa (CQUL), is specially dedicated to all PhD students registered in any of the Doctoral Programmes of the different Schools of the ULisboa, related to any aspects of Chemistry.

This meeting provides for both students and supervisors a unique opportunity to share their experience and information about the research work carried out in Chemistry under the different doctoral programmes at the ULisboa.
The programme of this meeting comprises (i) oral, flash and panel presentations, by the students at different stages of their research projects about their achievements, (ii) invited presentations by renowned speakers in topics of general interest, and (iii) an Alumni session where some of the former students, who received a PhD degree in Chemistry by the ULisboa in recent years, bring together their post-doctoral experiences of professional insertion in different sectors in business and academia.

This Meeting is the second one organized by the College of Chemistry of the ULisboa (CQUL) and follows the first meeting on “Chemistry in the Research of the University of Lisbon”, which was mainly addressed to Post-Doc researchers, and was held in July 2017 also at the Rectory of this University. Both of them should contribute to the establishment of collaboration links and networks, an important aim of the College.

We wish a pleasant and fruitful meeting to all the attendees and thank all the persons who have been involved in its organization.

We also thank the Rector, Prof. António Cruz Serra, for all his support to the initiatives of the College.

Manuel Almeida
*President of the Organizing Committee*

Maria José Calhorda
*President of the Executive Commission for Research*

Armando Pombeiro
*President of the College*

# PROGRAMME

| December 4th | |
|---|---|
| 13h00 | Check-in |
| 14h00-14h30 | Opening Session |
| **Afternoon Session** | |
| 14h30-15h20 | Invited Lecturer<br>**Giovanni Poli (Sorbonne Université)** |
| 15h20-16h35 | Oral (4x15 min) & Flash (3x5 min) Presentations<br>[O] Beatriz Barrocas (CQB-FCUL)<br>[O] Leonor Côrte-Real (CQE-FCUL)<br>[O] Tiago Cruz (CQE-IST)<br>[O] Mário Felício (iMM-FMUL)<br>[F] Rita Acúrcio (iMed.UL-FFUL)<br>[F] Luís Almeida (CQB-FCUL)<br>[F] Joana Andrade (ULHT) |
| 16h35-17h15 | Coffee Break & Poster Session |
| 17h15-18h30 | Oral (4x15 min) & Flash (3x5 min) Presentations<br>[O] Romina Guedes (iMed.UL-FFUL & UCoimbra)<br>[O] Inês Martins (CQE-IST, UAveiro & J.W.Goethe-Universitaet)<br>[O] Nuno Martins (CQE-IST)<br>[O] Cristina Matos (CQE-IST, CQE-FCUL)<br>[F] João António (iMed.UL-FFUL)<br>[F] Sofia Domingos (iMed.UL-FFUL, CQE-IST & UPorto)<br>[F] Alice D'Onofrio ($C^2$TN-IST) |

| December 5th | |
|---|---|
| 08h30 | Check-in |
| **Morning Session** | |
| 09h00-09h50 | Invited Lecturer<br>**Michael Mingos (Oxford University)** |
| 09h50-10h50 | Oral (3x15 min) & Flash (3x5 min) Presentations<br>[O] Patrique Nunes (CQE-IST)<br>[O] Sílvia Quaresma (CQE-IST)<br>[O] Sara Realista (CQB-FCUL)<br>[F] Olga Ferreira (CQB-FCUL & CERENA-IST)<br>[F] Catarina Garcia (ULHT & UAlcalá)<br>[F] Rafael Gomes (iMed.UL-FFUL) |
| 10h50-11h35 | Coffee Break & Poster Session |
| 11h35-12h30 | Oral (3x15 min) & Flash (2x5 min) Presentations<br>[O] Ana Rodrigues (CQE-IST)<br>[O] Fábio Santos (iMed.UL-FFUL)<br>[O] Gonçalo Tiago (CQE-IST)<br>[F] Catarina Lopes (iMM-FMUL)<br>[F] Marcin Makowski (iMM-FMUL) |
| **Afternoon Session** | |
| 14h15-15h05 | Invited Lecturer<br>**William Wakeham (Imperial College London)** |
| 15h05-15h45 | Flash (8x5 min) Presentations<br>[F] Joana Matos (CQE-IST & $C^2$TN-IST)<br>[F] Rafael Nunes (CQB-FCUL)<br>[F] Rosana Pinto (CQB-FCUL & CERENA-IST)<br>[F] Filipa Ramilo-Gomes (CQE-IST & iMed.UL-FFUL)<br>[F] Marta Ramos (CERENA-IST & ISEL)<br>[F] Roberto Russo (iMed.UL-FFUL & iMM-FMUL)<br>[F] Patrícia Serra (iMed.UL-FFUL)<br>[F] Patrícia Silva (iMM-FMUL) |
| Coffee Break | |
| 16h15-17h45 | Alumni Session<br>**Ana Neves (UExeter)**<br>**Bruno Castro (Nature)**<br>**Konstantin Luzyanin (ULiverpool)**<br>**Manuel Melo (ITQB)**<br>**Paulo Madeira (SAPEC)**<br>**Susana Nascimento (Hovione)** |
| 17h45-18h15 | Awards Ceremony & Closing Session |

**IL1**

# Basic Concepts in catalytic C-H Activation

Giovanni Poli, Julie Oble and Alexandre Pradal

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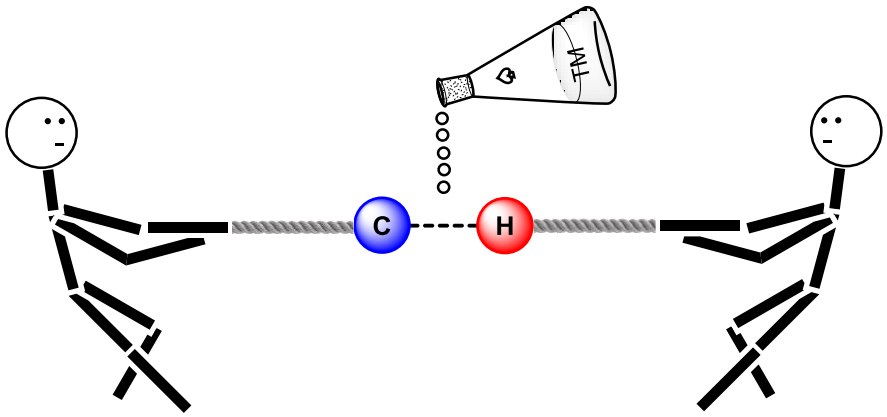
The direct and selective functionalization of a non acidic C-H bond – the "unfunctional" group by definition – enables the direct use of the cheapest and most abundant feedstock for the construction of more complex organic molecules, thus adding the C-H bond to the catalog of the classical functional groups such as halides, alcohols, carbonyls, etc. This research field, considered for its difficulty and importance the "Holy Grail" of chemistry, is becoming increasingly powerful and attracts the interest of theoreticians, organic chemists, as well as experts in organometallic catalysis.[1-2] Concepts, definitions, historical breakthroughs, as well as mechanistic details of this chemistry will be introduced.




**Acknowledgements**

Support for this work was provided by SU, CNRS and CMST COST Action, CA15106 (CHAOS).

**References**

[1] F. Roudesly, J. Oble, G. Poli, J. Mol. Cat. A. Chem. 426 (2017) 275-296.

[2] Chem. Rev. 117 (2017) 8481-9520 (Issue on C-H activation).

**Giovanni Poli** obtained his Laurea and PhD at the University of Milan. After three years as post-doctoral fellow at the Universities of Geneva and Lausanne, he became associate professor at the University of Florence in 1992. Since 2000 he is full professor at UPMC (Paris), now Sorbonne Université. Scientific interests: catalytic C-H activation, step and atom economy.

**IL2**

# The Chemical Bond – 100 years old, but still making an essential contribution

D. Michael P. Mingos

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The seminal papers of Lewis and Kossel published 100 years ago have had an outstanding impact on the development of the chemical sciences. Their insights depended on the attainment of inert gas configurations by the atoms in molecules, either directly by electron transfer, or electron-pair sharing and were based on pre-quantum mechanical concepts. The model, nevertheless, incorporated an evolutionary gene which has enabled it to survive and grow as chemistry has uncovered new classes of molecules and was sufficiently adaptable to utilise the essential ideas of quantum physics. The simplicity of the model has resulted in the development of a notation, which is universally used by chemists to describe the course of organic chemical reactions and predict their regio-selectivities. The limitations of the model to inorganic molecules became apparent at an early stage and required more sophisticated quantum mechanically descriptions to describe electron deficient and electron rich molecules. The model has been repeatedly enriched by quantum mechanically based theoretical insights, and I have been fortunate to contribute to some of these developments. The lecture will celebrate 100 years of the chemical bond model and look forward to future developments.[1-3]

**Acknowledgements**

Many research students and postdoctoral fellows have contributed to the ideas described in the lecture and in the process kept me young and enthusiastic. I thank them most sincerely.

**References**

[1] D.M.P. Mingos in The Chemical Bond I (Ed D.M.P. Mingos), Struct. Bond. 169 (2016) 1-56.

[2] A. Haaland, M. Tilset in The Chemical Bond II (Ed D.M.P. Mingos), Struct. Bond. 170 (2016) 1-70.

[3] R.H. Crabtree in The Chemical Bond III (Ed D.M.P. Mingos), Struct. Bond. 171 (2016) 63-78.

**Michael Mingos** was born in Basra, Iraq, in 1944 and was educated at University of Manchester (B.Sc. in Chemistry 1965) and University of Sussex (D.Phil, 1968). He has followed a peripatetic academic career in chemistry – Lecturer and Reader QMC and University of Oxford (Keble College), Sir Edward Frankland BP Professor and Dean at Imperial College and Principal of St Edmund Hall (1999-2009). His theoretical research has resulted in generalisations which have influenced the development and teaching of modern inorganic chemistry. His experimental work has verified some of his theoretical predictions, for example an icosahedral molecule containing 13 gold atoms – which is relevant for understanding the metal's nano-technological possibilities. He has also contributed to the understanding of the bonding properties of nitric oxide, an important cellular signaling molecule involved in many physiological processes.

**IL3**

# Employment prospects in Science, Technology, Engineering and Mathematics (STEM)

Sir William Wakeham FREng

*Department of Chemical Engineering, Imperial College London, United Kingdom*

The presentation will examine the employment prospects for graduates in Science, Technology, Engineering and Mathematics (STEM) in the UK at first cycle, masters and PhD level from UK universities in the recent past based upon extensive data available. This will be used together with surveys of employers of STEM graduates to identify the characteristics of graduates most in demand and that make a graduate more or less employable. Chemists and Chemical Engineers are included in the study and there are very large differences in their employment prospects. The findings of the study are undoubtedly applicable far beyond UK and have particular resonance in Portugal. The implications of the findings of the study for the education and training of STEM graduates in the modern world are explored from the perspective of both students and staff and have profound consequences for the careers of todays' graduates.

Professor **Sir William Wakeham** retired as Vice-Chancellor of the University of Southampton in September 2009. He was a member of Imperial College London from 1971 where he was Deputy Rector from 1996 to 2001. His academic publications include 10 books, and over 400 papers in the field of transport processes and thermodynamics.

He has been Chair of the University and Colleges Employers Association, a Member of the EPSRC and of the Board of SEEDA. In 2008 he chaired a Review of Physics in the UK and completed a review of the effectiveness of Full Economic Costing of Research in 2010.

He was Senior Vice-President of RAEng and its International Secretary until 2015. He has been President of the IChemE, and is a member of IET and IoP. He is also currently Chair of the Exeter Science Park Company, Non-Executive Director of Ilika plc, Chair of the South East Physics Network, Trustee of Royal Anniversary Trust, and the Rank Prizes Fund.

**O01**

# Synthesis and application of ruthenium modified titanate nanostructures for emergent pollutants photodegradation

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Nowadays, pharmaceuticals and personal care products (PPCPs) are one of the major source of water contamination, and, even in very low concentrations, they create severe environmental pollution problems. Considerable efforts have been devoted to develop methods more effective than the conventional processes to eliminate these pollutants. Adsorption and coagulation can be common practices applied to treat them but usually result in secondary pollution problems. Alternative approaches, like advanced oxidation processes (AOP), for example photocatalytic degradation, which involve generation and subsequent reaction of extremely active redox radicals, are often used to treat wastewater and have received great attention in the past years. These processes also include systems such as chemical oxidation (ozone, hydrogen peroxide and Fenton), electrochemical oxidation, photolysis oxidation or photo(electro)catalytic oxidation and have been discussed in several reviews.

In this work, titanate nanotubes and nanowires (TNT and TNW) were doped with ruthenium ions aiming to enhance their photocatalytic properties to be used for PPCPs degradation. The materials were prepared using a hydrothermal approach [1,2], and were structural, morphological and optical characterized by XRD, TEM, DRS, PL, XRF and XPS. No modifications on the structure and morphology were detected in the Ru-doped materials but an increase on the visible light absorption was observed. The photocatalytic activity was evaluated on the •OH production, using terephthalic acid as probe molecule, and on the photocatalytic removal of caffeine and sulfamethazine aqueous solutions. The results show that the RuTNT sample was the best catalyst, achieving 100% of photodegradation efficiency for caffeine (20 ppm solution) and for sulfamethazine (10 ppm solution), within 60 and 45 min under UV-vis radiation, respectively. All the secondary products were identified and quantified. Based on the obtained results, a mechanism for the charge-transfer in RuTNT nanoparticles is proposed and discussed.

**Acknowledgements**

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013. B.B. acknowledges financial support from SFRH/BD/101220/2014 and O.C.M. from IF/01210/2014. The authors also thank the Portuguese Mass Spectrometry Network (Node IST-Campus Alameda) for facilities. XPS analyses were performed at CEMUP – Centro de Materiais da Universidade do Porto.

**References**

[1] E.K. Ylhäinen, M.R. Nunes, A.J. Silvestre, O.C. Monteiro, J. Mater. Sci. 47 (2012) 4305-4312.

[2] B. Barrocas, A.J. Silvestre, A.G. Rolo, O.C. Monteiro, Phys. Chem. Chem. Phys. 18 (2016) 18081-18093.

**O02**

# Novel Ruthenium-Cyclopentadienyl complexes as potential candidates to surmount multidrug resistance in cancer

L. Côrte-Real[a], P. Gírio[a,b], A. Moreno[b], M. H. Garcia[a], P. Falson[b], A. Valente[a]

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Multidrug resistance (MDR) is one of the major clinical problems in cancer chemotherapy, being responsible for more than 90% of treatments failure of metastatic cancer using adjuvant chemotherapy.[1] One approach to circumvent this problem is to explore the design of MDR inhibitors which would also behave as cytotoxic agents. Ruthenium compounds are promising candidates to platinum-based drugs due to its general low toxicity, good tolerability and stability under physiological conditions, between others. In this frame, our research group is focused on the development of ruthenium(II) compounds with 'MCp'(Cp=$\eta^5$-$C_5H_5$) core that exhibit exceptional anticancer *in vitro* activity in several cancer cell lines.[2-4] These encouraging results, led us to evaluate the multidrug resistance response that these compounds may trigger upon addition.

For that, new compounds based on 'MCp'(Cp=$\eta^5$-$C_5H_5$) moiety and bearing a ligand functionalized with biotin (also known as vitamin H or B7) were newly synthesized (Figure 1). The compound's ability to block ABC transporters was evaluated in different human cells transfected with each MDR pump, ABCB1, ABCC1, ABCC2 and ABCG2, using flow cytometry alone or coupled to mass spectrometry (CyTOF technology) will be presented. To determine the affinity of our compounds with the MDR pumps and to predict the preferred structure, we also carried out molecular docking on X-ray structures and 3D models.

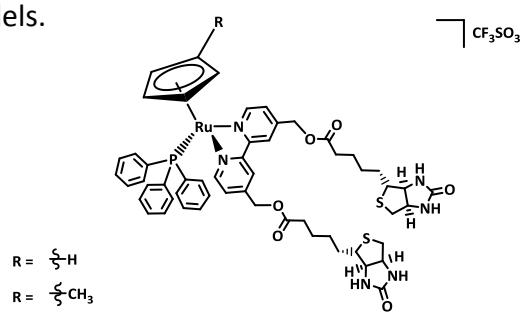



**Figure 1**. ´RuCp` complexes functionalized with biotin ligand.

**Acknowledgements**

This work was financed by the Portuguese Foundation for Science and Technology (FCT) – project UID/QUI/00100/2013. A.V. acknowledges the Investigator FCT2013 Initiative for the project IF/01302/2013 (acknowledging as well POPH and FSE-European Social Fund). L.C.-R. thanks FCT for her Ph.D. Grant (SFRH/BD/100515/2014).

**References**

[1] K.M. Pluchino, M.D. Hall, A.S. Goldsborough, R. Callaghan, M.M. Gottesman, Drug Resistance Updates 15 (2012) 98-105.

[2] A. Valente, M.H. Garcia; F. Marques, Y. Miao, C. Rousseau, P. Zinck, J. Inorg. Biochem. 127 (2013) 79-81.

[3] T.S. Morais, A. Valente, A.I. Tomaz, F. Marques, M.H. Garcia, Fut. Med. Chem. 8 (2016) 527-544.

[4] M.H. Garcia, A. Valente, T.S.F. Morais, A.I. Tomaz, WO 2016/087921.

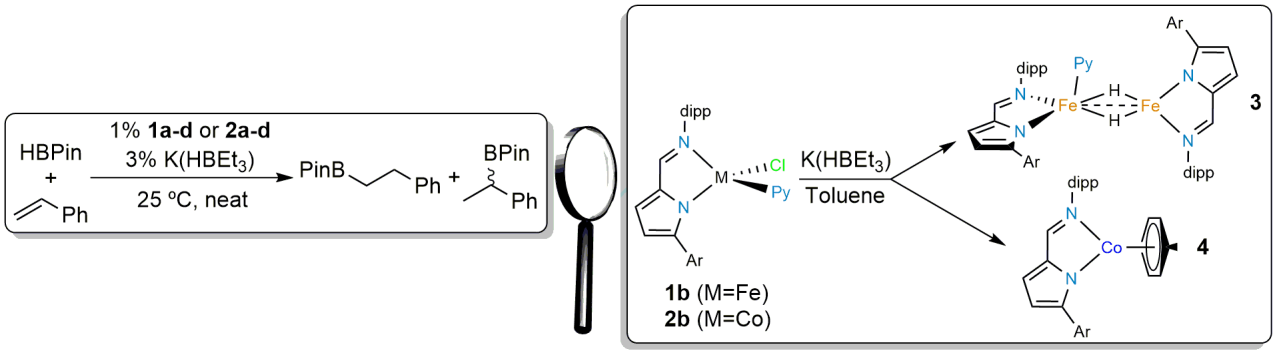
**O03**

# Hydroboration of terminal alkenes catalysed by iron and cobalt complexes of 5-aryl-2-iminopyrrolyl ligands

Tiago F. C. Cruz, Pedro T. Gomes, Luís F. Veiros

*Centro de Química Estrutural, Instituto superior Técnico, Lisbon, Portugal*

Hydroboration is an important source of important organoboron reagents relevant to organic synthesis, being present, for instance, in cross-coupling or oxidation reactions.[1] Since hydroboration is commonly catalysed by the expensive platinum group elements,[2] it is important to develop cheap and abundant mediators, a problematic that remains relatively unexplored.[3] In this work, families of iron and cobalt complexes of 5-aryl-2-iminopyrrolyl ligands (ArN$^-$^Ndipp) of the type [(ArN^Ndipp)M$^{II}$Cl(Py)] (M = Fe (**1a-d**), Co (**2a-d**)), activated by K(HBEt$_3$), catalysed the hydroboration of styrene with pinacolborane (HBPin). The reaction yielded the respective mixture of *anti*-Markovnikov and Markovnikov addition products in good yields, with enhanced selectivity in the Markovnikov product when the steric bulkiness of the ArN$^-$^Ndipp ligand is increased. The preparative stoichiometric reactions of [(ArN^Ndipp)M$^{II}$Cl(Py)], with Ar=2,4,6-$^i$Pr$_3$-C$_6$H$_2$ (**1b** for Fe or **2b** for Co) with K(HBEt$_3$) yielded the [(ArN^Ndipp)Fe$^{II}$(Py)(μH,H)Fe$^{II}$(ArN^Ndipp)] hydride complex **3** or the [(ArN^Ndipp)Co$^{I}$(η$^6$-toluene)] arene complex **4**, depending on the metal used.




**Acknowledgements**

Support for this work was provided by FCT through PTDC/EQU EQU/110313/2009, UID/QUI/00100/2013 and RECI/QEQ-QIN70189/2012. T.F.C.C. acknowledges financial support from PD/BD/52372/2013 – CATSUS PhD Program.

**References**

[1] V.P. Ananikov, M. Tanaka, Hydrofunctionalization, Vol. 43, Springer, 2013.

[2] C.C. Chong, R. Kinjo, ACS Catalysis 5 (2015) 3238-3259.

[3] J.V. Obligacion, P.J. Chirik, Org. Lett. 15 (2013) 2680-2683.

**O04**

# Small active peptides: biophysical studies of the peptide-membrane interactions

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[2]*Centro de Proteómica e Análise Bioquímica, Universidade Católica de Brasília, Brasília - DF, Brazil*

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Healthcare is facing a new paradigm relative to the therapeutic applications of antibiotics against infections. During the last 30 years, antibiotic over dosage from patients suffering bacterial, viral or fungal infections led to an increase in microorganisms' resistance [1]. Particularly, Gram-negative bacteria strains belonging to the *ESKAPE* group (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa* and *Enterobacter* species) showed high propensity to antibiotic resistance. The World Health Organization alerted in 2016 for the urgent need to overcome this reality, but lack of pharmaceutical industry research in the last 30 years for new antibiotic molecules has increased the probability of failure. Related to this issue, small peptides identified in different organisms' innate immune system have gained a special interest. These antimicrobial peptides (AMPs) are characterized for being small and highly amphipathic, hydrophobic and cationic [2], properties that promote the interaction between the peptide and the membrane of the target cell [3].

