OC1

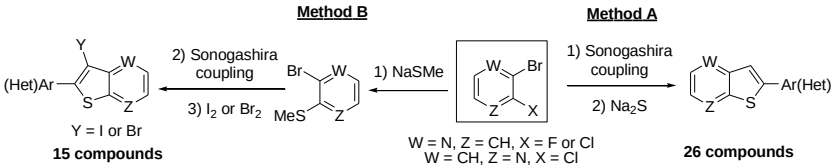
New strategies for the synthesis of 2-(hetero)arylthieno[2,3-*b*] or [3,2-*b*]pyridine scaffolds from 2,3-dihalopyridines

Maria João R. P. Queiroz, Agathe Begouin, Daniela Peixoto

Centro de Química, Escola de Ciências, Universidade do Minho Campus de Gualtar 4710-057 Braga

mjrpq@quimica.uminho.pt

In the past few years, our research group has synthesised new thieno[3,2-*b*]pyridines as antitumor agents.[1] Recently, we have been interested in the synthesis of new 2-(hetero)arylthienopyridine scaffolds starting from 2,3-dihalopyridines (**Scheme 1**). Two methodologies were used: either a one-pot Sonogashira coupling followed by a reaction with Na_2S, giving 2-(hetero)arylthienopyridines (Method A),[2] or a reaction with NaSMe followed by a Sonogashira coupling and a halocyclization, affording the corresponding 3-halo-2-(hetero)arylthienopyridines (Method B).[3] The key step of the latter method is the formation of the required bromo(methylthio)pyridines by a regiocontrolled S_NAr with NaSMe, that has to be performed before the Sonogashira coupling. If not, an addition of the SMe to the triple bond of the Sonogashira product occurs instead of the substitution of the chlorine or fluorine atom of the pyridine. In the light of this observation, the reaction mechanism of Method A using Na_2S will also be discussed.



Scheme 1: Synthesis of 2-(hetero)arylthienopyridines from 2,3-dihalopyridines

Further functionalizations were also performed on the compounds obtained, allowing the synthesis of new thienopyridine derivatives that will be studied as antitumor and/or antiangiogenic agents having tyrosine kinase membrane growth factor receptors of tumor or endothelial cells as targets.

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Synthesis, Characterization and Citotoxic Activity of Cyclopentadienyl Ruthenium(II) Complexes with Carbohydrate Derived Ligands

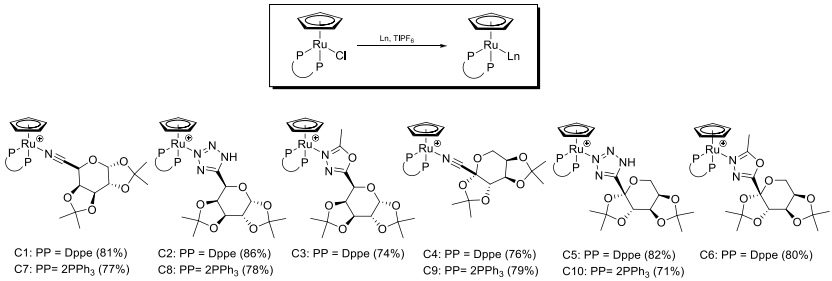
Ana C. Fernandes,[a] Pedro Florindo,[a] Inês J. Marques,[b] Carla D. Nunes[b]

[a]*Centro de Química Estrutural, Instituto Superior Técnico, Universidade Técnica de Lisboa,1049-001 Lisboa, Portugal;* [b]*Centro de Química e Bioquímica, Faculdade de Ciências da Universidade de Lisboa, Campo Grande 1749-016 Lisboa, Portugal*

anacristinafernandes@ist.utl.pt

Organometallic complexes containing monosaccharide ligands represent a small but challenging field in modern chemistry. Carbohydrates are the largest class of natural compounds and thereby readily available and renewable. They provide a large number of functional groups and several stereogenic centres *per* molecule, and each of the hydroxyl groups offers the opportunity of selective modification and coordination [1, 2]. Particularly, the synthesis of ruthenium compounds bearing carbohydrate derived ligands is an almost unexplored area.