In our work, we focused in the design of new AMPs that could target resistant Gram-negative bacteria. Specially, we focused in two synthetically designed AMPs (*Pa*-MAP 1.5 and *Pa*-MAP 1.9) that showed to be active against bacteria, including an antibiotic resistant strain (*Escherichia coli KPC*). Peptide-membrane interactions were studied by biophysical techniques (fluorescence spectroscopy, circular dichroism, dynamic light scattering, zeta-potential and atomic force microscopy) in lipid vesicles and bacteria cells. Results obtained showed that these peptides are capable to disrupt and destabilizes the membrane potential in both bacteria cells tested. These results suggest that these peptides could have a future therapeutic application as antimicrobials.

**Acknowledgements**

FCT-MCTES and MSCA-RISE (European Union) project INPACT. M.R.F. also acknowledges FCT-MCTES fellowship SPRH/BD/100517/2014.

**References**

[1] M.R. Felício, O.N. Silva, S. Gonçalves, N.C. Santos, O.L. Franco, Front. Chem. 5 (2017) 1-9.

[2] R.E.W. Hancock, E.F. Haney, E.E. Gill, Nat. Rev. Immunol. 16 (2016) 321-344.

[3] S.M. Ribeiro, M.R. Felício, E.V. Boas, S. Gonçalves, F.F. Costa, R.P. Samy, N.C. Santos, O.L. Franco, Pharmacol. Ther. 160 (2016) 133-144.

**O05**

# The 20S proteasome as a target: finding new inhibitors through computer-aided drug design methodologies and biological evaluation of the selected compounds

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[d]*Laboratório de Química Farmacêutica, Faculdade de Farmácia, Universidade de Coimbra, Portugal*

The ubiquitin proteasome system is a nonlysosomal pathway by which allows to regulate the controlled degradation of several proteins, not just in cell cycle and apoptosis but also in inflammatory and immune responses, carcinogenesis, for example. Usually, in protein homeostasis the defective proteins are ubiquitinated and are proteolysed into short peptides by the proteasome. Proteasome substrates include, namely, signalling molecules, tumour suppressors, cell cycle regulators and transcription factors. Proteasome inhibition results in an interruption of the degradation of these substrates, leading to activation of apoptotic pathways and cell death. Rapidly growing cells, such as cancer cells, are particularly susceptible to proteasome inhibition mechanisms [1-2].

This work relies on a computational-based drug discovery approach to find alternative new, selective (and more effective) small molecules as reversible proteasome inhibitors that can overcome the severe adverse drug reactions demonstrated by in use drugs. The efforts to discover new anticancer drugs described here combine different computer-aided drug design methodologies (i.e. molecular docking and structure-based virtual screening) in order to identify potential hit compounds (Figure 1). The selected compounds were tested in cell growth inhibition assays, being also performed inhibition assays for the chymotrypsin-like, trypsin-like and caspase-like activities of the proteasome using fluorogenic substrates.

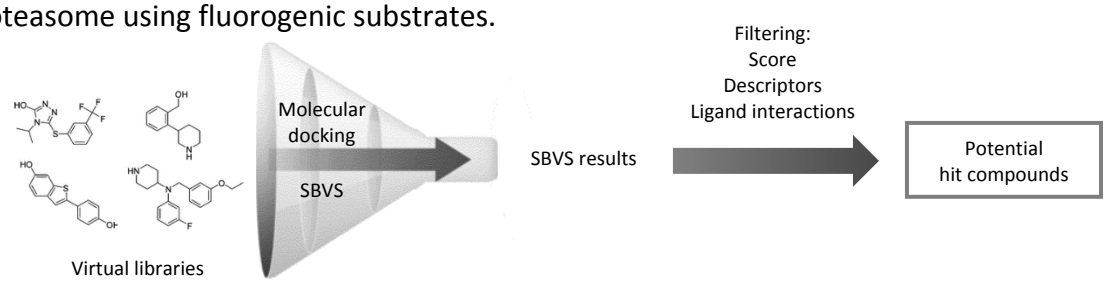


**Figure 1.** Computer-aided drug design workflow.

**Acknowledgements**

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**References**

[1] B. Ruggeri, S. Miknyoczki, B. Dorsey, A.M. Hui, Elsevier (2009) vol. 57.

[2] E.M. Huber, M. Groll, Angew. Chem. Int. Ed. Engl. 51 (2012) 8708-20.

**O06**

# NMR Crystallography in the characterization of new multicomponent crystal forms of neuroleptic drugs

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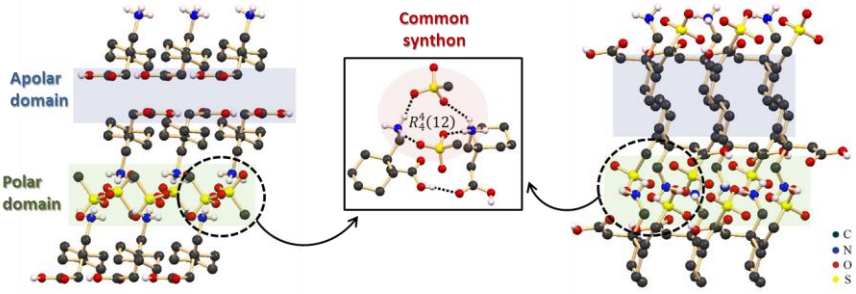
Launching new products in the maket is very expensive and extremely time consuming. Envisaging these aspects, pharmaceutical industry has shown a high interest on improving the efficacy of "old" drugs by enhancing their physicochemical properties (solubility, dissolution rate and bioavailability) without changing their pharmacological behavior. This has been adressed using several approaches including the preparation of multicomponent drug crystal forms (salts and co-crystals).[1,2]

Herein, we present an experimental SSNMR, single-crystal/powder X-ray diffraction (XRD), and computational study of the supramolecular assemblies of unusual lamellar Gabapentin (GBP) and Amantadine (AMA) salts/"solid" ionic liquids; two active pharmaceutical ingredients (APIs) used to treat neurodegenerative diseases, such as epilepsy and Parkinson, respectively.[3,4] In particular, for GBP ionic liquids, the effect of crystal packing interactions was investigated and quantified using SSNMR in tandem with periodic and cluster DFT calculations, by means of a stepwise *in silico* dismantlement of the 3D packing. To better understand the synergy between weak and strong hydrogen bonds, several computer cluster fragments were evaluated based on calculated packing-induced chemical shifts. In the case of AMA salts, the structural determination was carried out using powder XRD. DFT calculations were also used in tandem with SSNMR for structure validation (NMR crystallography). Solubility studies and thermal stability analysis were perfomed for all the prepared compounds, and the results show an improvement of this physicochemical properties.




**Acknowledgements**

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013. I.C.B.M. acknowledges financial support from SFRH/BD/93140/2013.

**References**

[1] D. Braga, L. Maini, F. Grepioni, Chem. Soc. Rev. 42 (2013) 7638-7648.

[2] S. Domingos, V. André, S. Quaresma, I.C.B. Martins, M.F.M. Piedade, M.T. Duarte, J. Pharm. Pharmacol. 67 (2015) 830-846.

[3] I.C.B. Martins, M.S. Santos, A. Fernandes, A. Antunes, V. André, L. Mafra, M.T. Duarte, Cryst. Growth Des. 16 (2016) 156-166.

[4] J. Jankovic, L.G. Aguilar, Neuropsychiatr. Dis. Treat. 4 (2008) 743-757.

**O07**

# Copper complexes bearing arylhydrazone, tetrazolate or pyrazolate ligands as catalysts for alkane oxidation

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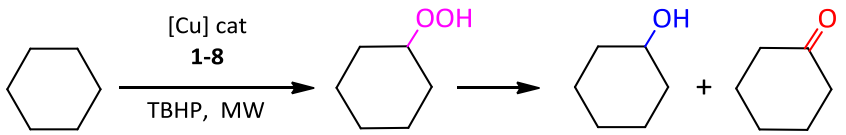
A series of copper(II)-based complexes have been synthesized and fully characterized: *i*) $[Cu(1\kappa N,O^2{:}2\kappa O\text{-}HL^1)(S)]_2$ [S = $CH_3OH$ (**1**), $(CH_3)_2NCHO$ (**2**)] and $[Cu(\kappa N\text{-}HL^1)(en)_2]\cdot CH_3OH\cdot H_2O$ (**3**), where $H_3L^1$ = (*E/Z*)-4-(2-(1-cyano-2-ethoxy-2-oxoethylidene)hydrazinyl)-3-hydroxybenzoic acid;[1] *ii*) $[Cu_2(phen)_2(ptz)_4]$ (**4**), $[Cu(phen)(pmtz)_2]$ (**5**) and $[Cu(phen)(pytz)_2]$ (**6**), where ptz = 5-phenyltetrazolate, pmtz = 5-(2-pyrimidyl)tetrazolate and pytz = 5-(2-pyridyl)tetrazolate);[2] and *iii*) $[Cu_2(\mu\text{-}N,N\text{-}3,5\text{-}(NO_2)_2pz)_2(PPh_3)_2]$ (**7**), [*trans*-$Cu_6(\mu\text{-}OH)_6(\mu\text{-}3,5\text{-}(CF_3)_2pz)_6$] (**8**), where pz = pyrazole.[3]

Compounds **1-8** were applied as alternative selective homogeneous catalysts for the industrially significant oxidation of cyclohexane to cyclohexanol and cyclohexanone. The peroxidative (with *tert*-butyl hydroperoxide, TBHP) oxidation of cyclohexane was performed under solvent-free and under low-power microwave (MW) irradiation (Scheme 1). Reaction parameters such as temperature, time oxidant nature, organic radical and acid influence were studied.




**Scheme 1.** Microwave-assisted neat oxidation of cyclohexane to cyclohexyl hydroperoxide, cyclohexanol and cyclohexanone with TBHP catalysed by the Cu complexes **1-8**.

**Acknowledgements**

This work has been supported by the FCT, Portugal (UID/QUI/00100/2013, PTDC/QEQ-ERQ/1648/2014 and PTDC/QEQ-QIN/3967/2014). N.M.R.M is thankful to FCT for the CATSUS PhD programme (PD/00248/2012) and his fellowship (SFRH/BD/52371/2013). The authors acknowledge the Portuguese NMR Network (IST-UTL Centre) for access to the NMR facility, and the IST Node of the Portuguese Network of mass-spectrometry for the ESI-MS measurements.

**References**

[1] N.M.R. Martins, K.T. Mahmudov, M.F.C.G. Silva, L.M.D.R.S. Martins, A.J.L. Pombeiro, New J. Chem. 40 (2016) 10071-10083.

[2] M. Saha, K.M. Vyas, L.M.D.R.S Martins, N.M.R. Martins, A.J.L. Pombeiro, S.M. Mobin, D. Bhattacherjee, K.P. Bhabak, S. Mukhopadhyay, Polyhedron 132 (2017) 53-63.

[3] R. Galassi, O.C. Simon, A. Burini, G. Tosi, C. Conti, C. Graiff, N.M.R. Martins, L.M.D.R.S. Martins, A.J.L. Pombeiro, Polyhedron 134 (2017) 143-152.

**O08**

# Fe(III) aminophenolate complexes as anticancer agents

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World Health Organization estimated cancer as the second leading cause of death worldwide.[1] In Portugal, 26,647 deaths were due to malignant neoplasms in 2015. Chemotherapeutic drugs treat or ease the symptoms of cancer. Platinum-based chemotherapeutic drugs integrate standard treatment against many types of cancer albeit their toxicity. The development of drugs based on biologically essential transition metals aims on improving metallodrugs toxicity issues. Iron, being redox-active and involved in the regulation of cell-growth and differentiation is an appealing candidate to achieve highly effective, as well as less toxic chemotherapeutic agents.

Iron(III)-complexes with tripodal aminophenolate ligands have been studied as mimics of enzyme active sites and metal-binding sites of iron proteins. Few reports deal with their application as therapeutic agents. Introduction of *o*-phenanthroline or derivatives as co-ligands should enforce the complexes' biological activity since metal complexes containing phenanthrolines are reported as active against various pathologic conditions.[2] We synthesized a family of Fe(III)-complexes bearing a tripodal aminophenolate ligand with phenanthroline co-ligands (Figure 1). The complexes exhibit cytotoxic activity against several human cancer cell lines. Cells treated with the complexes display typical morphological features of apoptosis (Fig. 1). Despite their similarity, the complexes induce distinct conformational changes in DNA. Co-ligands structural differences account for the different interaction modes of the complexes. Hence, initial studies showed promising anticancer activity granting promise for further studies.

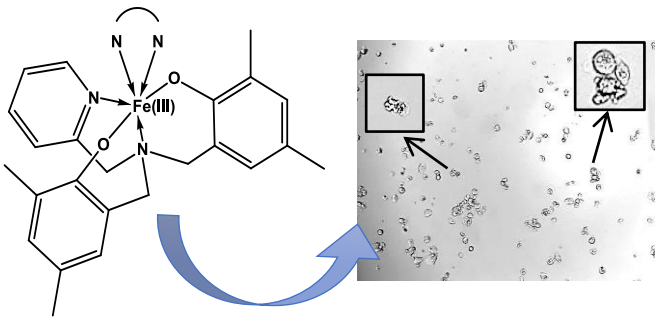


**Figure 1.**

**Acknowledgements**

Authors thank Dr. Fernanda Marques (C2TN-IST) for A2780 cell studies, the Portuguese NMR Network (IST Nodes) and financial support from FCT, TUBITAK Internal Funding, the Investigador FCT programme 2012 and 2013 (project IF/01179/2013, POPH and the European Social Fund), project UID/QUI/00100/2013 and PhD grants SFRH/BD/101214/2014 and SFRH/BD/108743/2015.

**References**

[1] http://www.who.int/mediacentre/factsheets/fs297/en/

[2] S. Jagadeesan, V. Balasubramanian, P. Baumann, M. Neuburger, D. Haussinger, C.G. Palivan, Inorg. Chem. 52 (2013) 12535-12544.

O09

# Therapeutic transition-metal Schiff bases complexes containing $B_6$-vitamers

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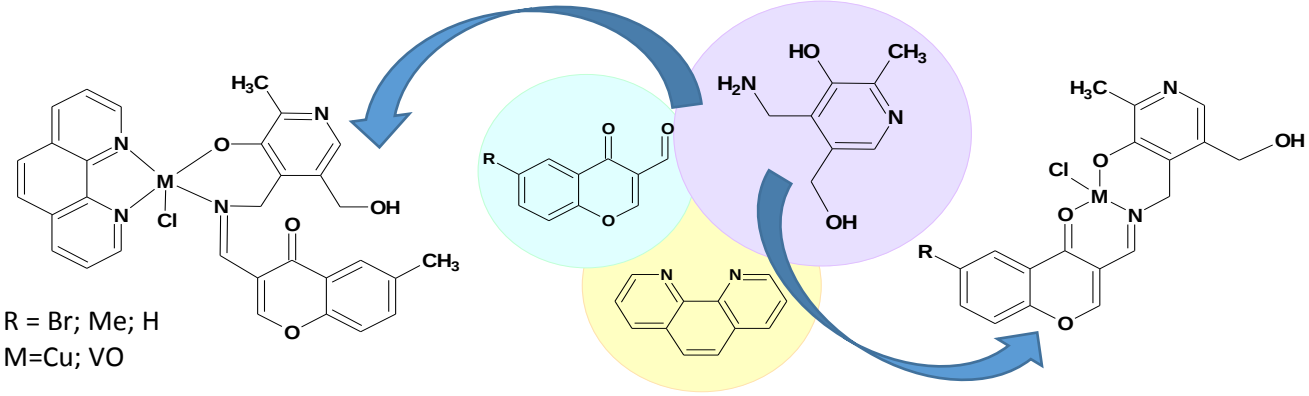
Copper deficiency or toxicity is implicated in a variety of pathological conditions. Therefore copper-complexes have been investigated for their therapeutic and diagnostic potential and have shown to be effective in cancer treatment due to their cytotoxic action on tumour cells [1].

Coenzyme vitamin-$B_6$ is known to be involved in numerous biochemical reactions that occur in cell metabolic processes. $B_6$-Vitamers have gathered increasing attention since Longenecker and co-workers have successfully mimicked enzymatic reactions by non-enzymatic reactions in which pyridoxal in the presence of an appropriate metal ion acts as catalyst [2]. The Schiff base (SB) complex formation has been linked with this reaction mechanism [3]. A VO(IV)-pyridoxal SB complex has shown high selectivity and cytotoxicity for two carcinoma cells lines in which the cell death mechanism involves apoptosis through ROS formation [4]. Additionally, vitamin B6 is an antioxidant that at high concentrations in cancer cells induces significant reductions in cell-proliferation [5]. Therefore, exploration of pyridoxal Cu-complexes has high potential for successfully develop effective chemotherapeutics.

In the current work, four SB Cu(II) and two SB VO(IV) complexes containing $B_6$-vitamers, were synthesized and characterized by several techniques. Preliminary results on antioxidant activity, interactions with DNA and cytotoxicity for two cancer lines (MCF7 and A2780) are reported.

Most complexes showed moderate to high cytotoxicity against MCF7, with the compound containing the phenantroline co-ligand showing the best performance in both cell lines.

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**References**

[1] C. Duncan, A.R. White, Metallomics 4 (2012) 127-138.

[2] D.E. Metzler, J.B. Longenecker, E.E. Snell, J. Am. Chem. Soc. 75 (1953) 2786-2787.

[3] A.E. Martell, Acc. Chem. Res. 22 (1989) 115.

[4] M. Strianese, A. Basile, S. Morello, M. Turco, C. Pellecchia, J. Cell Physiol. 228 (2013) 2202-2209.

[5] T.D. Shultz, D. Lee, D.R. Stickney, D.S. Gridley, Nutrition Research, 9(2) (1989) 133-151.

**O10**

# BioMOFs – A new way to improve azelaic acid solubility

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In the last years, Bioinspired Metalorganic Frameworks (BioMOFs) emerged as new drug delivery materials. These are new promising systems that can tackle the drawbacks of the traditional ones, such as low drug-storage capacity, too rapid delivery and possible toxicity. In this work, we present the results obtained when we embraced the challenge of synthesizing new BioMOFs, using safe metals and active pharmaceutical ingredients (API) as linkers, recurring to mechanochemistry, a green and not very traditional technique for the synthesis of this type of compounds.[1]

The new BioMOFs were synthesize using azelaic acid, an API commonly used to treat skin disorders, with several safe metals such as Mg, K, Na and Ag. These novel compounds were structurally characterized and their stability under different conditions (temperature, time and humidity) was explored (Figure 1a and 1b). The new material containing Ag is the most promising system, as a potential synergetic effect as a bactericide can be attained. Nevertheless, all the other systems are also relevant as they increase the solubility of azelaic acid, in some cases over ten times (Figure 1c).

These systems can be promising applications in the pharmaceutical field and therefore toxicity and antimicrobian activity are under study.

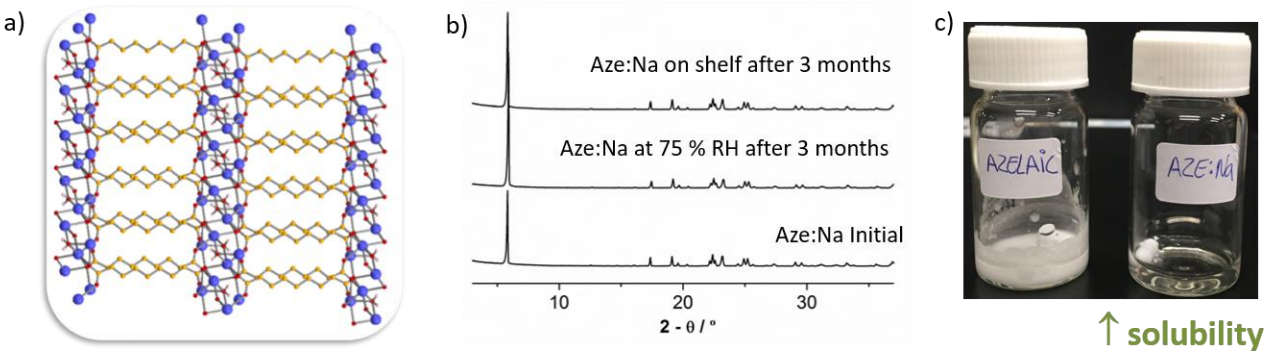


**Figure 1.** a) Molecular structure view of the new compound with azelaic acid and Na (AZE:Na); b) Stability study of AZE:Na at 75 % of Room Humidity and on shelf; c) Solubility study of AZE:Na

**Acknowledgements**

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**References**

[1] a) S. Keskin *et al.*, Ind. Eng. Chem. Res. 50(4) (2011) 1799; b) A.C. McKinlay *et al.*, Angew. Chem. Int. Ed. 49 (2010) 6260; c) P. Horcajada *et al.*, Chem. Rev. 112(2) (2012) 1232.

**O11**

# Homogeneous $CO_2$ reduction by salen-type complexes

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The versatility of salen-type (salen = N,N–bis(salicylidene)ethylenediamine) complexes has been shown, among others, in their extensive applications in electrochemistry owing to their electrochromic,[1] sensor[2] and catalytic[3] properties. Mono and binuclear complexes were synthesised, the latter being prepared by a template procedure. A template synthesis allowed the preparation of homobinuclear complexes and a newly developed stepwise procedure led to heterobinuclear complexes, with two distinct environments for the metal centres.[4,5] The compounds were characterised by FTIR spectroscopy, elemental analysis and HR-mass spectrometry. Studies with these complexes were performed on the homogeneous conversion of $CO_2$. Bulk electrolysis experiments were performed and gas chromatography with a thermal conductivity detector was used to detect and quantify the reduction products. Additionally, DFT calculations were performed to investigate the $CO_2$ reduction mechanism.

**Acknowledgements**

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**References**

[1] D.T. Whipple, P.J.A. Kenis, The Journal of Physical Chemistry Letters 1 (2010) 3451.

[2] G.W. Coates, D.R. Moore, Angew. Chem. Int. Ed. 43 (2004) 6618.

[3] J. Meléndez, M. North, R. Pasquale, Eur. J. Inor. Chem. 21 (2007) 3323.

[4] S. Realista, A.S. Viana, B.P. Cardoso, A.M. do Rego, P.D. Vaz, A.I. Melato, P.N. Martinho and M.J. Calhorda, RSC Adv. 5 (2015) 39495.

[5] S. Realista, P. Ramgi, B.P. Cardoso, A.I. Metalo, M.J. Calhorda, P.N. Martinho, Dalton Trans. 45 (2016) 14725.

**O12**

# Exploring the luminescent properties of tetracoordinate boron complexes

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The production of new luminescent organic and organometallic materials for the application in Organic Light Emitting Diodes (OLEDs) is making great improvements in order to achieve the next generation of flat-panel displays and lighting sources [1]. Light-emitting diodes (LEDs) prepared with four-coordinate boron compounds bearing bidentate *N,N* or *N,O*-ligand chromophores exhibit good properties [2]. Taking into account that the steric and electronic characteristics of the 2-iminopyrrolyl ligand core can be varied, the colour tuning becomes wider [3]. Therefore, they have been employed in the synthesis of a new family of 2-(*N*-arylformimino)pyrrolyl diphenylboron compounds with interesting luminescence properties [4]. Also, different 9-borafluorene molecules combined with several chomophores revealed good fluorescence emissions and quantum yields [5]. Aiming to explore different photoluminescence properties by using the internal heavy atom effect, $\pi$-conjugation extension and intramolecular group orthogonality, we report in this communication the synthesis of new 2-iminopyrrolyl-$BPh_2$ and 9-borafluorene chromophores (Figure 1) and their structural and photophysical characterisation.

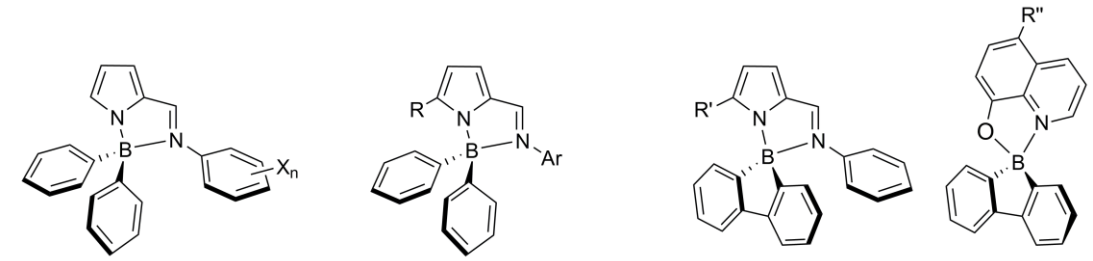


**Figure 1.** Boron complexes of the types **A**, **B**, **C** and **D** synthesized.

**Acknowledgements**

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**References**

[1] T.K.S. Wong, in H.S. Nalwa (Eds.), Handbook of Organic Electronics and Photonics, American Scientific Publishers: Stevenson Ranch, CA, 2008, Vol. 2, pp. 413-472.
[2] D. Li *et al.*, Chem. Soc. Rev. 42 (2013) 8416.
[3] P.T. Gomes *et al.* (IST), World Patent WO2013039413 (2013).
[4] For example: (a) D. Suresh *et al.*, Chem. Eur. J. 20 (2014) 4126; (b) D. Suresh *et al.*, Chem. Eur. J. 21 (2015) 9133; (c) P. Krishnamoorthy *et al.*, Dyes Pigm. 140 (2017) 520-532.
[5] (a) S. Yamaguchi *et al.*, J. Am. Chem. Soc. 124 (2002) 8816-8817; (b) A. Wakamiya *et al.,* Chem. Commun. (2008) 579-581; (c) V.D.B. Bonifácio *et al.*, J. Polym. Sci., Part A: Polym. Chem. 46 (2008) 2878-2883.

**O13**

# Boron-promoted Modular Assembly of Reversible and Multivalent Tumor-Targeting Drug Conjugates

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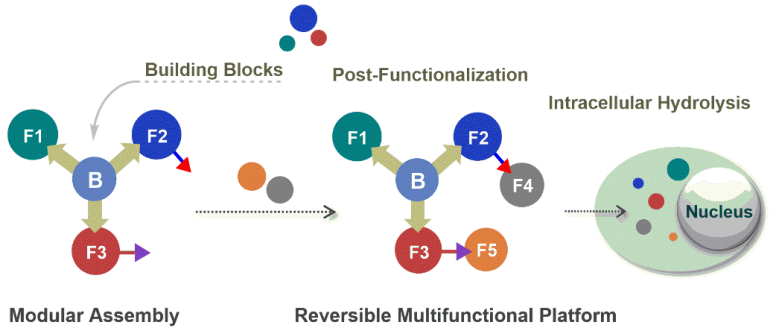
Recent developments of human biology allowed a more clear understanding of the intricate pathogenesis of complex diseases such as cancer. The evolution of normal cells to a neoplastic state is a multifaceted biological process in which normal cells acquire capabilities of sustaining proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis. Consequently, the most recent strategies to tackle cancer, aim at interrupting one or more of these stages using multifunctional constructs.[1] Targeting drug conjugates, like antibody (ADCs) and small-molecules (SMDCs), are multivalent conjugates that combine the lethality of potent cytotoxic drugs with the targeting ability of specific biomolecules that elicit a high affinity for antigens overexpressed in cancer cells.[2] Herein is described a new modular platform to construct cancer cell targeting drug conjugates (Scheme 1). Tripodal boronate complexes, featuring reversible covalent bonds, were design to accommodate, a cytotoxic drug (bortezomib), polyethylene glycol chains and folate targeting units. The B-complex core was assembled in one step, and proved stable in different biocompatible conditions, namely human plasma (half-life up to 60 h) and reversible in the presence of glutathione (GSH). The stimulus responsive intracellular cargo delivery was confirmed by confocal fluorescence microscopy and a mechanism for GSH induced B-complex hydrolysis was proposed based on mass spectrometry and DFT calculations. This platform enabled the modular construction of multifunctional conjugates exhibiting high selectivity towards folate positive MDA-MB-231 cancer cells with IC50 values in the nanomolar range.[3]




**Scheme 1.** Modular assembly of multifunctional/reversible targeting drug conjugates promoted by boron.

**Acknowledgements**

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**References**

[1] a) D. Hanahan, R.A. Weinberg, Cell 144 (2011) 646; b) N. Sethi and Y. Kang, Nat. Rev. Cancer 11 (2011) 735; c) M.A. Swartz *et al.*, Cancer Res. 72 (2012) 2473.

[2] a) P. Akkapeddi *et al.*, Chem. Sci. 7 (2016) 2954; b) I. Vergote, C.P. Leamon, Ther. Adv. Med. Oncol. 7 (2015) 206.

[3] F.M.F. Santos *et al.*, Angew. Chem. Int. Ed. 56 (2017) 936.

**O14**

# Oxidation of cyclohexane catalyzed by copper(II) complexes of arylhydrazone in ionic liquids

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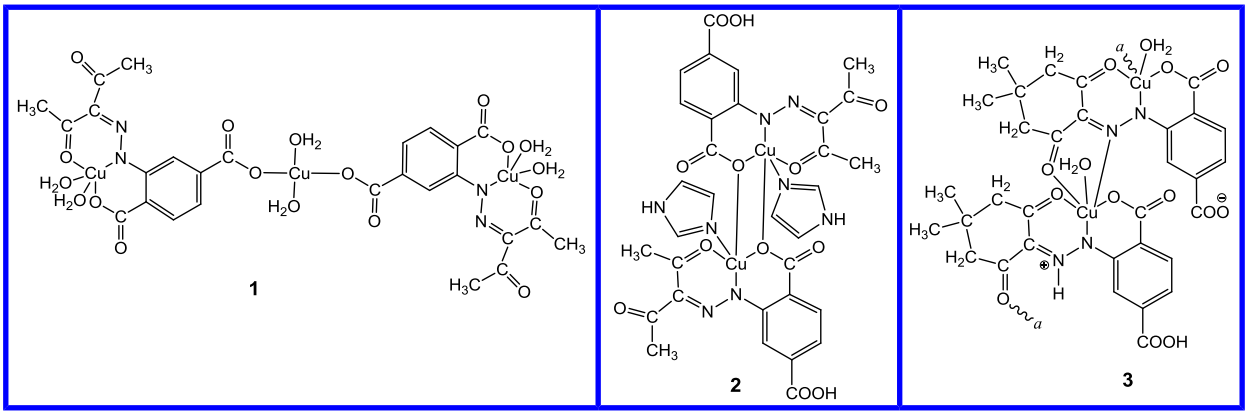
Several known copper(II) complexes of arylhydrazone of β-diketone were synthesized (Scheme 1)[1] and applied as catalysts for cyclohexane oxidation. The reaction was carried out in microwave and using an organic solvent (acetonitrile) or an ionic liquid.

The effect of reaction time, in the presence of acidic additive, will be discussed. The difference in catalytic behavior due to the presence of the ionic liquid will be addressed. The different structures of the complexes (Scheme 1) will also be related with the experimental results of the reaction.




**Scheme 1.** Schematic representations of **1**–**3**.

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**References**

[1] R. Jlassi, A.P.C. Ribeiro, M.F.C. Guedes da Silva, K.T. Mahmudov, M.N. Kopylovich, T.B. Anisimova, H. Naili, G.A.O. Tiago, A.J.L. Pombeiro, Eur. J. Inorg. Chem. (2014) 4541-4550.

**F01**

# Small-molecule immune system modulators: An *in silico* strategy towards cancer immunotherapy

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Immunotherapy is nowadays a powerful strategy in cancer therapy. In particular, modulation of immune checkpoint receptors have gain special attention. These immune regulators limit proliferation and activity of T cells and other immune cells enrolled in these signaling pathways.[1] Under normal conditions, they are essential in modulation of immune responses; however, they are also one of the major mechanisms used by tumors to evade immune system recognition and destruction. To date, several immune checkpoint receptors have been identified and used as therapeutics in oncology, as programmed cell death protein 1 (PD-1). When engaged by one of its ligands (PD ligand 1 (PD-L1) and PD ligand 2) PD-1 limits autoimmunity. PD-1 ligands are upregulated in many human cancers and their blockade could lead to activation of T cells and therefore enforce tumor recognition. In fact, PD-1/PD-L1 pathway is one of the most successful pathways in the context of clinical cancer immunotherapy. The most successful therapies relay on the use of antibodies. However, despite their outstanding success, they still have numerous disadvantages as severe immune-related adverse. Recently, the hypothesis of small-molecule modulators as a safer therapeutic alternative have been raised.[2] However, limited efforts have been directed toward immune checkpoint receptors. Our study is focus on the discovery of small molecules targeting PD-L1 that can block PD-1/PD-L1 interaction in order to overcome antibody therapy disadvantages. The limited structural information concerning PD-L1 led us to a detailed structural characterization based on *in silico* studies in order to assess structural flexibility or binding pockets. Following a computer assisted drug discovery approach to achieve PD-L1 inhibitors we accomplished a virtual screening campaign based on the crystal structure of PD-L1 and databases of small molecules. Potential PD-L1 inhibitors were selected based on their affinity for PD-L1 using several parameters. In fact, immune checkpoint blockade using small molecules represent a step forward in cancer immunotherapy.

**Acknowledgements**

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**References**

[1] (a) D.M. Pardoll, Nat. Rev. Cancer 12 (2012) 252; (b) S.L. Topalian, C.G. Drake, D.M. Pardoll, Cancer Cell 27 (2015) 451.

[2] (a) K. Barakat, J. Pharma Care Health Sys (2014) 1; (b) Z.M. Krzysztof, G. Przemyslaw, G. Katarzyna, Z.J. Bartosz, M. Bogdan, D. Alexander, D. Grzegorz,H.A. Tad, Oncotarget 7 (2016) 30323.

**F02**

# Bio-inspired polydopamine films for electrochemical biosensors

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Electrochemical biosensors are powerful analytical devices of utmost importance in the fields of biomedicine, food safety, environmental monitoring, among others. Research work on biomimetic and bio-inspired approaches has recently intensified to overcome the fundamental challenges regarding immobilization of biorecognition elements [1]. Mussel-inspired chemistry is such a strategy, emerging as a simple tool for surface functionalization with catechol, amine and imine groups, and allowing covalent binding of target biomolecules, through a Schiff base formation or Michael type reaction [2]. In addition, the use of such adhesive polymer facilitates nanomaterials conjugation, aiming to amplify enzyme's catalytic activity [3]. Although spontaneous driven polymerization of dopamine is currently the standard method for polydopamine synthesis, electropolymerization has a great potential to better control thin film synthesis, allowing modulation of its oxidation state [4], thus solving the problems of reproducibility and stability that still exist.

In this work, we have prepared polydopamine films by spontaneous synthesis in aerated solutions and through electropolymerization, on carbon electrodes. The modified electrodes have been extensively characterized using a combination of techniques, to evaluate their morphology, thickness, wettability, electrochemical and dielectric properties, allowing a proper selection of PDA films to be used as biosensing interfaces. The catalytic activity of immobilized Laccase on PDA films was investigated toward an electroactive aromatic amine, ABTS, by cyclic voltammetry and chronoamperometry. It was verified, that a simple and effective co-immobilization of Laccase, PDA and iron oxide nanoparticles outcomes in a significant enhancement of enzyme catalytic activity signals, revealing the promising use of PDA-based nanostructured interfaces in biosensor devices.

**Acknowledgements**

The authors are grateful to Professor M. D. Carvalho(†), CQB-FCUL, for the synthesis of nanoparticles, and to Professors Alessandra Morana and Francesco La Cara (IBAF-CNR, Naples, Italy) for providing Laccase. Support for this work was provided by FCT through UID/MULTI/00612/2013, PEst-OE/QUI/UI0612/2013, IF/00808/2013 (POPH, UE-FSE), PTDC/CTM-NAN/0994/2014 and SFRH/BD/129566/2017.

**References**

[1] P.O. Saboe *et al.*, Energy Environ. Sci. 10 (2017) 14.

[2] Y. Liu *et al.*, Chem. Rev. 114 (2014) 5057-5115.

[3] I. Almeida *et al.*, J. Coll. Int. Sci. 485 (2017) 242-250.

[4] G. Tan *et al.*, Electrochim. Acta 228 (2017) 343-350.

**F03**

# Halimane diterpenes from *Plectranthus ornatus* Codd. against *Mycobacterium tuberculosis* H37Rv

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Natural products are a unique source of lead compounds for medicinal chemistry drug development. The *Plectranthus ornatus* Codd. plant is often used in traditional medicine, particularly in some regions of Brazil for antimicrobial purposes. Several diterpene compounds have been successfully isolated from some *Plectranthus* spp. and studied for their anti-tubercular activity against the non-virulent *Mycobacterium smegmatis* [1,2].

In previous works, a new halimane diterpene from *P. ornatus* was isolated in large quantities [1,3]. The halimane isolated has a structural similarity with the Rv3377c/Rv3378c targets, which have an important role to the bacterial survival and to its virulence [4]. Therefore, we assessed the anti-tubercular activity of this halimane and some of its hemi-synthetic derivatives, previously prepared, against *M. tuberculosis* H37Rv (Mtb).

The compounds cytotoxicity was tested measuring LDH release and no considerable cytotoxic effects were found up to 25 µg/mL. Afterwards, they were assessed on the survival of Mtb during the infection of PBMC cells, by CFU experiment, using ethambutol and isoniazid as positive controls. The CFU obtained 48h after treatment until day 13, were very promising results on compound (11*R**,13*E*)-halima-5,13-diene-11,15-diol ($2.1x10^5$ CFU/mL), proving to be as effective as ethambutol ($2.0x10^5$ CFU/mL), a known drug for Mtb treatment.

To the best of our knowledge, this is the first report on halimane diterpenes isolated from *P. ornatus* tested for cytotoxicity in macrophages, and in a preliminar assay for anti-tubercular activity. Further studies are forthcoming to potentiate the anti-Mtb activity.

**Acknowledgements**

This work was supported by a STSM Grant from COST Action CM1407 “Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery” and by FCT (Fundação para a Ciência e Tecnologia-Portugal) grant UID/DTP/04567/2016.

**References**

[1] P. Rijo, B. Rodríguez, A. Duarte, M.F. Simões, The Natural Products Journal 1 (2011) 57-64.

[2] P. Rijo, M.F. Simões, A.P. Francisco, R. Rojas, R.H. Gilman, A.J. Vaisberg, B. Rodríguez, C. Moiteiro, Chemical & Biodiversity 7 (2010) 922-932.

[3] P. Rijo, C. Gaspar-Marques, M.F. Simões, M.L. Jimeno. B. Rodríguez, Biochemical Systematics and Ecology 35 (2007) 215-221.

[4] H.C. Chan, X. Feng, T.P Ko, C.H. Huang, Y. Hu, Y. Zheng, S. Bogue, C. Nakano, T. Hoshino, L. Zhang, P. Lv, W. Liu, D.C. Crick, P.H. Liang, A.H.J. Wang, E. Oldfield, R.T. Guo, J. Am. Chem. Soc. 136 (2014) 2892-2896.

F04

# A protective group for boronic acids that selectively inhibit Human Neutrophil Elastase

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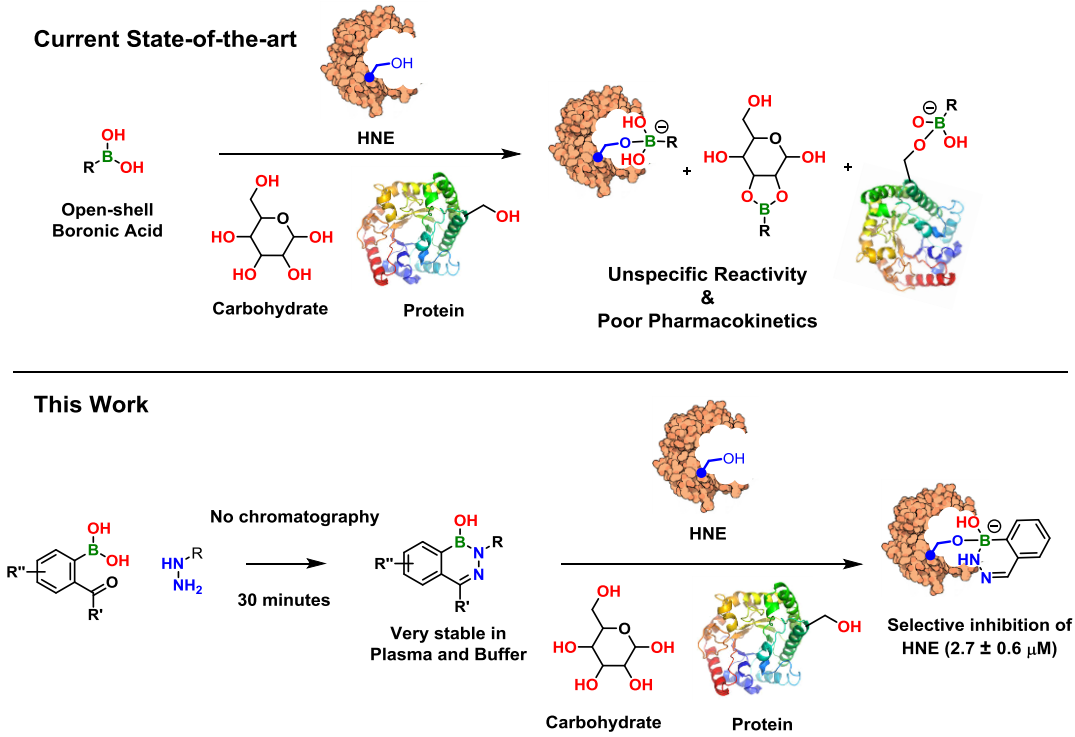
Boronic Acids (BAs) are a preeminent functionality extensively used to design biologically active compounds and functional biomaterials. Due to boron's open shell, this class of inhibitors also exhibits unspecific reactivity with endogenous nucleophiles that often increases their off target toxicity. Here diazaborines are presented as a new class of boron based warheads for serine proteases inhibition, in which the boron functionality is stabilized in the form of an aromatic BN heterocycle. In this study, diazaborines were readily synthesized in a single step in yields up to 96%, without any chromatographic operation and were shown to selectively inhibit HNE serine protease with IC50's values in the low µM range. Synthetic and theoretical studies performed on this system suggest that, like BAs, the reaction mechanism involves the formation of a reversible covalent bond between the diazaborine boron center and the catalytic serine oxygen. Finally and differently from BA, diazaborines were shown very stable in different biocompatible conditions like buffer and human plasma.

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F05

# Identification of LRRK2 inhibitors using a targeted screening strategy

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Parkinson's disease (PD) is the second most common progressive neurodegenerative disease worldwide, affecting approximately 1.5% of the population above 60 years of age and 4% of the population at the age of 80.[1, 2]

Leucine-rich repeat kinase 2 (LRRK2), also known as dardarin, is a multi-domain serine-threonine kinase belonging to the ROCO protein family, which has been associated with a diverse set of cellular functions and signalling pathways.[3] Although the endogenous role of LRRK2 protein remains largely unknown, research into the molecular bases of PD has uncovered a role for mutant forms of LRRK2 in autosomal dominant forms of the disease, suggesting that pathogenic variants of this protein are usually associated with an increase in kinase activity [3]. Therefore, inhibition of LRRK2 kinase function with small molecules is now considered one of the most promising therapeutic strategies for the treatment of PD [3].