As part of our endeavour to produce a library of carbohydrate-containing organometallic compounds, we here report the synthesis and cytotoxic evaluation against human *HeLa* cancer cells (cervical carcinoma) of ten new η^5-cyclopentadienylruthenium cationic complexes of general formula $[Ru(\eta^5\text{-}C_5H_5)(PP)Ln][PF_6]$, in which Ln are galactose and fructose carbohydrate derivative ligands, functionalized with nitrile, tetrazole and 1,3,4-oxadiazole *N*-coordinating moieties (**Scheme 1**). The electronic density and the stereochemichal environment of the metal centre are played using two different phosphanes as coligands, PPh_3 and Dppe. All new compounds were characterized by IR, ^1H, ^{13}C, ^{31}P-NMR spectroscopies.



Scheme 1: Synthesis of the Ru(II) organometallic complexes.

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OC3

Pd-catalysed amination on a soluble polymer support: a sustainable version of homogeneous C-N cross-coupling reaction

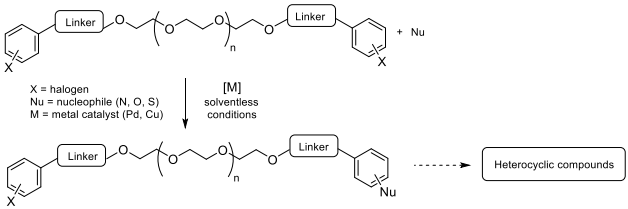
Luísa C. R. Carvalho,[a] Marina J. Dias Pires,[a] Eduarda Fernandes,[b] M. Manuel B. Marques[a]

[a]*REQUIMTE, Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, Campus de Caparica, 2829-516 Caparica, Portugal;* [b]*REQUIMTE, Departamento de Ciências Químicas, Rua Jorge Viterbo Ferreira nº 228, 4050-313 Porto, Portugal*

mmbmarques@fct.unl.pt

Heterocyclic systems represent an important class of compounds in biologically active pharmaceuticals, natural products, and materials, and therefore the selective functionalization of these molecules is of great interest.[1a] The aryl amine moiety can be found in a wide variety of heterocyclic compounds, and metal-catalyzed cross-coupling reactions of anilines with aryl halides constitute the main methods for assembling this type of substructure.[1b] During the last year we have been focused on the development of novel benzimidazole based compounds as COX inhibitors, and Pd-catalysed aryl amination reaction has been used to produce key intermediates.[2]

Recently, polyethylene glycol (PEG) appears as an environmental friendly alternative to the use of volatile, toxic and hazardous organic solvents.[3] Thus, we decided to investigate the possibility of using PEG 2000 as a soluble polymeric support for the preparation of arylated heteroarenes. Herein, we will present an innovative palladium-catalysed amination protocol on a solid support, solvent-free and homogeneous medium that can be considered as a sustainable version of this key reaction (**Scheme 1**). This work opens the possibility to build aromatic scaffolds while avoiding both organic solvents and purification steps with the advantage of an easy and fast monitoring.



Scheme 1: Metal-catalysed cross-coupling reaction on PEG.

Acknowledgements: We thank the Fundação para a Ciência e Tecnologia for financial support SFRH/BD/63407/2009 and PEst-C/EQB/LA0006/2011.

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Photoactive molecules by design

João P. C. Tomé

QOPNA and Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal

jtome@ua.pt

Porphyrinsand Chlorins constitute a group of natural compounds which play key roles in several vital functions of life, such as: respiration, photosynthesis and many enzymatic processes. The possibility of mimic those functions and explore several others, especially when combined with light, have been highly explored by the scientific community.[1] The possibility of decorate the periphery of their cores, with different motifs and select their central metals opens the possibility to fine-tune the physico-chemical properties/functionalities of novel molecules/materials to be used in many scientific and technological areas, especially when combined with nanostructures.[2] In Aveiro, in collaboration with other national and international groups, we have successfully been designing and synthesizing several of those photoactive molecules/materials (**Figure 1**) to be used in: i) photomedicine, mainly as photosensitizers for antibiotic resistant pathogenic microorganisms photodynamic inactivation (PDI) and for cancer photodynamic therapy (PDT); ii) optical (chemo)sensors, to detect and trap anionic pollutants from contaminated environments; iii) (photo)catalysts, to be used in industrial and environmental applications.[3] In this short communication, it will be highlighted some of our recent works, presenting the usedsynthetic strategies and some of the obtained photo-physical, -chemical and –biological results in the indicated applications.