With the aim of discovering new and innovative small molecules that can inhibit LRRK2 and be further used in the treatment of PD, a targeted screening strategy combining virtual screening and structure-based drug design with yeast-based screening assays is being developed.

Since no crystal structure of LRRK2 is currently available, the first goal of this work was to identify a protein structure, using homology modelling, which could be used in the rational design of LRRK2 inhibitors. To accomplish this purpose, a series of LRRK2 kinase domain models were generated and optimized. Janus kinase 2 (JAK2)-based LRRK2 homology model was selected for further validation through docking studies on a diverse set of previously reported LRRK2 inhibitors. A yeast-based phenotypic assay was implemented and the biological activity of selected LRRK2 inhibitors was evaluated. The main results of these studies will be presented and discussed.

**Acknowledgements**

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**References**

[1] A. Elbaz, L. Carcaillon, S. Kab, F. Moisan, Revue Neurologique 172 (2016) 14-26.
[2] L.V. Kalia, A.E. Lang, Lancet 386 (2015) 896-912.
[3] R. Wallings, C. Manzoni, R. Bandopadhyay, FEBS J. (2015) 2806-2826.
[4] C. Pereira, L.M. Martins, L.I.S. Saraiva, Biochimica et Biophysica Acta 1840 (2014) 2025-2031.

F06

# Towards clickable radio-immuno conjugates as theranostic agents for TEM-1 targeting

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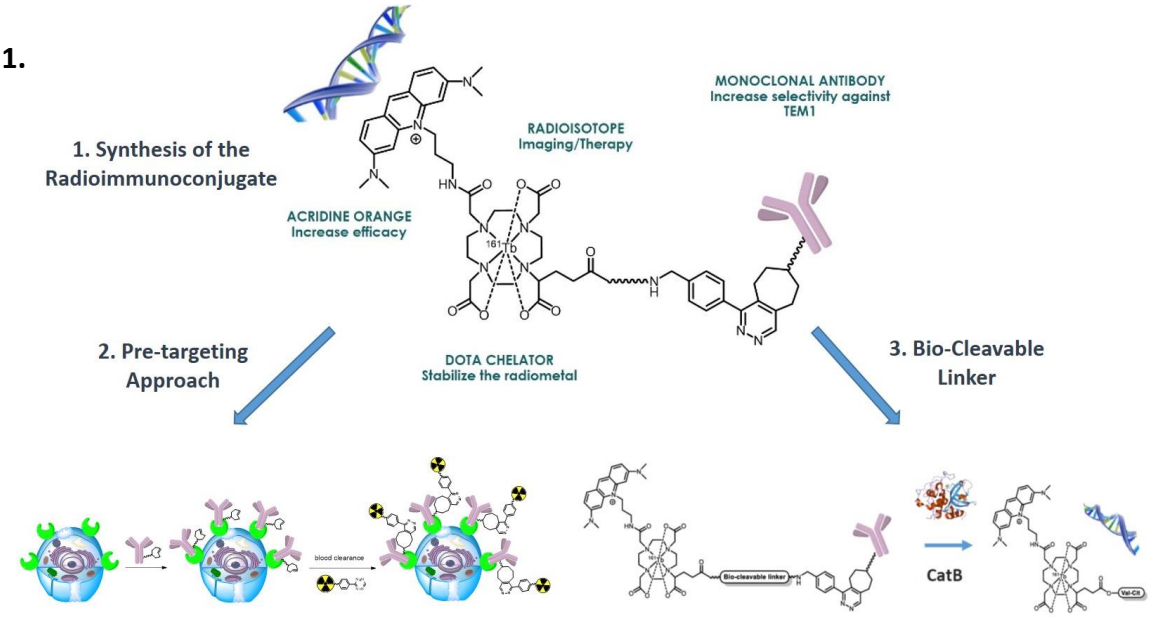
Terbium has four clinically relevant isotopes with identical chemical properties, which are excellent candidates for theranostic applications: $^{149}$Tb (α emitter), $^{152}$Tb ($\beta^+$ emitter), $^{155}$Tb (γ emitter), and $^{161}$Tb ($\beta^-$ and Auger emitter) [1]. We are studying the synthesis, characterization and biological evaluation of multifunctional radioconjugates where the radiometal is stabilized by a clickable macrocyclic chelator that should react with an antibody fragment for specific recognition of tumor cells. Therefore, the chelators will also contain a tetrazine moiety for *in vivo* click reactions with trans-cyclooctene derivatives, a DNA intercalator to enhance the biological effects of short-range Auger electrons and a bio-labile linker to release *in vivo* the DNA-targeted radiometallated fragment (Figure 1).

Prior to the studies with the Tb radioisotopes, several experiments are underway to optimize the design of our final radio-immuno conjugates, including:

- Choice of the more appropriate chelator structure
- Evaluation of a small panel of antibody fragments targeting **TEM-1**,[2] using better available radionuclides like $^{125}$I and $^{111}$In.

The development of such conjugates and the investigation on innovative strategies to improve their pharmacological behavior will provide new insights for the development of Tb-based radiopharmaceuticals on which few studies have been reported so far.

**Figure 1.**




**Acknowledgements**

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**References**

[1] C. Müller *et al.*, J. Nucl. Med. 53 (2012) 1951-1959.

[2] S. Dunn, G. Coukos *et al.*, Oncotarget. 5 (2014) 6994-7012.

F07

# Minimising fluid contamination through bioactive filters

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Over two-thirds of Earth surface is covered by water, and its contamination with micro/macroorganisms on submerged surfaces, the so-called industrial biofouling, is an actual challenge causing not only serious environmental and economic issues but also health risks. Particularly in fluid transport systems (e.g. water purification, desalination units), biofouling detachment from contaminated surfaces is promoted by the fluid flows itself, leading to its subsequent bio-contamination. On the other hand, this natural and spontaneous phenomenon is conventionally treated with the direct release of toxic agents into the contaminated fluid and/or into the surroundings of the contaminated surfaces, triggering additional environmental penalties as a result of agents inherent ecotoxicity.

In this work, a recent non-toxic potential solution for biofouling control of surfaces is described (WO2016/093719A1). Functional reactive biocidal agents were used for the tethering of Econea biocide to antifouling polymeric coatings, which were further applied for the protection of ceramic monolithic filters surfaces. FTIR, NMR and bioactivity studies confirmed that the functionalization and immobilization were successfully achieved without changing the bioactivity of the biocide, particularly for the tested Gram-positive bacteria (*Staphylococcus aureus* and *Enterococcus faecalis*). Bioactivity assessments performed on coated ceramic monoliths containing the immobilized biocide showed promising antimicrobial and bacteriostatic behaviour against Methicillin-Resistant *Staphylococcus aureus* bacteria. The bacteriostatic properties of the obtained coated filters are an auspicious result, since they can overcome the constraint on bacteria treatment resistance commonly associated with toxic agents releasing strategies.

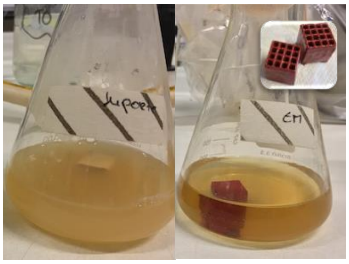

**Figure 1.** Illustration of the inhibition growth of the bacteria *S. aureus* MRSA CIP 106760 on a coated ceramic monolithic filter (200 cpsi) with a silicone based coating containing tethered Econea (about 0.6 wt.%) (on right), when compared with an uncoated filter (on left).

**Acknowledgements**

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**References**

[1] T.R. Bott, Industrial Biofouling (1st Ed.), Elsevier: Oxford, UK, 2011, pp. 1-199.

F08

# Improving the antitumor potential of 6,7-dehydroroyleanone through Mitsunobu Reactions

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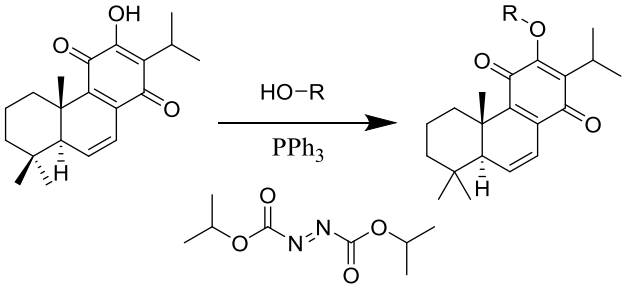
The *Plectranthus* genus is a known source of bioactive diterpenoids with antitumor potential [1]. The cytotoxic abietane diterpene 6,7-dehydroroyleanone was extracted and isolated from *P. madagascariensis* essential oil and this process was optimized in order to achieve high yields [2].

Initially, its preliminary toxicity was assessed through a lethality test against *Artemia salina* L. brine shrimp, and its antitumor potential further explored in different cancer cell lines: colon colorectal carcinoma (HCT116), human breast adenocarcinoma (MCF-7) and lung cancer carcinoma (NCI-H460).

The promising results regarding 6,7-dehydroroyleanone cytotoxic profile appealed to the creation of a small library of potential anticancer agents.

Mitsunobu reactions rely on the displacement of an alcohol with a pronucleophile (Nu−H) mediated by phosphine and azocarboxylate reagents, which activate the pronucleophile through deprotonation and convert the alcohol to a reactive alkoxyphosphonium species [3]. Thus, microwave-assisted Mitsunobu reactions were carried out in order to explore the reactivity of the abietane royleanone. Given its special acidity of the C-12 hydroxyl group, the insertion of nucleophiles – such as functionalized primary and secondary alcohols – are expected to change the original 6,7-dehydroroyleanone scaffold. Ultimately, its preliminary toxicity was evaluated according to the previously used model of *Artemia salina*.




**Acknowledgements**

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**References**

[1] C. Lukhoba, M. Simmonds, A. Paton, Journal of Ethnopharmacology 103 (2006) 1-24.

[2] D. Ladeiras, C. Monteiro, F. Pereira, C. Reis, C. Afonso, P. Rijo, Curr. Pharm. Des. 22(12) (2016) 1682-1714.

[3] J. Buonomo, C. Aldrich, Angewandte Chemie - International Edition 54(44) (2015) 13041-13044.

F09

# Copper promoted fast and efficient synthesis of *trans*-4,5-diamino-cyclopent-2-enones in aqueous media: a clickable potential new platform for chemical biology

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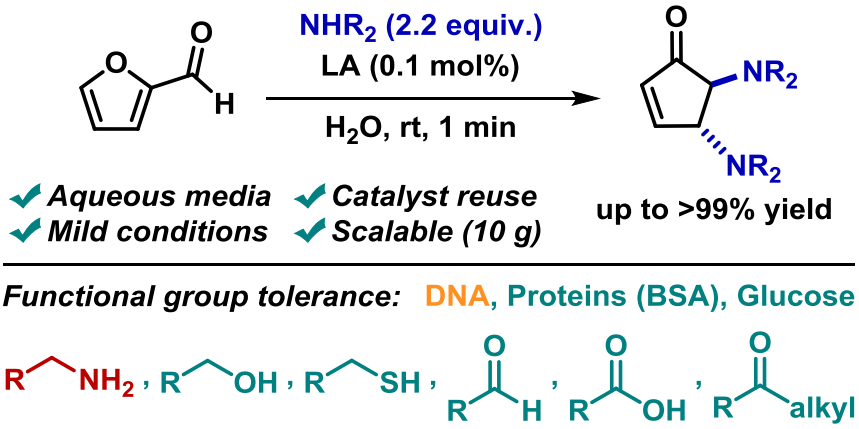
*Trans*-4,5-diamino-cyclopent-2-enones (CP) are usually prepared from the condensation of furfural and secondary amines promoted by a Lewis acid.[1] Methodologies consisting in ionic liquid 1-methylimidazolium tetrafluoroborate,[1b] heteronuclear clusters with general formula $[Ni^{II}_2Dy^{III}_2L_4Cl_2(CH_3CN)_2]\cdot 2CH_3CN$[1c] and Erbium(III) chloride in ethyl lactate as a more sustainable alternative[1d,e] have been described for the preparation of CP in organic solvents. Nonetheless, a mild procedure for the synthesis of CP in aqueous media has not been described. Herein, this work aims for the development of a suitable catalytic system for the formation of CP on aqueous media at room temperature. Furthermore, the mild reaction conditions, catalyst reusability and outstanding functional group tolerance suggests that this CP platform is suitable for applications in chemical biology.[2]




**Scheme 1**. Lewis acid promoted synthesis of *trans*-4,5-diamino-cyclopent-2-enones in aqueous media.

**Acknowledgements**

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**References**

[1] a) S.-W. Li, R.A. Batey, Chem. Commun. 8 (2007) 3759-3761 (Scheme 1); b) D. Ramesh, T.S. Reddy, M. Narasimhulu, S. Rajaram, N. Suryakiran, K.C. Mahesh, Y. Venkateswarlu, Chem. Lett. 38(6) (2009) 586-587; c) K. Griffiths, C.W.D. Gallop, A. Abdul-Sada, A. Vargas, O. Navarro, G.E. Kostakis, Chem.-A Eur. J. 21(17) (2015) 6358-6361; d) A. Procopio, P. Costanzo, M. Curini, M. Nardi, M. Oliverio, G. Sindona, G. ACS Sustain. Chem. Eng. 1(5) (2013) 541-544; e) M.S. Estevão, C.A.M. Afonso, Tetrahedron Lett. 58(4) (2017) 302-304.

[2] Manuscript under revision.

**F10**

# Using AFM to study erythrocytes' morphology and elasticity on Amyotrophic Lateral Sclerosis

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Amyotrophic Lateral Sclerosis (ALS) is a devastating and fatal neurodegenerative disease, leading to severe respiratory insufficiency, muscle atrophy, paralysis and death [1,2]. Human venous thromboembolism is considered as a common complication in ALS patients [3], suggesting changes in their hemodynamic properties [4,5]. This can derive from abnormalities in the erythrocyte membrane (e.g. viscoelasticity), which depend (among other factors) on its lipid content, such as in phosphatidylcholine or sphingolipids [6].

The main goal of our study was to evaluate changes in the viscoelastic and morphological properties of erythrocytes from ALS patients. These changes may have an impact on peripheral hypoxia, which could be potentially related to functional outcome. Human blood samples from ALS patients (n=10) were analysed and compared with healthy donors (control, n=7) to evaluate changes on the morphology and membrane elasticity of erythrocytes. Samples were analysed by atomic force microscopy (AFM), zeta-potential and fluorescence generalized polarization. AFM scanning images were performed on erythrocytes from both groups to evaluate their morphology. Using specific imaging software, we were able to quantify different morphological parameters (e.g., cell area, diameter, height and volume).

Erythrocytes from ALS patients have higher diameter than erythrocytes from the control group (8.51±0.02 µm vs. 8.30±0.02 µm, respectively; $p<0.0001$). Their area were also higher (57.23±0.23 µm$^2$ (ALS) vs. 54.19±0.16 µm$^2$ (control); $p<0.0001$). Erythrocytes from ALS patients are thicker than erythrocytes from the control (0.593±0.002 µm vs. 0.572±0.003 µm; $p<0.0001$), but have slightly lower volume (21.10±0.25 µm$^3$ vs. 21.81±0.22 µm$^3$; $p=0.031$). Erythrocyte membrane roughness was also assessed, with ALS patients presenting lower roughness than the control ($p=0.048$). From AFM erythrocyte elasticity studies, we could conclude that erythrocytes from ALS patients are stiffer than the control (5.03±4.79 kPa vs. 0.13±0.02 kPa; $p<0.0001$) and have also higher penetration depth (829.6±5.36 nm vs. 811.3±7.305 nm; $p=0.0437$). Therefore, erythrocytes from ALS patients are more capable to deform than those from the control group. Zeta-potential analysis showed that the membranes of erythrocytes from ALS patients are less negatively charged than for the control group ($p<0.0001$). A lower number of sialic acid residues on the erythrocyte surface may eventually explain this result. The membranes from erythrocytes from ALS patients are also more fluid than the control ($p=0.024$), as shown by fluorescence spectroscopy using different membrane probes. This could be associated with changes on the cell membrane lipid composition and packing.

Using AFM and others biophysical techniques, it was possible to conclude that erythrocytes from ALS patients revealed electrostatic, mechanical and morphologic changes on their cellular membrane. These findings could contribute to dissect the complex interplay between respiratory function, progression rate, lipid profile and survival in ALS.

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**References**

[1] A.C. Pronto-Laborinho *et al.*, Biomed Res. Int. 2014 (2014) 1-24.

[2] S. D'Angelo *et al.*, Neurochem. Int. 63 (2013) 626-634.

[3] C. Wagner *et al.*, Comptes Rendus Phys. 14 (2013) 459-469.

[4] M. Gladman *et al.*, Neurology 82 (2014) 1674-7.

[5] J.D. Berry, L. Korngut, Neurology 82 (2014) 1668-9.

[6] D.E. Warschawski *et al.*, Biochim. Biophys. Acta 1808 (2011) 1957-1974.

**F11**

# Studying the selectivity and activity of the designed antimicrobial peptide *Ec*AMP1R2

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The ever-growing spread of antimicrobial resistance among bacterial pathogens constitutes one of the major threats to the public health of this century. The sought of new antimicrobial molecules is of paramount importance, and antimicrobial peptides (AMPs) have been pointed as exciting alternatives to conventional antibiotics, as they effectively kill a broad spectrum of pathogens through the selective disruption of their membranes, a mechanism that is arguably less prone to elicit resistance. Most AMPs have been described to disturb membranes either by pore formation or by a detergent-like mechanism. We have studied the membrane activity and selectivity of *Ec*AMP1R2, a non-cytotoxic designed AMP with high specificity towards *Escherichia coli*. In order to shed some light on the mechanisms of action of *Ec*AMP1R2 at the molecular level, studies using biomembrane models and *E. coli* cells were carried out. For this purpose, large unilamellar vesicles (LUVs) were used, including mixtures mimicking the inner (IML) and the outer (OML) membranes of *E. coli.* Using a combination of fluorescence spectroscopy and light scattering spectroscopy, we have found that *Ec*AMP1R2 discriminates between zwitterionic (mammalian-like) and anionic (bacterial-like) membranes. Indeed, *Ec*AMP1R2 showed an increased affinity towards OML membranes, enriched in lipopolysaccharide, but also towards IML membranes, containing cardiolipin. Besides, we show that *Ec*AMP1R2 alters the dipole potential and increases the lipid order of negatively-charged membranes, without affecting membrane fluidity. Finally, we have found that *Ec*AMP1R2 promoted the (hemi)-fusion of IML vesicles without a neutralization of the zeta-potential. This result suggests that the interaction of *Ec*AMP1R2 with IML vesicles results in a phospholipid redistribution such that it is able to alter the membrane curvature, with interesting biological consequences.

**Acknowledgements**

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F12

# Synthesis and characterization of SPIONs for biomedical applications

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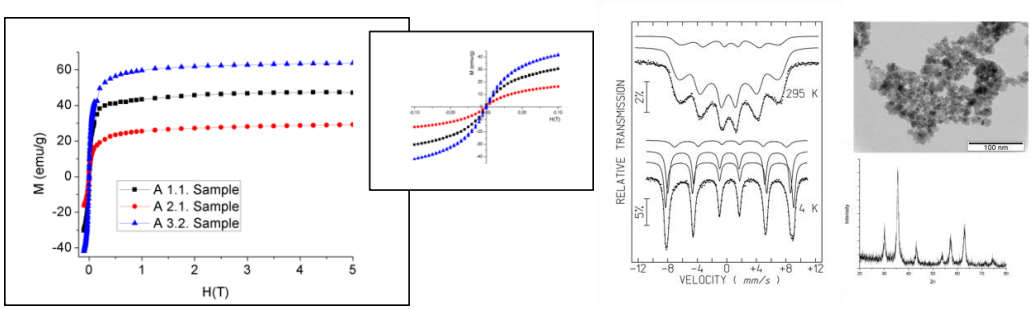
Superparamagnetic iron oxide nanoparticles (SPIONs) have shown great potential in biomedicine. These are small particles of magnetite or maghemite and their coating is an important process, to reduce their aggregation tendency, improving their dispersity and stability, essential for biomedical applications.[1]

SPIONs were synthesized through a reduction-precipitation method, based on Qu et al.[2] and surfactants such as PEG 1000/6000 and Dextran T10/T70 were introduced.

All the obtained samples were structurally and magnetically characterized by transmission electron microscopy (TEM), X-ray powder diffraction (XRD), Mössbauer spectroscopy and SQUID magnetometry.

SPIONs with the more suitable properties have an average diameter of 9 nm and saturation magnetization of ~64 emu/g at 300 K (Figure 1 a)). Their XRD diffractograms (Figure 1 b)) show the characteristic peaks of spinel, with ~60% of maghemite and ~40% of magnetite, according to Mössbauer spectra. Concerning coated SPIONs, the magnetization values closer to those observed for naked SPIONs were obtained with the small chain polymers.




a) b)

**Figure 1.** SPIONs characterization a) Saturation magnetization curves at RT, b) Mössbauer spectra, TEM image and XRD diffractogram

Good saturation magnetization values for the specific size and morphology of the synthesized SPIONs were achieved, comparable with the results reported in the literature.[3] Concerning the SPIONs coating, it was observed that longer chain polymers have a higher influence on the magnetization value of the SPIONs causing its decrease, which is undesirable.

Future work will be directed towards magnetic performance of coated SPIONs.

**Acknowledgements**

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**References**

[1] G.Kandasamy *et al.*, International Journal of Pharmaceutics 496 (2015) 191-218.

[2] S. Qu *et al.*, Journal of Colloid and Interface Science 215 (1999) 190-192.

[3] G. Goya *et al.*, Journal of Applied Physics 94 (2003) 3520-3528.

**F13**

# Molecular dynamics simulations of biomolecular halogen bonds: application to phage T4 lysozyme/halobenzene systems

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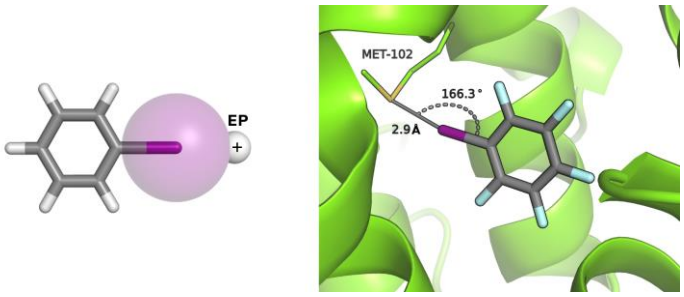
Halogen bonds (XBs) are non-covalent R–X···B interactions where heavy halogens (X = Cl, Br, I) act as electrophilic species interacting with Lewis bases (B). This highly directional type of interaction is mostly explained by the existence of a positive region on the molecular electrostatic potential located at the tip of the halogen (called σ-hole), arising from polarization of the R–X covalent bond. Following the recognition of the significance of XBs in biomolecular structures [1], their application in rational drug design, amongst other areas, has been increasingly explored. In this context, the development of computational tools accurately modelling XB is of paramount importance. This is particularly challenging in the case of force field (FF)-based methods, where XBs are typically modelled by introducing a positive extra-point (EP) of charge to mimic the σ-hole (see Figure, left) [2]. Though different schemes for EP parameterization have been proposed for AMBER or other FFs, their application to lengthy molecular dynamics (MD) simulations is still uncommon. In this work, we assessed the performance of distinct EP models and their transferability to the popular united-atom GROMOS FF, using bacteriophage T4 Lysozyme as a prototype system. The L99A mutant of this enzyme contains a large non-polar cavity that binds iodobenzene and related ligands, via XBs (see Figure, right) [4]. MD simulations were carried out and the network of intermolecular interactions, particularly XBs targeting different acceptors in the protein, was analysed. The results showed the dramatic impact of varying the X–EP distance and the associated sets of charges on the description of XBs. This, together with the implications for computer-aided drug design will be discussed.




**Acknowledgements**

Support for this work was provided by FCT through UID/MULTI/00612/2013 and IF/00069/2014. R.N. acknowledges financial support from PhD scholarship SFRH/BD/116614/2016.

**References**

[1] P. Auffinger, F.A. Hays, E. Westhof, P.S. Ho, PNAS 101 (2004) 16789-16794.

[2] M.H. Kolář, P. Hobza, Chem. Rev. 116 (2016) 5155-5187.

[3] R. Nunes, P.J. Costa *et al.* (2017), in preparation.

[4] L. Liu, W.A. Baase, B.W. Matthews, J. Mol. Biol. 385 (2009) 595-605.

F14

# Nitric oxide releasing-porous materials for therapeutic benefits

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Nitric oxide (NO) is a signalling molecule that plays a fundamental role in several physiological and pathological processes, and its use in therapeutic applications provides a potential alternative to conventional drugs [1]. Due to NO's gaseous nature, high toxicity and short half-life, establishing suitable methods for its delivery to the target sites in a controllable manner is a challenge [2]. A new class of NO-donors has been developed using porous materials with metal active sites in which NO can be chemisorbed. Titanosilicates and clay based materials were already assessed by our group as potential NO-releasing materials and demonstrated excellent storage capacity and a controlled release of pure NO, both in gaseous and liquid phases. However, studies concerning fundamental issues such as biocompatibility, controlled NO release in biological media and the effectiveness of these materials in the control of biological processes were still scarce and this work will contribute on that domain.

Thus, materials' biocompatibility was evaluated through toxicity assays using a primary human epidermal keratinocytes (HEKn). NO release studies under in vitro biological conditions were performed using a direct measurement with a NO sensor and an indirect NO quantification with the Griess assay.

The control of the biological processes in the presence of the different NO donors was evaluated through the inhibition of mitochondrial respiration and the acceleration/activation of cell migration, which is a fundamental process in wound healing.

Toxicology results are very encouraging, showing acceptable toxicities when concentrations below 450 µg/mL were used, which is a very high concentration. Titanosilicates presented better controlled release comparing with clays, with higher amounts of total NO released. Moreover, ETS-4 proved to be very versatile in manipulating the desired amount of released NO. This material demonstrated the ability to inhibit mitochondrial respiration at several concentrations, in a NO-released concentration dependence. Cell migration studies showed that NO-release therapy with NO-loaded ETS-4 promotes a migration acceleration of up to 10 %, clearly demonstrating the potential new approach for wound healing therapy.

**Acknowledgements**

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**References**

[1] S.Y. Low, Mol. Aspects Med. 26 (2005) 97-138.

[2] S.T. Gregg, Q. Yuan, R.E. Morris, B. Xiao, Mater. Today Commun. 12 (2017) 95-105.

F15

# Targeting epigenetic regulator EZH2: a computational approach

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Cancer figures among the leading causes of morbidity and mortality worldwide. Recently, the role of epigenetic pathways in cancer disease development and progression have been studied and new anticancer targets have been proposed. Polycomb repressive complex 2 (PRC2) is an epigenetic regulator that catalyses the trimethylation of lysine 27 in Histone 3 (H3K27me3), a process that facilitates chromatin compaction and gene silencing.[1] The overexpression of EZH2, the catalytic subunit of PRC2, is implicated in the development and progression of a variety of cancers with the worst prognosis.[2] Thus, EZH2 appears as a promisor epigenetic target, and the development of new small-molecule inhibitors is currently a challenge.

In this work, we use computer-aided drug design methods (CADD) to identify starting points for designing new EZH2 inhibitors. Specifically, we used LigandScout Advanced 4.1.4 software [3] for pharmacophore creation to support hit finding and lead optimization studies. In a first stage, 3D-structure- and ligand-based pharmacophore models were prepared and validated. Using this protocol, we were able to identify a ligand based model that retrieved most of the known active inhibitors. This pharmacophore model consists of 14 features (Hydrophobic, hydrogen-bond acceptor and donor and aromatics). In addition, several merged and shared-feature pharmacophore were created to explore structure-activity relationships (SAR) and improve the prediction capacity of the previous models. The performance of all models was tested using a virtual screening library of known inhibitors of EZH2, inactive and decoy molecules (using LigandScout). The most predictive models were again further optimized by systematic modification of the chemical features. The results revealed valuable information about the key interactions and the 3D-geometries associated with bioactivity against EZH2. The models will be used for hit finding campaigns and lead optimization medicinal chemistry decision support. Furthermore, the CADD methods provided a foundation for our SAR hypotheses that are crucial for the design of more accurate and reliable 3D-pharmacophores as the project evolves.

**Acknowledgements**

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**References**

[1] I. Comet, E.M. Rising, B. Leblanc, K. Helin, Nature Rev. Cancer 16 (2016) 803.

[2] A. Laugesen, J.W. Hojfeldt, K. Helin, Cold Spring Harb. Perspect. Med.( 2016) 6.

[3] LigandScout Molecular Design Software from Inte:Ligand GmbH (http://www.inteligand.com).

F16

# Biodiesel from Beef Tallow. Boiling Water versus Microwave Assisted Fat Rendering

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Biodiesel is a feasible renewable alternative to conventional fossil fuel that can be produced by transesterification of oils/fats.[1] The most common feedstock for biodiesel production is vegetable oils. The arable land needs to produce energy crops compete with food production.[2] To improve the biodiesel sustainability is necessary to use of non-edible and cheap oily feedstocks such as waste cooking oils and animal fats.[3]

In this study, two different processes of animal fat rendering, boiling water and microwave assisted (MW), were used to recover the tallow from waste bovine fat tissues.

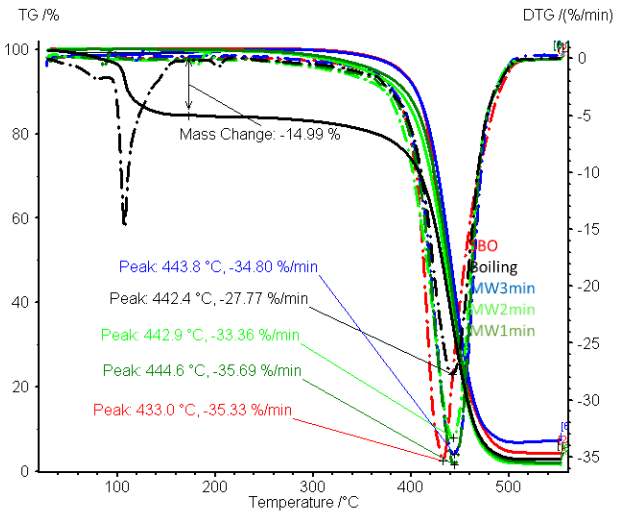


**Figure 1.** Thermogravimetry characterization of tallows and SBO.

The methanolysis tests were carried out at methanol reflux temperature using Ca based catalyst obtained by calcination of scallop shells, methanolysis of alimentary grade soybean oil (SBO) was used as reference. Acetone was used as co-solvent (acetone/methanol = 0.36 V/V). The experimental procedure is given elsewhere.[4]

Thermograms presented in Fig. 1 showed a minimization of the moist content of the extracted fat by MW rendering. The infrared spectra of tallow obtained in different rendering processes show that, MW promotes fat unsaturation and increases free fatty acid content (FFA) when compared with conventional boiling water process.

The FAME yield achieved from MW and boiling water tallow, 84.1 % and 85.3 %, were lower than that obtained by SBO 92.2 %. Due to higher acidity of tallow, the alkaline Ca catalyst is partially neutralized promoting soap formation.

In order to reduce the energy consumption, minimize fat unsaturation and FFA increase the MW rendering process must be optimized (power/time/fat weight).

**Acknowledgements**

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**References**

[1] R. Luque, J.C. Lovett, B. Datta, J. Clancy, J.M. Campelo, A.A. Romero, Energy & Environmental Science 3 (2010) 1706-1721.

[2] J. Popp, Z. Lakner, M. Harangi-Rákos, M. Fári, Renewable and Sustainable Energy Reviews 32 (2014) 559-578.

[3] P. Adewale, M.J. Dumont, M. Ngadi, Renewable and Sustainable Energy Reviews 45 (2015) 574-588.

[4] M. Catarino, M. Ramos, A.P. Soares Dias, M.T. Santos, J.F. Puna, J.F. Gomes, Waste Biomass Valorization 8 (2017) 1699-1707.

F17

# Bioconjugation of boronic acids *via* a 3-Hydroxy-Quinolinones platform

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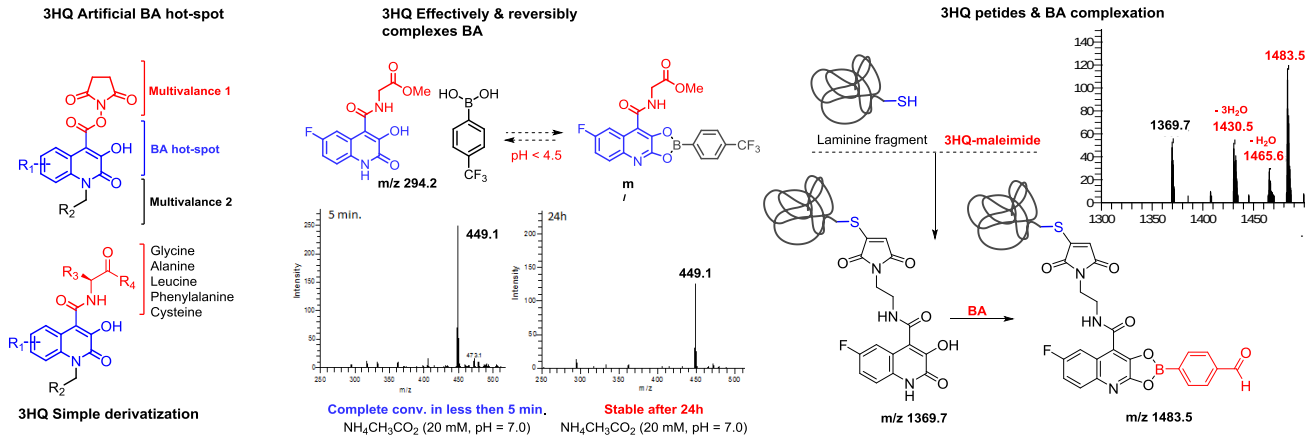
Protein bioconjugation has been one of the hot topics in medicinal chemistry during the recent years, expanding the tools available for biological investigation and bringing innovative therapies to the clinic. In this field, there is an increasing demand for bioconjugations reactions that are not only bioorthogonal, but also reversible under selected conditions, in order to achieve the maximum control possible over the system.[1]

Boronic acids are excellent candidates for this kind of applications as they are stable under physiological conditions and show in general good biocompatibility, they are also known for reversibly binding to diols in aqueous environment, a feature that we exploited to develop a new bioconjugation technique.[2,3]

3-Hydroxy Quinolinones (3HQs) are an interesting class of compounds that exist in a tautomeric equilibrium between the amide form and a diphenolic one, with the first one favoured over the latter in aqueous environment.[4] Although less favoured, the diphenolic form is, however, capable of binding boronic acids, leading to the formation of a highly aromatic structure that results in an overall stabilization of the system.

Based on this discovery, we developed a series of 3HQs derivatives, these compounds showed remarkable binding capabilities with boronic acids in buffer solution and were further developed to be inserted in peptidic fragments via classic maleimide-thiol ligation reaction.

The peptides modified with our molecule gained the ability to bind boronic acids in aqueous environment with moderate to good efficiency, allowing us to create a variety of constructs with cytotoxic drugs and fluorescent probes using this versatile platform.




Preliminary results obtained with the 3HQ technology

## Acknowledgements

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## References

[1] E.M. Sletten, C.R. Bertozzi, Angew. Chem. Int. Ed. (2009) 6974.

[2] B. Akgun, D.G. Hall, Angew. Chem. Int. Ed. 55 (2016) 1-6.

[3] D.Y.W. Ng, M. Arzt, Y. Wu, S.L. Kuan, M. Lamla, T. Weil, Angew. Chem. Int. Ed. 53 (2014) 324-328.

[4] S.B. Strashnova, O.V. Kovalchukova, B.E. Zaitsev, A.I. Stash, Russian Journal of Coordination Chemistry 34 (2008) 775-779.

F18

# Viral surface glycoproteins in HIV: structural elucidation and molecular dynamics

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The efficacy of some of the available antiretroviral drugs is very limited against HIV-2 and, most importantly, none of the current drugs effectively prevents entry into the cells. HIV envelope glycoproteins mediate binding to the receptor CD4 and to CCR5 and/or CXCR4 co-receptors at the surface of the target cell, enabling fusion with the cell membrane and viral entry [1,2].

The main goal of this work relies on the study and modulation of the envelope surface glycoproteins of the HIV-2 involved in the entry mechanism of the virus. Aiming to pinpoint specific structural features that could correlate with known genotypic determinants of HIV-2 tropism located in the gp125 V3 loop region, a three-dimensional (3D) structure of C2V3C3 domain of HIV-$2_{rod}$ gp125 was generated by homology modelling.[3] To disclose the importance of these structural features and compare with experimental results, wild type model was generated besides six other models incorporating specific modifications using MOE software package.

The binding of the glycoprotein with receptor CD4 lead to conformational changes and determine the co-receptor specificity. Modifications on the aromatic residues of V3 suggest an important feature to determine co-receptor usage.[1] It was seen that modifications at specific positions in different variants originate an increment in the CCR5. In these variants, there was a significant alteration on the aromatic system, suggesting that the presence of aromatic systems increment CXCR4 usage. The models were furthermore subjected to MD simulations to account for structural flexibility and structure optimization and infer if the mobility led to modification of the molecular interactions. Energy minimization and molecular dynamic simulations were performed using Gromacs 2016.01 packages.

**Acknowledgements**

Fundação para a Ciência e a Tecnologia for PhD Grant SFRH/BD/100643/2014 of P.S. and UID/DTP/04138/2013.

**References**

[1] H. Uchtenhagen, R. Friemann, G. Raszewski, A.L. Spetz, L. Nilsson, A. Achour, PLoS One 6 (2011) e18767.

[2] J.R. Mascola, Science 349 (2015) 139-140.

[3] Y.W. Davenport, A.P. West, P.J. Bjorkman, J. Virol. 90 (2016) 2112-2118.

**F19**

# Cholesterol-conjugated peptide inhibitors of influenza virus: biophysical characterization

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The influenza virus is responsible for respiratory diseases affecting millions of people worldwide. Infections can be controlled by vaccines and antiviral drugs [1]. However, the virus is constantly under mutations, leading to growing resistance to antivirals [2]. Influenza hemagglutinin (HA), a potential target for antivirals, is involved in receptor binding and promotes the pH-dependent fusion of virus and cell membranes after endocytosis [3,4]. Cholesterol-conjugated HA-derived membrane fusion inhibitor peptides have been previously studied on live viruses. Three HA-derived peptides were analyzed by fluorescence spectroscopy, including membrane partition to assess the interaction with biomembranes systems, human blood cell-binding (followed with a dipole potential probe) and preferential localization in lipid bilayers (using aqueous-soluble and lipophilic quenchers). The conjugated peptides were more active than the unconjugated. (Influenza-PEG4)2-Chol peptide presented higher membrane affinity at pH 7.4. However, that affinity decreased in acidic environment, a possible advantage due to membrane release after viral endocytosis. Our results provide new insight into possible strategies toward the development of new influenza virus inhibitors.

**Acknowledgements**

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**References**

[1] A. Loregian *et al.*, Cell. Mol. Life Sci. 71(19) (2014) 3659-3683.

[2] F. Krammer, P. Palese, Nat. Rev. Drug Discov. 14(3) (2015) 167-82.

[3] B.S. Hamilton, G.R. Whittaker, S. Daniel, Viruses 4(7) (2012) 1144-1168.

[4] E. Vanderlinden, L. Naesens, Med. Res. Rev. 34(2) (2014) 301-339.

**P01**

# Broad spectrum antiviral activity is modulated by biophysical properties of fusion inhibitory peptides

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Human paramyxoviruses cause human respiratory diseases with a significant focus in infants and children. This viral class comprises the causing source of common croup – parainfluenza viruses – as well as agents of lethal encephalitis, like Nipah virus. Infection is initiated by viral glycoprotein-mediated fusion between viral and host cell membranes. Paramyxovirus viral fusion proteins (F) insert into the target cell membrane, and form a transient intermediate that pulls the viral and cell membranes together as two heptad-repeat regions refold to form a six-helix bundle structure that can be specifically targeted by fusion-inhibitory peptides. Antiviral potency can be improved by sequence modification and lipid conjugation, and by adding linkers between the peptide and lipid components. We investigated the membrane insertion kinetics and cell membrane affinity of broad spectrum parainfluenza F-derived peptides that inhibit both parainfluenza and Nipah viruses. Fluorescence-based techniques were used to exploit peptides-membrane interaction. The engineering approach based on biophysical parameters resulted in a peptide that is a highly effective inhibitor of both paramyxoviruses and a set of criteria to be used for engineering broad spectrum antivirals for emerging paramyxoviruses.

**Acknowledgements**

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**References**

[1] C. Mathieu, M.T. Augusto, S. Niewiesk, B. Horvat, L.M. Palermo, G. Sanna, S. Madeddu, D. Huey, M.A.R.B. Castanho, M. Porotto, N.C. Santos, A. Moscona, Sci. Rep. 7 (2017) 43610.

P02

# Multifunctional platform of targeting drug conjugates based on boron complexes

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Neoplastic state represents the main focus at which medicinal chemistry strategies point nowadays to tackle cancer. Interrupting its evolution involves a variety of biological process be considered, therefore multifunctional constructs that combine the lethality of a cytotoxicity drug with the targeting ability of specific biomolecules, are required. Despite conceptually simple, the assembly of multifunctional construct is often hampered by the complexity of the synthetic steps. In addition, stability and reversible proprieties are necessary to internalize and release cargo into cells. On the basis of our experience [1] we envisioned that a promising strategy to create such compounds, known as Targeting Drug Conjugates (TDC) could take advantage of iminoboronate formation. Boronic acids are Lewis acids able to establish reversible complexes due to their capacity to form negatively charged tetravalent framework with Lewis base donors such as amine. We conceived that TDC could be readily created by assemblage of simple building blocks promoted by a boron tether and easily post functionalized; and that B-N bond of the iminoboronate might stabilize the structure and lend controlled reversibility in physiological environment.

Here is presented the development of multifunctional second generation boronate complex (B-complex). Based on our previous experience we convinced that boron-core (B-core) stability would be affected by the imine carbon substituent.[2] Therefore 2-hydroxy-4-methoxy(R)phenone with different R substituent were synthesized and then assembled with phenyl boronic acid and aminophenol. The stability of these resulting B-cores has been evaluated in aqueous media at neutral pH through UV/Vis absorption measurements, and the hydrolysis resistance in the presence of glutathione (GSH) tested on the B-core showing the higher half time. Taking into consideration the stability and reversibility of the B-core, the building blocks corresponding of those exhibiting the best results will be selected as the components to build the multifunctional conjugates featuring a cytotoxic drug, a polar small chain and a target unit (Figure 1). Subsequently the final boron-core complex assembly, biological assays will be performed to evaluate its selectivity and cytotoxicity against human cancer cells.

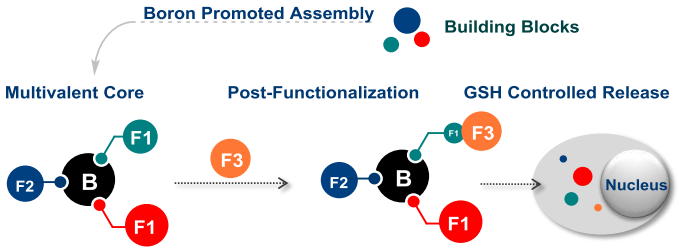


**Figure 1.** Modular and reversible assembly of TDC.

**Acknowledgements**

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**References**

[1] H. Faustino, M.J.S.A. Silva, L.F. Veiros, G.J.L. Bernardes, P.M.P. Gois, Chem. Sci. 7 (2016) 5052-5058.