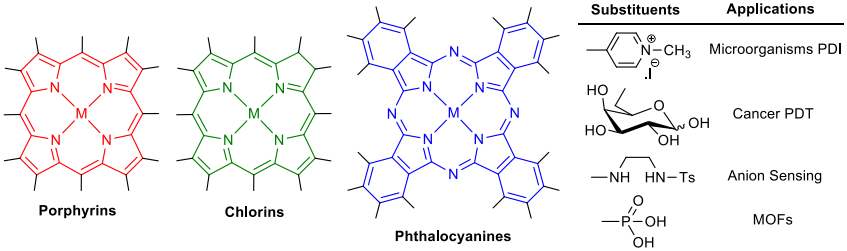

Figure 1: Some photoactive compounds from Aveiro

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OC5

Multidimensional optimization of pyranoxanthones with potential antitumor activity

J. Soares,[a] C. Azevedo,[a,b] A. Palmeira,[a] D. Sousa,[a,c] R. Lima,[a,c] M. Pedro,[a] M. Vasconcelos,[c] C. Afonso,[a] S. Reis,[d] M. Pinto[a]

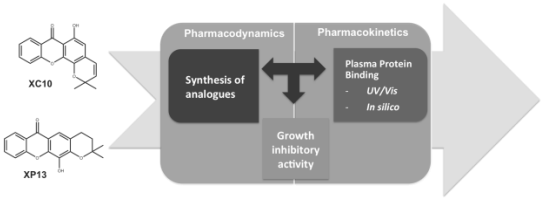
[a]*CEQUIMED-UP, Department of Chemistry, Laboratory of Organic and Pharmaceutical Chemistry, Faculty of Pharmacy, University of Porto, Rua Jorge Viterbo Ferreira, 228, 4050-313 Porto, Portugal;* [b]*Department of Physics, Chemistry and Pharmacy, University of Southern Denmark, Campusvej 25, 5230 Odense, Denmark;* [c]*Cancer Drug Resistance Group, Instituto de Patologia e Imunologia Molecular da Universidade do Porto (IPATIMUP), Rua Dr. Roberto Frias s/n, 4200-465 Porto, Portugal;* [d]*REQUIMTE, Laboratory of Applied Chemistry, Faculty of Pharmacy, University of Porto, Rua Jorge Viterbo Ferreira, 228, 4050-313 Porto, Portugal*

jfxsoares@ff.up.pt

Pyranoxanthones are a family of *O*-heterocycles that have a wide variety of biological activities, particularly antitumor activity.[1,2] Our group has been focusing on the synthesis of a library of pyranoxanthone derivatives and two compounds (XC10 and XP13) emerged as potential antitumoragents.[2] Considering that on the pipeline that drives "hit-to-lead" compounds to drug candidates, multidimensional optimization, which involves the control of both pharmacodynamic and pharmacokinetic behaviors, is essential, it has been envisioned for these "hit compounds (scheme 1).

In this work, we report the synthesis of XC10 and XP13 and seven analogues using classical and non-classical methodologies. Moreover, their growth inhibitory activity in four human tumor cell lines was evaluated. Among the several factors that affect pharmacokinetics, the binding to plasma proteins is one of the most prominent. Therefore, the interaction of XP13, XC10 and the synthesized analogues with human serum albumin (HSA) was studied. The binding to HSA was evaluated by fluorescence quenching technique and UV–Vis absorption derivative spectroscopy. The crucial distance between the bound compound and an albumin tryptophan residue was investigated by Förster resonance energy transfer technique.[3] In order to shed some light on the binding of XC10 and analogues to HSA, an *in silico* study was also performed. Using AutoDockVina program, molecular docking to a HSA crystal structure (pdb code: 2VUE) was performed, and the ligand conformations and docking scores were analyzed.

The obtained results allowed us to guide the design of new drug candidates with better pharmacodynamic and pharmacokinetic profiles.



Scheme 1: Multidimensional optimization of XC10 and XP13

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