[2] F.M.F. Santos *et al.*, Angew. Chemie - Int. Ed. 56 (2017) 9346-9350.

**P03**

# Aerobic glycolysis: more efficient deviating energy towards cellular division than respiration?

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Several fast-proliferating cells show high glycolytic rates [1], even in the presence of enough oxygen to support respiration (aerobic glycolysis). In cancer cells, this is known as the Warburg Effect, though it also occurs in other cell types such as lymphocytes and *Saccharomyces cerevisiae* (Sc). Since respiration generates ATP more efficiently than glycolysis, the reason why aerobic glycolysis is favoured during fast-proliferation is a fundamental biological question.

Possible explanations for these observations include: (1) aerobic glycolysis easily feeds nutrients into other metabolic pathways due to its high networking in cellular metabolism, facilitating biomass production [2]; and (2) aerobic glycolysis provides higher rates of ATP production [2], despite the lower yield of ATP per glucose molecule consumed. Our group is proposing an alternative hypothesis: aerobic glycolysis is favored because it is more efficient in directing cellular energy towards cellular division. This proposal is supported by preliminary results, which show that for the same growth rate, cells with higher respiration rates waste larger amounts of energy.

To address this issue, we will use microcalorimetry, a sensitive technique capable of following cellular metabolism in real time and under non-invasive conditions [3]. A novel, adimensional parameter, the proliferation dissipation index (PDI), which is proportional to the cellular energy deviated to cell division, will be used to quantitatively measure how resources are used for cell growth or other functions, such as maintenance. PDI is defined as the ratio of the cell culture heat dissipation rate by the rate of cell division. Our main biological model, Sc is able to proliferate on an aerobic glycolysis-dependent metabolism (1), if it has a fermentable carbon source (e.g. glucose), or on a respiration-dependent metabolism (2), if the carbon source is respirable (e.g. ethanol). Thus, a PDI analysis on both these periods will reveal which process deviates cellular energy towards cell division more efficiently. If PDI is higher in (2), then fast proliferation is supported more efficiently by aerobic glycolysis than respiration, validating the proposed working hypothesis.

**Acknowledgements**

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**References**

[1] N. Slavov, B.A. Budnik, D. Schwab, E.M. Airoldi, A. van Oudenaarden, Cell Rep. 7(3) (2014) 705-14.

[2] R.J. DeBerardinis, J.J. Lum, G. Hatzivassiliou, C.B. Thompson, Cell Metab. 7(1) (2008) 11-20.

[3] A.M. James, Thermal and Energetic Studies of Cellular Biological System,. IOP Publishing: Bristol, 1987.

**P04**

# Age-related chemical variation of *Pseudotsuga menziesii* bark

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Barks make up a substantial proportion of trees and represent an attractive opportunity as feedstock for biorefineries since they are readily available in very large quantities at forest industrial sites. Barks are complex cellular materials including different tissues e.g. phloem, periderm, and rhytidome in various proportions with a richly diverse chemical composition [1]. Their utilization requires therefore knowledge on the specific structural and chemical features.
Douglas-fir (*Pseudotsuga menziesii*) show a conspicuous outer bark which, at young ages, includes only one periderm, while at older ages includes cork-rich periderms in the rhytidome [2] (Figure 1).
In the present study, the chemical composition and the antioxidant properties of polar extractives of *Pseudotsuga menziesii* barks with different ages are described. The bark samples were collected from three mature 45-48 year old trees from the top (with approximately 12 years of age and without cork tissue) and from the bottom part of the stem (with approximately 45 years of age and with cork).

**Figure 1.** Rhytidome of Douglas-fir bark from a 45-yr-old tree.

The bark samples were extracted successively with dichloromethane, ethanol and water and the extractive contents were determined. Suberin contents were determined on the extracted bark samples with cork using 3% $NaOCH_3$ for depolymerization. Acid insoluble and soluble lignin contents were determined by acid hydrolysis and UV spectroscopy methods.
The polar extracts were analyzed for total phenolics using the Folin-Ciocalteau assay and for their antioxidant properties using the DPPH method.

**Acknowledgements**

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**References**

[1] J. Ferreira, T. Quilhó, H. Pereira, J. Wood Chem. Technol. 37 (2017) 10-25.

[2] S. Cardoso, J. Ferreira, T. Quilhó, H. Pereira, Ind. Crops Prod. 99 (2017) 135-141.

P05

# Iminoboronates, a recent class of fluorescent dyes and its application as biosensors

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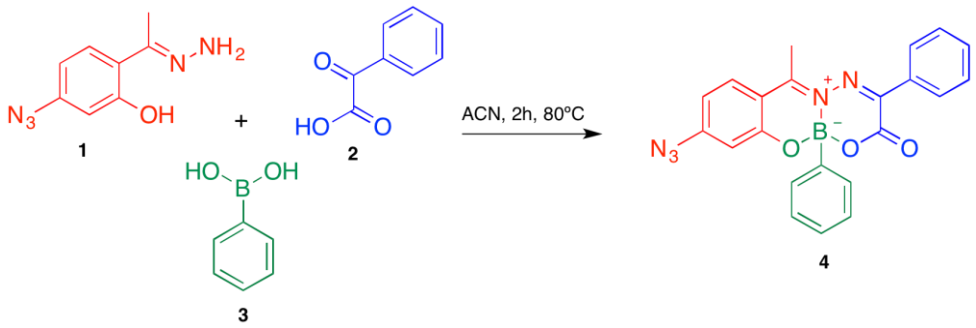
Our lab has been developed an extensive work in boron compounds area and several applications have been established taking advantage of their versatility. Based on this, it was developed a small library of fluorescent iminoboronates and the influence of their chemical structure in optical properties started to be understood. These molecules are a new class of fluorescent dyes based on complexes of boronic acid salicylidenehydrazone (BASHY), obtained from modular synthesis and easy to manipulate. Furthermore, these dyes are electronically tunable due to its ICT nature and have a considerable photostability.

Thus, considering the good results of BASHY's library, the main goal is to prove the utility of modular approach and the adaptation of BASHY to bioimaging applications. Hydrogen sulphide, known as the third gasotransmitter, is a recognized signalling molecule in the cardiovascular system and is a potential biomarker of ischemia and injury. The scientific progress in the area of fluorescent probes and bioimaging has led to the construction of more demanding probes, particularly the design of probes able to provide information about organelle-specific mechanisms. In respect to $H_2S$, it is necessary to clarify the regulation of lipid homeostasis signalling, in this context, boronic acid salicylidenehydrazone (BASHY) dyes may be adequate, considering their affinity and accumulation on lipid droplets.




**Scheme 1.** BASHY probe (4) is synthetized from three building blocks: salicylhydrazone precursor (1), phenylglyoxylic acid (2) and phenyl boronic acid moiety (3).

**Acknowledgements**

We thank the Fundação para a Ciência e Tecnologia (PTDC/QEQMED/5512/2014; PTDC/QEQ-QOR/1434/2014; UID/DTP/04138/2013; SAICTPAC/0019/2015) for financial support.

**References**

[1] Z. Wang, C. Gui, E. Zhao, J. Wang, X. Li, A. Qin *et al.*, Appl Mater. Interfaces 8 (2016) 10193.
[2] F.M.F. Santos, J.N. Rosa, N.R. Candeias, C.P. Carvalho, A.I. Matos, A.E. Ventura *et al.*, Chem Eur. J. 22 (2016) 1631.
[3] A.D. Laurent, B. Le, G. Denis, Theor. Chem. Acc. 135 (2016) 1.

P06

# Synthesis of new derivatives from Oleuropein

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Olive tree (*O. europaea*) is a natural source of oleuropein (Figure 1), a secoiridoid present only in plants from *Oleaceae* family. Although it can be found in fruits and small branches, oleuropein is present in higher amounts in olive leaves, which are considered a cheap and easily available source of oleuropein, since are industrial by-products with no practical applications.[1] Oleuropein has potent biological and pharmaceutical properties: anticancer, cardioprotective, neuroprotective, gastroprotective, anti-diabetes and anti-obesity, in large part attributed to its antioxidant and anti-inflammatory effects.[2]

Extraction and analytical methods have been developed and widely reported for qualitative and quantitative studies of olive polyphenols, including oleuropein. Published transformations of oleuropein are generally related to the removal of hydroxytyrosol and glucoside moieties. Since few research has been done at this level [3], we will describe the synthesis of new scaffolds from oleuropein at the level of elenolic acid unit, through semi-synthetic transformations.

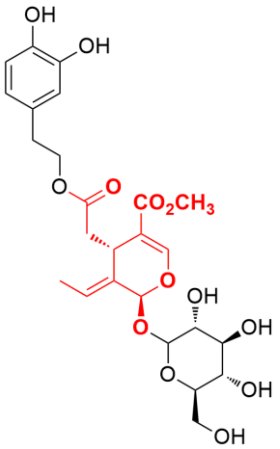


**Figure 1.** Molecular structure of oleuropein. Elenolic acid unit highlighted (red).

**Acknowledgements**

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**References**

[1] M.L. de Castro, R. Japón-Luján, Trend. Anal. Chem. 25 (2006) 501-510.

[2] I. Hassen, H. Casabianca, K. Hosni, J. Funct. Foods. 18 (2015) 926-940.

[3] L. Abaza, A. Taamalli, H. Nsir, M. Zarrouk, Antioxidants 4 (2015) 682-698.

P07

# Photo-immunoconjugates for Cancer Photodynamic Therapy

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Photodynamic Therapy (PDT) is considered a promising alternative against various types of cancer [1], namely to improve the treatment options and prognosis for colorectal cancer (CRC) patients.[2] Of the interaction between a photosensitizer (PS), visible light and molecular oxygen ($O_2$) results reactive oxygen species (ROS), that kill malignant cells by triggering a cascade of cytotoxic reactions.[3] First and second generation photosensitizers are non-selective for tumor cells and cause toxicity in healthy cells.[4] However, third generation photosensitizers – first or second PSs conjugated with biomolecules or targeting agents – improve specificity and efficacy of cancer PDT.[5] The coupling of monoclonal antibodies (mAbs) with a PS – photo-immunoconjugate (PIC) – is an approach that allows specific targeting and photosensitization of receptor positive cells only (Figure 1).[6] Also, nanoparticles (NPs) have been used as PSs delivery vehicles, improving their specificity to the target cancer cell, reducing damage to the healthy ones.[5] The main goal of this scientific work is the preparation of PICs and immunonanoparticles (INPs) encapsulating PSs to target cancer cells through receptor-mediated specificity, and to establish a comparison of efficacy between them and the already approved PSs.

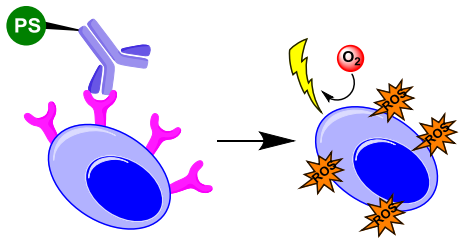


**Figure 1.** Photodynamic action of photosensitizers conjugated with antibodies.

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**References**

[1] G.M.F. Calixto, J. Bernegossi, L.M. Freitas, C.R. Fontana, M. Chorilli, Molecules, 21 (2016) 342.

[2] A. Kawczyk-Krupka, A.M. Bugaj, W. Latos, K. Zaremba, K. Wawrzyniec, M. Kucharzewski, A. Sierón, Photodiagnosis Photodyn. Ther. 13 (2016) 158-174.

[3] P. Agostinis, K. Berg, K.A. Cengel, T.H. Foster, A.W. Girotti, S.O. Gollnick, S.M. Hahn, M.R. Hamblin, A. Juzeniene, D. Kessel, M. Korbelik, J. Moan, P. Mroz, D. Nowis, J. Piette, B.C. Wilson, J. Golab, CA Cancer J. Clin. 61 (2011) 250-281.

[4] P.M.R. Pereira, B. Korsak, B. Sarmento, R.J. Schneider, R. Fernandes, J.P.C. Tomé, Org. Biomol. Chem. 13 (2015) 2518-2529.

[5] U. Chilakamarthi and L. Giribabu, Chem. Rec. 17 (2017) 1-29.

[6] B. Korsak, G.M. Almeida, S. Rocha, C. Pereira, N. Mendes, H. Osório, P.M.R. Pereira, J.M.M. Rodrigues, R.J. Schneider, B. Sarmento, J.P.C. Tomé, C. Oliveira, Int. J. Cancer 141 (2017) 1478-1489.

**P08**

# Targeting glucose metabolism for cancer treatment: searching hit compounds for hexokinase II inhibiton

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Glucose metabolism has been regarded as a potential target pathway to be explored for cancer treatment. Several enzymes involved in glycolysis are overexpressed in different types of cancer cells, namely hexokinase II (HKII) [1]. This enzyme is involved in the first and most determinant step of the process, catalysing the phosphorylation of glucose to give glucose-6-phosphate, also involved in the pentose phosphate pathway [2,3]. Therefore, the inhibition of the HKII catalytic centre (Figure 1) is proposed as a strategy to reduce main source of energy to cancer cells, and substantially decrease cancer cell proliferation. In order to find hit compounds with drug-like properties able to interfere with the HKII catalytic centre and thereby block its activity, the DrugBank database (approved and withdrawn compounds) was screened using molecular docking calculations through Gold 5.20 software. Different conformations of molecules were generated (MOE2016 0802) and then docked into the HKII catalytic active site. The structure-based virtual screening protocol was previously validated, by evaluating different three-dimensional (crystallographic) HKII structures, different amino acids at the catalytic pocket centre, different scoring functions and catalytic pocket radius. Our results suggest several hit compounds with the potential to act as new HKII inhibitors. Furthermore, considering the highest scored drugs and their interactions profile, our data also suggest that repurposing may be envisaged in a few instances.

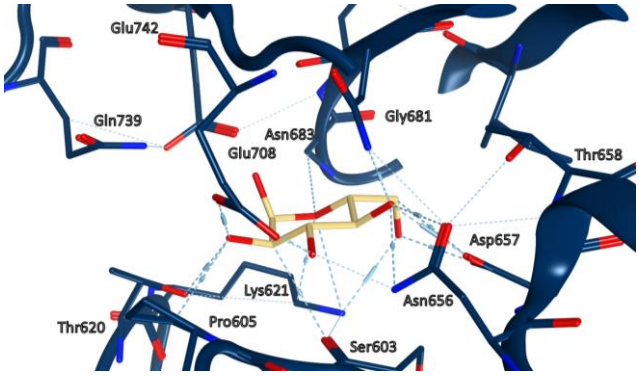


**Figure1.** Representation of the HKII catalytic centre (*C*-terminus – dark blue) in interaction with a glucose molecule (yellow) (PDB code: 2NZT).

**Acknowledgements**

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**References**

[1] N. Hay, Nat. Rev. Cancer 16(10) (2016) 635-649.

[2] U.E. Martinez-Outschoorn, M. Peiris-Pagès, R.G. Pestell, F. Sotgia, M.P. Lisanti, Nat. Rev. Clin. Oncol. 14(1) (2017) 11-31.

[3] R.B. Hamanaka, N.S. Chandel, J. Exp. Med. 209(2) (2012) 211-215.

**P09**

# Combining 25-hydroxycholesterol with a fusion inhibitor peptide: interaction with model biomembranes and human blood cells

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The fusion between the viral and the target cell membrane is a crucial step in the life cycle of enveloped virus. The blocking of this process is a well-known therapeutic approach that led to the development of the fusion inhibitor peptide enfuvirtide, clinically used against HIV [1]. Despite this significant advance on HIV treatment, the appearing of resistance has limited its clinical use [2]. Such limitation has led to the development of other fusion inhibitor peptides as C34 that present the same structural domain as enfuvirtide (heptad repeat sequence), but have different functional domains, like pocket- and lipid-binding domains [3]. Recently, the antiviral properties of 25-hydroxycholesterol (25HC) were demonstrated, which boosted the interest on this sterol [4]. The combining of two distinct antiviral molecules, C34 and 25HC, may help to suppress the emergence of resistant viruses.

In this work, we characterize the interaction between C34-25HC conjugate with biomembrane model systems and human blood cells. Lipid vesicles and monolayers with defined lipid compositions were used as biomembrane model systems.

C34-25HC interacts preferentially with membranes rich in sphingomyelin (a lipid enriched in lipid rafts), and presents a poor partition to membranes composed solely of phosphatidylcholine and cholesterol. We hypothesize that cholesterol causes a repulsive effect that it is overcome in the presence of sphingomyelin. Importantly, the peptide shows a preference for human peripheral blood mononuclear cells (PBMC) relative to erythrocytes, which shows its potential to target CD4 positive cells.

**Acknowledgements**

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**References**

[1] A. Pessi, J. Pept. Sci. 21 (2015) 379-86.

[2] Y. Su, H. Chong, Z. Qiu *et al.*, J. Virol. 89 (2015) 5801-11.

[3] W. Shi, Z. Qi, C. Pan *et al.*, Biochem. Biophys. Res. Commun. 374 (2008) 767-72.

[4] S.Y. Liu, R. Aliyari, K. Chikere et *al.*, Immunity 38 (2013) 92-105.

**P10**

# Exploring the effect of different fluorinated anions on $CO_2$ separation through supported ionic liquid membranes

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In the last 15 years, ionic liquids (ILs) have found their place as new functional materials. In particular, they have shown to be extremely successful in $CO_2$ separation applications, due to their inherent designer nature, that enables the tailoring of their properties by proper selection of cation and/or anion or via the addition of specific functional groups. A broad diversity of ILs has been used to prepare supported ionic liquid membranes (SILMs) and the effect of IL chemical structure on the gas permeation and separation properties of these membranes has been investigated [1]. Since some SILMs have shown potential for industrial applications, particularly for low pressure systems such $CO_2$ separation from flue gases, many efforts are being put in the development of new task-specific ILs to enhance the already advantageous combination of gas permeability and selectivity of SILMs [2-4]. In particular, the superior performance of ILs bearing fluorinated anions, such as the bis(trifluoromethylsulfonyl)imide $[NTf_2]^-$, tetrafluoroborate $[BF_4]^-$, and hexafluorophosphate $[PF_6]^-$, due to their $CO_2$-phylic behaviour and high $CO_2$ permeabilities, is well recognized.

In this study, we explore the gas permeation properties of ILs based on the 1-ethyl-3-methylimidazolium ($[C_2mim]^+$) cation and different fluorinated anions such as 2,2,2-trifluoromethylsulfonyl-N-cyanoamide ($[TFSAM]^-$), bis(fluorosulfonyl)imide ($[FSI]^-$), nonafluorobutanesulfonate ($[C_4F_9SO_3]^-$), tris(perfluoroalkyl)trifluorophosphate ($[FAP]^-$), and bis(perfluoroethylsulfonyl)imide ($[BETI]^-$) anions. Moreover, the re-design and structural unfolding of the asymmetric anion $[C_2mim][TFSAM]$ through the use of IL mixtures was also investigated. The $CO_2$ and $N_2$ permeation properties (permeability, diffusivity and solubility) through all the prepared SILMs were determined using a time-lag apparatus [5].

**Acknowledgements**

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**References**

[1] P.J. Scovazzo, Membr. Sci. 343 (2009) 199-211.

[2] L.C. Tomé, D.J.S. Patinha, C.S.R. Freire, L.P.N. Rebelo, I.M. Marrucho, RSC Adv. 3 (2013) 12220-12229.

[3] L.C. Tomé, C. Florindo, C.S.R. Freire, L.P.N. Rebelo, I.M. Marrucho, PCCP 16 (2014) 17172-17182.

[4] A.S.L. Gouveia, L.C. Tomé, I.M. Marrucho, J. Memb. Sci. 510 (2016) 174-181.

[5] A.S.L. Gouveia, L.C. Tomé, E.I. Lozinskaya, A.S. Shaplov, Y.S. Vygodskiic, I.M. Marrucho, Phys. Chem. Chem. Phys. 19 (2017) 28876-28884.

P11

# 3D bimetallic catalysts for $H_2$ generation from borohydride hydrolysis

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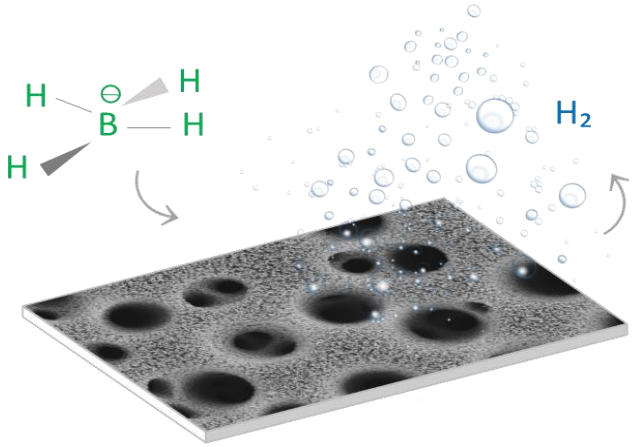
Hydrogen ($H_2$) is a valuable energy source from the point of view of global energy demand and environmental sustainability [1]. Although $H_2$ can be stored in containers as compressed gas or in cryogenic state, these forms of storage are costly and of considerable risk to the users [1,2]. Sodium borohydride ($NaBH_4$) is a non-flammable, carbon free compound that stores a high hydrogen content. Hydrolysis of $NaBH_4$ is a spontaneous reaction that generates pure $H_2$ at ambient conditions [3]. However, the hydrolysis reaction is slow, which turns the catalyst the central issue for developing borohydride systems for portable applications [1,3]. Noble metal catalysts based on Pt or Ru can generate $H_2$ with very high rates but they are expensive and scarce [4]. As alternative, low-cost noble metal-free binary alloys based on transition metals have shown promising activities [4,5]. In this work, catalysts containing Ni in the range of 10–60 % were prepared. The catalysts have a 3D foam-like structure with high degree of pores interconnectivity and show fast reactivity as well as on/off functionality towards $H_2$ generation from borohydride hydrolysis.

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**References**

[1] P. Brack, S.E. Dann, K.G.U. Wijayantha, Energy Sci. Eng. 3 (2015) 174-188.

[2] S. Li, F. Wang, Int. J. Hydrogen Energy 41 (2016) 3038-3051.

[3] U.B. Demirci, O. Akdim, J. Andrieux, J. Hannauer, R. Chamoun, P. Miele, Fuel Cells 10 (2010) 335-350.

[4] N. Patel, A. Miotello, Int. J. Hydrogen Energy 40 (2015) 1429-1464.

[5] S. Eugénio, U.B. Demirci, T.M. Silva, M.J. Carmezim, M.F. Montemor, Int. J. Hydrogen Energy 41 (2016) 8438-8448.

**P12**

# Titanium Salan Complexes: Synthesis and Reactivity

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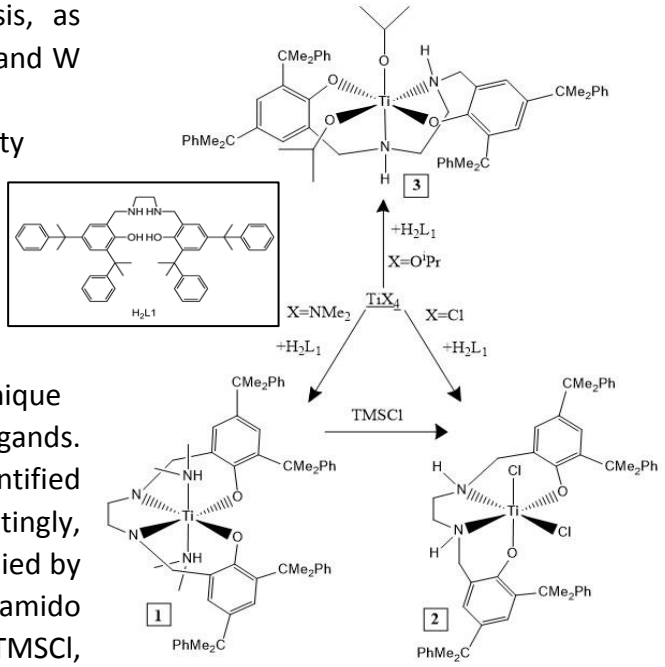
Diamine bisphenolate ($N_2O_2^{2-}$) ligands are important scaffolds in transition metals (TM) and lanthanides (Ln) chemistry.[1] In this area, we have been interested in the chemistry of early TM and Ln complexes displaying tripodal diamine bisphenolate ligands.[2] Applications in polymerization catalysis, using Ti and Zr complexes,[3] in radical process such as $O_2$ activation and C-C coupling, using Ti and V complexes,[4a] and oxidation catalysis, as epoxidation and sulfoxidation, using Ti, V, Mo, and W complexes,[4b, c] were reported.

The work presented here explores the reactivity of Ti complexes supported by a different type of diamine bisphenolate ligands, usually identified as salan ligands, in this case **$H_2$L1.** Using different titanium starting materials, it was possible to obtain complexes **1**, **2**, and **3**, shown in Scheme 1. Complex **1** presents one unique $C_2$ isomer that displays trans-phenolate ligands. Differently, **2** revealed 4 isomers that were identified by NMR as $C_1$-cis-dichloro complexes. Interestingly, the reaction of **$H_2L_1$** with $Ti(NMe_2)_4$ is accompanied by $H^+$ transfer with formation of a tetraanionic diamido bisphenolate ligand. Upon reaction of **1** with TMSCl, complex **2** is obtained, showing that the ethylenediamido fragment can be protonated, coming back to the original dianionic form of the ligand. An analogous process, namely the intramolecular migration of 2 protons from coordinated dimethylamine to the tetraanionic ligand occurs upon reaction of **1** with $CO_2$ that inserts in the Ti-$NMe_2$ bonds.




**Scheme 1:** Synthesis of Salan-Titanium (IV) complexes.

Catalytic applications of the latter complexes are under way.

**Acknowledgements**

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**References**

[1] A. *Tzubery*, E.*Y. Tshuva*, Inorg. Chem., 51 (2012) 1796-1804.

[2] S. Barroso, A.M. Coelho, S. Gómez-Ruiz, M.J. Calhorda, *Ž. Žižak*, G.N. Kaluđerović, A.M. Martins, Dalton Trans. 43 (2014) 17422-17433.

[3] P. Adao, F. Avecilla, M. Bonchio, M. Carraro, J.C. Pessoa, I. *Correia, Eur. J. Inorg. Chem. 35 (2010) 5568-5578.*

[4] a) *S. Barroso*, *P. Adão*, *M.T. Duarte*, A. *Meetsma*, *J.C. Pessoa*, *M.W. Bouwkamp*, A.M. Martins, Eur. J. Inorg. Chem. 27 (2011) 4277-4290*;* b) S. Barroso, P. Adão, A.M. Coelho, J.C. Pessoa, A.M. Martins, J. Mol. Cat. A: Chem. 412 (2016) 107-116; c) S. Barroso, F. Madeira, M.J. Calhorda, M.J. Ferreira, M.T. Duarte, A.M. Martins, Inorganic Chemistry 52 (2013) 9427-9439.

P13

# Magnetic deep eutectic solvents in refinery desulfurization: comparison between liquid-liquid extraction and ultrasound assisted liquid-liquid microextraction

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Sulfuric compounds in fossil fuels have become one of the main sources of environmental pollution. Terms like “deep desulfurization” and “ultra-low sulfur fuel” became very important in order to follow the strict regulations that have been legislated around the world. Currently, the sulfur content on the highway fuels is limited to less than 10 ppm, in many countries [1].

Hydrodesulfurization is the conventional industrial process for removing sulfur from fossil fuels. However, its drawbacks, such as, high cost of operation and low effectiveness removing refractory heterocyclic sulfur compounds are prompting the development of innovative complementary technologies for fuel oil desulfurization [2]. Extractive desulfurization (EDS) is one of the most promising desulfurization processes due to its simple operation and low cost. Nevertheless, the commonly used extractants are organic solvents, which brings environmental and health concerns due to their volatility and flammability. Ionic liquids (ILs) have been widely explored as alternative solvents for sulfur removal, and although they have many desirable properties, such as non-flammability, non-volatility and high tunability, they also present major disadvantages like, high cost and, in some cases, toxicity. To overcome these limitations, Deep Eutectic Solvents (DESs) have been proposed as alternative to ILs, since DES can be seen as a low cost and more environmentally friendly ionic solvent [3,4].

In this work, a series of $FeCl_3$-based deep eutectic solvents have been synthesized and studied as key players for sulfur removal using two different extractive approaches: simple liquid-liquid extraction (LLE); and ultrasound assisted liquid-liquid microextraction (UALLME). In both cases, the extraction of thiophene and dibenzothiophene from model oils with sulfur content of 500 ppm was considered. It is important to note that, in the case of UALLME, the magnetic property of the synthetized DESs was crucial in the facile separation of the two phases. For the most promising system, the re-use of the alternative solvent were analyzed, as well as the deep desulfurization by multiples extraction cycles.

**Acknowledgements**

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**References**

[1] C.S. Vimal, RSC Adv. 2(3) (2012) 759-783.

[2] A. Rashid, A.A. Ahmed, S.A. Salem, Y. Guangren, B.Q. Abdul, G. Shurong, C. Xiaochun, RSC Adv. 4 (2014) 35302-35317.

[3] L. Jing-Jing, X. Huan, T. Xiao-Dong, Z. Miao, Energy and Fuels 30 (2016) 5411-5418.

[4] Z. Hua, A.B. Gary, V.W. Durgesh, R. Sudhir, Z. Qi, ACS Sustain. Chem. Eng. (2016).

P14

# N,O-Iminoboronates: Useful Scaffolds for the Construction of Reversible linkers

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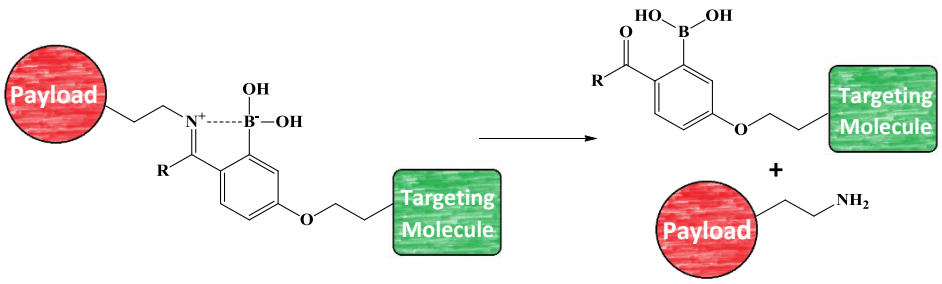
Chemotherapy uses small potent molecules with high activity towards specific tumor targets. However, with such high activity comes high off target toxicity and severe side effects. Fortunately, chemotherapy can be now targeted thanks to powerful linkers that connect a ligand molecule with affinity to interesting biological receptors and a cytotoxic drug. These linkers must have very specific properties, such as high stability in plasma, no toxicity, no interference with ligand affinity nor drug potency, and at the same time, be able to self-lyse once inside the target cell. Bipolar environments as seen between tumor extracellular and intracellular medias are usually exploited by this linkers in order to release the therapeutic warhead.

This work explores a new model for the same task, specific cancer drug delivery.[1] Iminoboronates were studied due to its remarkable selective stability towards a wide pH range and endogenous molecules.[2] Bioconjugates were design to prove this iminoboronate linker's effectiveness. The ability to be uptaked by a cancer cell through endocytosis process and delivery of specific payload are two features expected for this construct.




**Acknowledgements**

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**References**

[1] P.M.P. Gois *et al.*, Commun. 50 (2014) 5261-5263.

[2] P.M.P. Gois *et al.*, J. Am. Chem. Soc. 134(24) (2012) 10299-10305.

P15

# Cu(I) complexes of scorpionate ligands for three-component click reaction in aqueous medium

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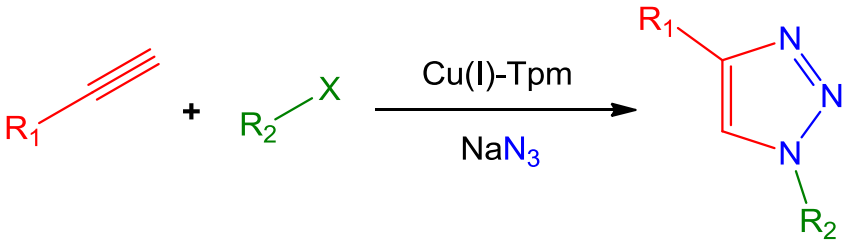
Since the initial development of tris(pyrazol-1-yl)methane (Tpm) ligands (scorpionates) [1], a significant number of complexes, based on copper, have been synthesized with these ligands to be used for several catalytic processes and, most notably, in C-H bond activation methods [2]. Due to the ability of Tpm ligands to produce a stable Cu(I) [3], they would be excellent candidates for copper-catalyzed azide-alkyne cycloaddition (CuAAC) process.




Therefore, as part of our interest on transition metal complexes of scorpionates with applications in catalysis, we have obtained novel Cu(I) complexes of several Tpm derivatives. The obtained complexes were fully characterized and applied as catalysts for three-components CuAAC process under normal and microwave irradiations.

**Acknowledgements**

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**References**

[1] S. Trofimenko, J. Am. Chem. Soc. 70 (1970) 5118.

[2] L.M.D.R.S. Martins, A.J.L. Pombeiro, Coord. Chem. Rev. 265 (2014) 74.

[3] M. Cvetkovic, S.R. Batten, B. Moubaraki, K.S. Murray, L. Spiccia, Inorg. Chim. Acta 324 (2001) 131.

**P16**

# Understanding *Flavivirus* capsid protein structure and their ability to interact with host lipid systems

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Flaviviruses, such as Dengue (DENV), West Nile (WNV) and Zika (ZIKV) viruses, are transmitted to humans mainly by the bite of mosquitoes, being a serious public health treat.[1,2] Despite the global spread and disease severity, there is no specific and effective treatment, in part due to a poor understanding of flaviviruses life cycle. The capsid (C) protein, conserved in terms of sequence and structure among flaviviruses, is a major drug target. For example, DENV C mediates the viral life cycle, namely by binding to host lipid droplets (LD), a step essential for viral replication.[3,4] Here, we investigated WNV and ZIKV C proteins binding to host lipid systems. Zeta potential shows that WNV C interacts with LD surface proteins, requiring $K^+$ ions, as we previously shown for DENV C.[4,5] ZIKV C also binds to LD, although in this case $Na^+$ and $K^+$ are interchangeable. Dynamic light scattering shows that WNV C binds very low-density lipoproteins (VLDL) but not low-density lipoproteins (LDL). Interestingly, ZIKV C binds to LDL, but not to VLDL. WNV C (un)binding forces upon interaction with LD and VLDL were determined by atomic force microscopy (AFM)-based force spectroscopy. AFM confirmed that WNV C binds specifically to LD and VLDL (but not LDL), in a $K^+$-dependent process. Furthermore, ZIKV, WNV and DENV C protein sequences display similar predicted hydrophobicity, α-helical propensity and tertiary structure, which can thus be targeted via similar approaches. Combining all this with our background on DENV C protein and pep14-23 development [6] (an inhibitor of DENV C binding to host lipid systems, designed and patented by us), we will now use this information for drug development strategies against flaviviruses.

**Acknowledgements**

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The authors thank T. Freitas (iMM, FMUL) for technical assistance.

**References**

[1] S. Mukhopadhyay, R.J. Kuhn, M.G. Rossmann, Nat. Rev. Microbiol. 3 (2005) 13-22.

[2] L. Wang, S.G. Valderramos, A. Wu *et al*., Cell Host Microbe 19(5) (2016) 561-5.

[3] M.M. Samsa, J.A. Mondotte, N.G. Iglesias *et a*l., PLoS Pathog. 5 (2009) e1000632.

[4] F.A. Carvalho, F.A. Carneiro, I.C. Martins *et al*., J. Virol. 86 (2012) 2096-2108.

[5] I.C. Martins, F. Gomes‑Neto, A.F. Faustino *et al*., Biochem J. 444 (2012) 405-415.

[6] A.F. Faustino, G.M. Guerra, R.G. Huber *et al*., ACS Chem. Biol. 10 (2015) 517-526.

P17

# Anion Recognition by Dihomooxacalix[4]arene tetraurea Derivatives: Cone *versus* Partial Cone Conformation

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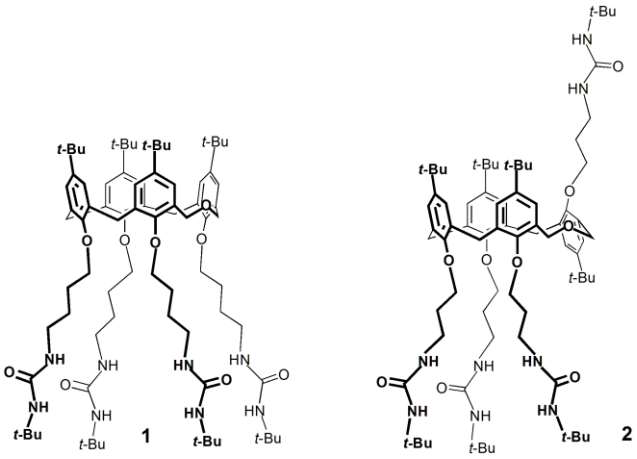
Calixarenes represent an extremely versatile class of macrocycles, able to bind and transport ions and neutral molecules. Over the last 15 years, the study of calixarene-based anion receptors has considerably increased,[1,2] mainly because anions play important roles in several biological and chemical processes. The NH groups of ureas and thioureas are strong hydrogen bond donors, and they have been incorporated in the calixarene scaffolds.

Following our interest in the synthesis and study of dihomooxacalix[4]arene-based receptors (calix[4]arene analogues in which one $CH_2$ bridge is replaced by one $CH_2OCH_2$ group) [3] for anionic species,[4,5] we report herein the binding properties of two *p-tert*-butyldihomooxacalix[4]arene tetra-substituted derivatives with *tert*-butyl urea moieties at the lower rim via a butyl (**1**) or propyl (**2**) spacer, respectively, towards a large variety of anions. The binding affinity of **1** (cone conformation) and **2** (partial cone conformation) was assessed by proton NMR and UV-Vis absorption spectrophotometric studies. The results are discussed in terms of the size of the spacer (four or three carbon atoms) and of the conformation.



**Acknowledgements**

Authors thank FCT, Projects refs. PTDC/QUI/69858/2006 and UID/QUI/00100/2013.

**References**

[1] S.E. Matthews, P.D. Beer, Supramol. Chem. 17 (2005) 411.

[2] N.Y. Edwards, A.L. Possanza, Supramol. Chem. 25 (2013) 446.

[3] P.M. Marcos, in: P. Neri, J.L. Sesseler, M.-X. Wang (Eds.), Calixarenes and Beyond, Springer International Publishing, 2016, pp. 445-466.

[4] P.M. Marcos, F.A. Teixeira, M.A.P. Segurado, J.R. Ascenso, R.J. Bernardino, S. Michel, V. Hubscher-Bruder, J. Org. Chem. 79 (2014) 742.

[5] F.A. Teixeira, P.M. Marcos, J.R. Ascenso, G. Brancatelli, N. Hickey, S. Geremia, J. Org. Chem. 82 (2017) 11383.

**P18**

# *Eucalyptus globulus* and *Picea abies* industrial barks: phytochemical profile and antioxidant activity of polar extracts

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In Europe two of the major species used in the pulp and paper industries are *Eucalyptus globulus* and *Picea abies*, in the south Mediterranean and in the Scandinavian region, respectively, leading to a production of a major byproduct, the bark. These barks are mainly burned in the industrial site to produce energy/heat although other end-uses might prove more interesting economically, such as chemicals and bio-products.

Bark extractives have attracted a lot of attention regarding the composition of apolar and polar extraction fraction regarding the existence of bioactive compounds (mainly related to phenolics) with antioxidant properties, that can find uses in the food, pharmaceutical and cosmetic industries.[1,2]

In this work we determined the phytochemical profile and antioxidant activity of ethanol and water extracts from *E. globulus* and *P. abies* bark stocks from pulp mill yards. Since this industrial bark is contaminated with substantial amount of wood inherent of the debarking process, a previous screening was achieved and both materials were studied separately.

Total phenol, flavonoids and condensed tannin contents were determined as well as the antioxidant activity through the ferric-reducing antioxidant power (FRAP) and the free radical scavenging activity (DPPH) methods.

*E. globulus* bark and wood showed a fairly similar phytochemical profile while *P. abies* bark presented higher content of phenols, flavonoids and tannins than wood. The antioxidant activity of both barks was significantly superior to than respective woods.

Both barks revealed to be important sources for the extraction of molecules with antioxidant activity (especially if ethanol is used in the extraction) such as polyphenolic compounds, which are well recognized potent bioactive compounds.

**Acknowledgements**

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**References**

[1] E. Conde, E. Cadahia, M. Garciavallejo, F. Tomasbarberan, Wood Fiber Sci. 27 (1995) 379-83.

[2] M. Co, A. Fagerlund, P. Sjöberg, K. Sunnerheim, L. Engman, C. Turner, Phytochem. Anal 23 (2012) 1-11.

P19

# Seeking Sustainability: a different way to produce catalyst particles

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In the last decades, chemists become more concerned about the impact of the chemistry and industrial chemistry in the world. These concerning's were translated in a search for more sustainable processes, methods and products in different grounds: Environmental, Social and Economic [1]. Many future scenarios and solutions have been proposed, and in many of them, catalysts appear with an important role to play. To achieve these future scenarios, some challenges are need to be faced in the catalysis field, for example the nanoarchitecture of the catalysts [2].

In this work, the proposal is to produce particles of catalysts using the Supercritical Anti Solvent micronization (SAS) process. SAS is already been used in the production of particles of compounds to the pharmaceutical or food industry, as well as to obtain some precursors of catalysts [3,4]. The SAS technique enables the production of particles controlling the size of the particle, the size distribution and the morphology, according with the experimental conditions.

This method to obtain the catalysts particles is particularly interesting for heterogeneous catalysis, but in the homogeneous catalysts perspective, it can be used to recover the catalyst from the reaction medium.

**Acknowledgements**

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**References**

[1] R.A. Sheldon, Green Chem. 19 (2017) 18-43.

[2] M. Beller, G. Centi, L. Sun, ChemSusChem 10 (2017) 6-13.

[3] M.A. Cardoso, S. Antunes, F. van Keulen, B.S. Ferreira, A. Geraldes, J.M.S. Cabral, A.F. Palavra, J. Chem. Tecnol. Biotechnol. 84 (2009) 215-222.

[4] I. De Marco, E. Reverchon, J. of Supercritical Fluids 58 (2011) 295-302.

**P20**

# Cytotoxic Lead molecule search: general toxicity and cytotoxicity of seven *Plectranthus* species

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Cancer is one of the most common causes of morbidity and mortality today, being the cause of 8.2 million deaths in 2012 (World Health Organization) [1]. The *Plectranthus* spp. plants are the focus of several scientific investigations, due to their ethnopharmacological use by indigenous populations. The *Plectranthus* genus is a known source of bioactive diterpenes with antitumor potential [2]. Abietane diterpenes display an array of biological activities including cytotoxic and antiproliferative activities against human tumor cells. Abietane diterpenes such as 7α-acetoxyroyleanone and royleanone have been demonstrated to possess alkylating properties, but no clear correlation between the alkylating properties and cytotoxicity has been observed [3].

In this work, we prepared acetonic extracts of seven *Plectranthus* spp. to search new cytotoxic lead molecules. The extracts of *P. swynnertonii*, *P. ciliatus*, *P. woodii*, *P. cylindraceus*, *P. spicatus*, *P. ramosior* and *P. petiolaris* were obtained by sonication (10% (w/v) of dry plant) and the highest yield obtained was from *P. ramosior* (13.49% (w/w)). The general toxicity was initially screened using the *Artemia salina* (brine shrimp) lethality assay. Only five of the extracts showed high toxicity with the *Artemia salina* assay (*P. ciliatus* 60.14%, *P. ramosior* 43.35%, *P. mutabilis* 51.50%, *P. cylindraceaus* 43.50%, *P. swynnertonnii* 65.88%). The $LD_{50}$ values were then determined; *P. ciliatus* (0.984mg/L), *P. ramosior* (0.88mg/L), *P. mutabilis* (0.55 mg/L) *P. cylindraceaus* (0.504mg/L), *P. swynnertonnii* (0,036mg/L). The antitumor potential of five of the most toxic was further explored in different cancer cell lines: colon colorectal carcinoma (HCT116), human breast adenocarcinoma (MCF-7) and lung cancer carcinoma (NCI-H460). The results showed that *P. ramosior* and *P. ciliates* were the most toxic extracts and are under study to obtain the compounds responsible for the cytotoxicity shown.

**References**

[1] World Health Organization (WHO), Cancer, Fact sheet N. 297 (2014), Geneve.

[2] C. Lukhoba, M. Simmonds, A. Paton, Journal of Ethnopharmacology 103 (2006) 1-24.

[3] O. Burmistrova, M. Fatima, P. Rijo, J. Quintana, J. Bermejo, F. Estevez, Journal of Natural Products (2013) 10-1021.

P21

# Photodegradation of citalopram: transformation products and kinetics

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Citalopram, a selective serotonin reuptake antidepressant inhibitor (SSRI), has a high consumption in the world for the treatment of depression.[1] There are numerous studies that have detected this drug in effluents and surface waters but there are few studies of the fate and transformation products (TPs) in the environment or in the wastewater treatment plant (WWTP).[2,3] The processes of formation of TPs are important pathways for emerging compounds in environment, their identification is fundamental to understand the risks that may cause in the environment.

The objective in this study is to identify the formation of TPs of citalopram that might be found in the environment, by means of simulations of photo-degradation under controlled conditions that may occur in the aquatic environment and in the wastewater treatment plant. Sample (20 mL) was spiked with citalopram in concentration of 4 mg $L^{-1}$. The high concentration of the compound is to elucidate the formation of TPs (the concentration found in the environment is in the order of ng $L^{-1}$) and the pH was monitored (5.0–5.6) but not modified to simulate the real environmental condition. TPs were identified and elucidated by ultra-high-performance liquid chromatography (UHPLC) coupled to a hybrid quadrupole time of flight mass spectrometer (QTOF MS) operating in both positive-ion and negative-ion mode.

The experiments resulted in 7 possible identified TPs. There was an increase in TPs formation, namely TP-PH1 ($C_{19}H_{17}N_2O_2F$), TP-PH2 ($C_{19}H_{19}N_2O_2F$), and TP-PH3 ($C_{20}H_{20}N_2O_3$), over time. Another TP, namely TP-PH4 ($C_{20}H_{19}N_2O_2F$), showed stability over time. Desmethylcitalopram (TP-PH6, $C_{19}H_{19}N_2OF$) and citalopram N-oxide (TP-PH5, $C_{20}H_{21}N_2O_2F$) human metabolites, were detected in these experiments and showed that the compounds can be formed under UV-light.

The probable structures of TPs were established based on two prediction tools softwares: EAWAG-BBD: Pathway Prediction and Bruker MetabolitePredict. Analyses were based on accurate mass and on the fragmentation observed in the MS spectra and the mass errors were less than 5 ppm. A possible degradation pathway was proposed for the formations of TPs and the stability and formation of TPs was monitored in the experiments.

**Acknowledgements**

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**References**

[1] OECD, Health at a Glance: Europe 2012, OECD Publishing (2012).

[2] E.N. Evgenidou *et al.*, Science of the Total Environment 505 (2015) 905-926.

[3] B. Subedi, K. Kannan, Science of the Total Environment 514 (2015) 273-280.

P22

# PhotoMOF: Development of Photoactive Metal-Organic Frameworks for Energy Applications

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Presently, there is still a need to develop new technologies for clean energy storage and conversion. In virtue of climate protection and energy sustainability, different materials are being studied for different clean energy production. For this purpose, a sub-branch of coordination polymers, metal-organic-frameworks (MOFs), are emerging as a new class of porous crystalline materials, with diverse functional properties [1]. Their combination of long-range order, high thermal stability, low framework density and synthetic flexibility, enables a wide range of tunable properties useful in functional devices. Even though the field of MOF-based electronic devices is very recent, there have been demonstrations where MOF structures play an active role in light-harvesting devices, specifically solar cells [2]. Our goal is to design new MOF frameworks with a broad light harvesting range, exciton formation and charge separation, and a good overall charge mobility, to be applied in organic photovoltaic's (OPVs). Tuning the electronic structure of the organic ligand will provide a way to improve the absorption of solar radiation, namely diphenylanthracene (DPA) or perylenediimides (PDIs) derivatives. The described ligands were already incorporated in a limited number of MOF frameworks, by solvothermal procedures, indicating that there's still room to discover a diversity of structures with different topologies. Mechanochemistry will be used to prepare new based carboxylate-MOFs, pillared MOFs with bridging (carboxylic binding groups) and axial ligands (*e.g.* pyridines), affording a greener approach to our strategy. A comparative study will be developed using the solvothermal approach to correlate and identify new crystalline frameworks by powder X-ray diffraction (PXRD) or single crystal X-ray diffraction (SCXRD).

**Acknowledgements**

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**References**

[1] S.-L. Li, Q. Xu, Energy Environ. Sci. 6 (2013) 1656-1683.

[2] V. Stavila, A.A. Talin, M.D. Allendorf, Chem. Soc. Rev. 43 (2014) 5994-6010.

P23

# Platinum complexes with acyclic amino(*imino*)carbene ligands: application for the catalytic hydrosilylation of terminal alkynes

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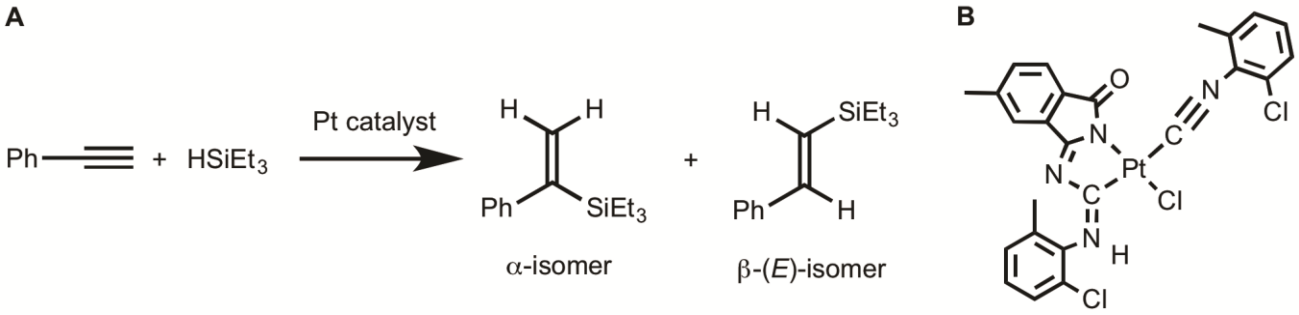
Complexes with acyclic amino(*imino*)carbine ligands have previously demonstrated high catalytic efficiency in the Suzuki–Miyaura and Sonogashira cross-coupling.[1,2] In the development of these studies,[2,3] we prepared analogous platinum-aminocarbene derivatives and evaluated their catalytic properties as calalysts for the hydrosilylation of terminal alkynes.

Hence, twelve platinum-aminocarbene complexes were generated via the metal-mediated addition of 3-iminoisoindolin-1-ones HN=C$^a$($C_6R^2R^3R^4R^5$CON$^b$H) ($R^2$–$R^5$ = H; $R^3$ = Me, $R^2$, $R^4$, $R^5$ = H; $R^3$, $R^4$ = Cl, $R^2$, $R^5$ = H) to isocyanides in *cis*-[$PtCl_2(CNR^1)_2$] ($R^1$ = Cy, *t*-Bu, Xyl, 2-Cl-6-Me$C_6H_3$). Characterization of the complexes was accomplished using elemental analyses (C, H, N), FT-IR, ESI$^+$-MS, $^1$H, and $^{13}$C{$^1$H} NMR spectroscopy.[2,3] All prepared complexes were evaluated as catalysts for the hydrosilylation of terminal alkynes with organosilanes (Scheme 1A). System required a catalyst loading of 0.1 mol%, and operated at 80–100 $^o$C in toluene for 4–6 h. Various aliphatic and aromatic hydrosilanes ($Et_3SiH$, $Pr_3SiH$, *i*-$Pr_3SiH$, $PhMe_2SiH$) and terminal alkynes (PhC≡CH, *t*-BuC≡CH, 4-(*t*-Bu)$C_6H_4$C≡CH) gave vinyl silane products in 48–95% yields. Maximum TON of $8.4\times10^3$ was achieved with the representative catalyst shown on Scheme 1B. Initial observations on mechanism of the catalytic action of platinum-aminocarbene catalysts suggest a molecular catalytic cycle.




**Scheme 1.** Model hydrosilylation of terminal alkynes with silanes (A) and the representative catalyst (B).

**Acknowledgements**

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**References**

[1] K.V. Luzyanin, M.F.C. Guedes Silva, V.Y. Kukushkin, A.J.L. Pombeiro, Inorg. Chim. Acta 362 (2009) 833-888.

[2] K.V. Luzyanin, A.J.L. Pombeiro, M. Haukka, V.Y. Kukushkin, Organometallics 27 (2008) 5379-5389.

[3] R.S. Chay, B.G.M. Rocha, A.J.L. Pombeiro, V.Y. Kukushkin, K.V. Luzyanin, ACS Omega (*submitted*).

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# Ca waste nanomaterials and base functionalized MWCNTs utilization in biodiesel production

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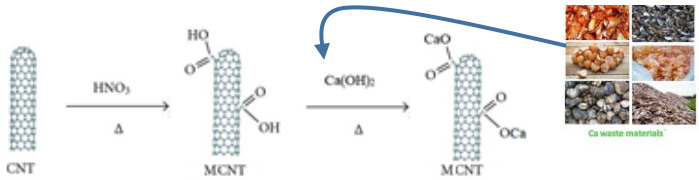
Nowadays, around 90% of biodiesel is produced by the transesterification reaction of triglycerides with low molecular weight alcohols using acid/basic catalysts. Homogeneous catalytic transesterification is still the major industrial biodiesel production process using alkali hydroxides and methoxides. However, it has disadvantages such as catalyst reusability, catalyst lixiviation and separability. Lately, researchers have been focusing on heterogeneously catalysed process. [1]

Considering heterogeneous catalysts, CaO is one of widely-used catalyst due to its highly availability in nature, low cost, and high activity. CaO decomposed from waste egg and oyster shells ($CaCO_3$) at high temperature and has been shown to exhibit high activity for the transesterification of soybean oil due to its superior basic strength. However, heterogeneous catalysts, are currently, somewhat time consuming, need more reaction time to achieve high FAME yields and presents some mass transfer limitations.

One solution might be the use of CaO nanocatalysts, as they present higher surface area and higher catalytic activity, thus allowing to achieve a significant improvement on transesterification efficiency, resulting into faster reactions i.e., shorter reaction times, low reaction temperatures and lower catalyst concentration. WFOs and animal fats can be used as raw materials in the transesterification reaction for biodiesel production, turning it into an eco-friendly and cost-effective process. [2-4]

Another possibility for the use of Ca waste materials in biodiesel production might be using Carbon NanoTubes (CNTs) functionalized, through oxidation process with nitric acid, followed by treatment with $Ca(OH)_2$. This treatment is thought to give CNTs basic properties, thus enabling them to be used as solid base [5].




**Acknowledgements**

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**References**

[1] D.M. Marinkovic, J.M. Avramovic, M.V. Stankovic, O.S. Stamekovic, D.M. Jovanovic, V.B. Veljokovic, Energy and Conversion Management 144 (2017) 399-413.

[2] A. Islam, Y.H. Taufiq-Yab, E.S. Chan, M. Moniruzzaman, S. Islam, M.N. Nabi, Energy and Conversion Management 88 (2014) 1200-1218.

[3] S. Chatuverdi, P.N. Dave, N.K. Shah, Journal of Saudi Chemical Society 16 (2012) 307-325.

[4] S. Sirisomboonchai, M. Abuduwayiti, G. Guan, C. Samart, S. Abliz, X. Hao, K. Kusakabe, A. Abudula, Energy and Conversion Management 95 (2015) 242-247.

[5] F. Maia, N. Mahata, B. Jarrais, A.R. Silva, M.F.R. Pereira, C. Freire, J.L. Figueiredo, Journal of Molecular Catalysis A: Chemical 305 (2009) 135-141.

**P25**

# Functionalization of *N*-Terminal cysteine via iminoboronate and thiazolidine cyclisation

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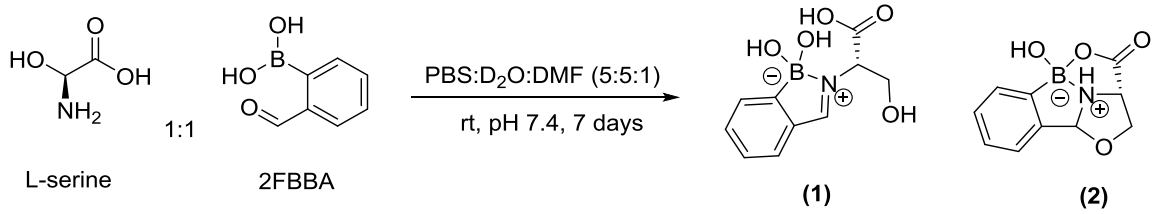
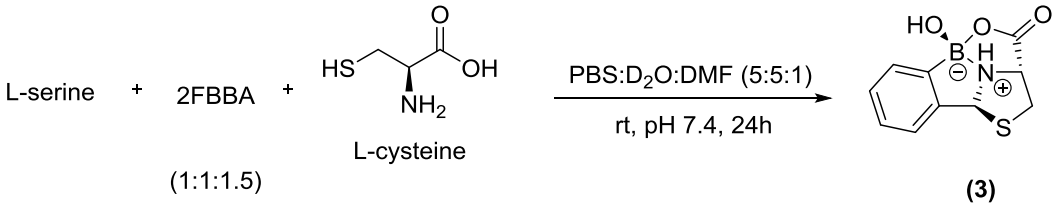
By far the most explored property has been the nucleophilic reactivity of amino acid residues with respect to proteins bioconjugation. In fact, lysine and cysteine have been the election targets especially due their own reactivity since they bear the most reactive nucleophiles in their residue chain.[1] Despite this, there are also other nucleophilic substrates available to react, such as serine hydroxyl.[2] We have shown the high reactivity of formyl benzeno boronic acid (2FBBA) with *N*-terminal cysteines to form a boronated thiazolidine featuring a B–N bond under mild aqueous conditions (pH 7.4, 23°C).[3] We reasoned that other type of *N*-terminal amino acids such as serine or threonine could participate in similar reactions. In fact, preliminary data shows that when 2FBBA reacts with serine, it generates a mixture of iminoboronate **(1)** and oxazolidine **(2)**, although in low conversion (Scheme 1). Notwithstanding, the addition of cysteine shifts the equilibrium to the cyclization of thiazolidine in the competition assay **(3)** (Scheme 1). Herein we will provide some results on the development of this methodology for orthogonal modification of *N*-terminal cysteine in peptides and proteins.

***Specificity Assay with 2-Formyl benzene boronic acid***




***Competition Assay with L-cysteine***




**Scheme 1.** Specificity and Competition Assay adding L-cysteine to the reaction mixture of 2FBBA with L-serine. The reactions' conversion were evaluated by $^1$H-NMR spectra based on the comparison of the signal of aldehyde (≈ 9.8 ppm), imine (≈ 8.4–8.7 ppm), thiazolidine proton (≈ 6.2 ppm) and oxazolidine proton (≈ 6.1 ppm).

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**References**

[1] (a) G.L. Bernardes, J.M. Chalker, B.G. Davis, Ideas in Chemistry and Molecular Sciences (2010); (b) P.M. Cal, J.O.B. Vicente, E. Pires, A.V. Coelho, L.F. Veiros, C. Cordeiro, P.M.P. Gois, J. Am. Chem. Soc. 134 (2012) 10299; (c) P.M. Cal, R.F. Frade, C. Cordeiro, P.M.P. Gois, Chem. Eur. J. 21 (2015) 8182; (d) P.M. Cal, G.J. Bernardes, P.M.P. Gois, Angew. Chem. Int. Ed. 53 (2014) 10585.

[2] O. Koniev, A. Wagner, Chem. Soc. Rev. 44 (2015) 5495.

[3] H. Faustino, M.J.S.A. Silva, L.F. Veiros, G.J.L. Bernardes, P.M.P. Gois, Chem. Sci. 7 (2016) 5052.

**P26**

# Characterization of the phytochemical composition of young phloem from *Pinus pinaster* Aiton and *Pinus pinea* L.

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The forest in Portugal occupies about 35% of the national territory, where 23% corresponds to pine forests of maritime pine (*Pinus pinaster* Aiton) and stone pine, or Portuguese pine (*Pinus pinea* L.) with great socio-economic impact. Factors impacting on tree growth and resistance to biotic and biotic stress are therefore important and research on these areas is underway. For instance, pine species differ greatly in their susceptibility to pinewood nematode, *Bursaphelenchus xylophilus*, and differences in susceptibility might be related to phytochemical differences [1].

One line of research involves the study of secondary metabolites Plant cells synthesize a vast supply of natural compounds that are not strictly necessary for their growth and reproduction, which are known as secondary metabolites and have a wide range of chemical, physical and biological activities. Numerous differences in amount and nature of the chemical components of the bark can be found even within a single species, depending on the age and growth site of the trees, the fraction of bark, climate and geographical conditions.

This study aims to evaluate the production of secondary metabolites and gain knowledge about the phytochemical composition of young phloem from maritime pine and Portuguese pine. Six trees of each species were studied from three sites; “Herdade da Apostiça”; “Melides” and “Leiria”. The sampling was carried out in the young branches, in order to study the period between 2011 and 2012. The young phloem was examined for the content of hydrophilic extractives using ethanol/water solution as solvent. Extraction yields were calculated and the chemical composition of the extracts analyzed for total phenolics (Folin-Ciocalteau assay) and antioxidant properties using the DPPH method.

**Acknowledgements**

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**References**

[1] C.S. Pimentel, P.N. Firmino, T. Calvão, M.P. Ayres, I. Miranda and H. Pereira, Plant Pathology (2016).

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# The synthesis and applications of molybdenum(II) organometallic complexes coordinated with functionalized phenanthroline ligands

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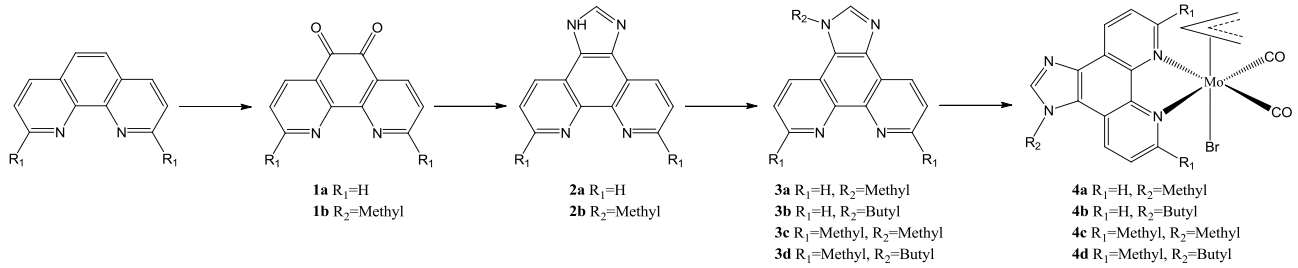
A set of phenanthroline derivatives were synthesized from 1,10-phenanthroline and 2,9-dimethyl-1,10-phenanthroline as shown in Scheme 1 [1]. These ligands were reacted in inert atmosphere and at room temperature with the precursor complex $[MoBr(\eta^3\text{-}C_3H_5)(CO)_2(CH_3CN)_2]$ resulting in the formation of the new family of molybdenum(II) organometallic complexes $[Mo(\eta^3\text{-}C_3H_5)Br(CO)_2(1\text{-}R_1\text{-imidazo[4,5-f]-}R_2\text{-[1,10]phenanthroline})]$ ($R_1$=butyl, methyl, $R_2$=dimethyl, H) [2]. All the ligands and complexes prepared were characterized by FTIR, $^1H$ and $^{13}C$ NMR. The new complexes prepared were used as homogeneous catalysts for the oxidation of cyclooctene, styrene, cis-3-hexen-1-ol, trans-2-hexen-1-ol, R(+)-limonene, geraniol and 1-octene with TBHP (*tert*-butyl hydroperoxide) as the oxidant. The data were collected through GC-MS. The effects of reaction time, temperature and amount of catalysts were discussed.




**Scheme 1.** Synthesis of the Molybdenum(II) organometallic complexes.

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**References**

[1] A.A. Webster, S.K.K. Prasad, J.M. Hodgkiss, J.O. Hoberg, Dalton Trans. 44 (2015) 3728-3736.

[2] M.S. Saraiva, S. Quintal, F.C.M. Portugal, T.A. Lopes, V. Félix, J.M.F. Nogueira, M. Meireles, M.G.B. Drew, M.J. Calhorda, J. Organomet. Chem. 693 (2008) 3411-3418.

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