7th Portuguese National Meeting of Organic Chemistry
Welcome

It is normal for the organisers of a meeting to express their hopes at the outset that all will go well, and to make a few general statements about how significant the gathering will be.

The National Meetings of Organic Chemistry – best known as ENQOs, have in the past created in the life of the Division of Organic Chemistry of the Portuguese Chemical Society (SPQ) the opportunity for its members to meet every two years, exchange views and discuss their scientific achievements. Hopefully the 7ENQO will achieve the outstanding success of previous gatherings.

This year, during the last day devoted to the 1st Portuguese-French Meeting, colleagues from France will meet with Portuguese organic chemists to pave the way for a closer scientific collaboration in the future. Indeed such is the way science, in general, and chemistry, in particular, will have to move if our European Nations are to remain scientifically relevant, in view of the speed of progress and discovery occurring in other blocks around the world.

Every journey is made of small steps. Let us hope that the 7ENQO will represent yet another step in the already long life of SPQ and an occasion for gauging the progress of our science and enjoying our city.

Welcome to the 7ENQO in Lisbon!

The Organising Committee
Organising Committee

Ana M. Lobo (FCT-UNL)
Teresa Pinho e Melo (Univ. Coimbra)
Abel Vieira (FCT-UNL)
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  MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR
Program
Monday, 16th July

09h00 - 10h30
Registration

10h30 – 11h00
7ENQO Opening Session

11h00 – 12h30
Plenary Lectures

Auditorium 2:

Chairperson: Artur Silva

11h00 – 11h45
PL1: Peter Somfai
Allylsilanes beyond Sakurai-allylations: synthetic approaches towards (+)-alexine utilizing a novel [3+2]-annulation reaction

11h45 – 12h30
PL2: Carlos Afonso
Ionic liquids: six years of development, applications and commercialization

12h30 – 14h30
Break for lunch

14h30 – 15h15 Plenary Lecture

Auditorium 2:

Chairperson: Ana Oliveira-Campos

PL3: Carmen Nájera
Recoverable catalysts for asymmetric synthesis

15h15 – 17h00
Poster Session (PC1-PC40)
Coffee break
17h00 – 18h00
Oral Communications

**Auditorium 2:**

Chairperson: Ana Oliveira-Campos

17h00-17h15
OC1: Maria João Queiroz  
*Metal-assisted reactions in the synthesis of new fluorescent heteroaromatic systems from dehydroamino acids*

17h20-17h35
OC2: Andrea Figueiredo  
*O-hydroxylated 2-stryrylchromones with potential antioxidant activity*

17h40-17h55
OC3: Arantxa Gómez-Esqué  
*Biogenetically inspired enantioselective approach to indole alkaloids*

**Meeting-room:**

Chairperson: Luísa Sá e Melo

17h00-17h15
OC4: Ricardo Figueiredo  
*Tuberculosis: molecular targets and drug development*

17h20-17h35
OC5: M. I. Ismael  
*Synthesis and anticholinesterase activity of pseudo-C-nucleosides containing oxopyrimidine, tetrazole and isoxazole rings*

17h40-17h55
OC6: Marta Correia-da-Silva  
*Chemical sulfation: synthesis of potential anticoagulant phenolic compounds*

19h00
Welcome reception (Gardens of Gulbenkian Foundation, Av. Berna)
Tuesday, 17th July

09h00 – 10h30

*Plenary Lectures*

**Auditorium 2:**

**Chairperson:** Ana Lobo

09h00 – 09h45

**PL4:** Maria Fernanda Proença

*New developments in the synthesis of imidazole-based compounds*

09h45 – 10h30

**PL5:** Henry S. Rzepa

*A twisted link between chemistry, maths, molecular biology (and music)*

10h40 – 11h00

*Coffee break*

11h00 – 12h40

*ORGLIST Symposium*

**Auditorium 2:**

**Chairperson:** Henry Rzepa

11h00 – 11h10

*Introduction*

11h10 – 11h45

**OL1:** Scott Boyer

*Computational models to aid safety-directed drug design*

11h45 – 12h20

**OL2:** Valerie J. Gillet

*Deriving structure-activity relationship in heterogeneous datasets*

12h20 – 12h40

**OL3:** Bruce F. Milne

*Two-parameter classifier for prediction of PKC-ζ modulating behaviour of xanthenes*
12h40 – 14h30  
Break for lunch

14h30 – 15h15  
Plenary Lecture

Auditorium 2:

Chairperson: Madalena Pinto

PL6: Victor F. Ferreira  
Synthesis of new derivatives of natural naphthoquinones

15h15 – 16h15  
Oral Communications

Auditorium 2:

Chairperson: Rui Moreira

15h15-15h30  
OC7: Alice M. Dias  
A versatile synthetic approach for isoguanine derivatives

15h35-15h50  
OC8: Pedro J. M. Abreu  
Natural products from African and Caribbean medicinal plants: highlights on current research

15h55-16h10  
OC9: M. Lurdes S. Cristiano  
Investigation into the reactivity of tetrazoles and benzisothiazoles

15h15 – 16h30  
ORGLIST Symposium

Meeting room:

Chairperson: Henry Rzepa

15h15 – 15h50  
OL4: Nuno Palma  
Regioselectivity of catechol-O-methyltransferase catalyzed reaction: combined theoretical and experimental studies
15h50 – 16h25
OL5: Carlos Cobas
From MestReC to Mnova: a revolutionary approach to NMR

16h25
Conclusion

16h40-17h40
Organic Chemistry Division - SPQ Meeting

20h00
Conference dinner

Wednesday, 18th July
Portuguese-French Symposium

09h00 – 09h15
Opening Session

09h15 – 10h45
Plenary Lectures

Auditorium 2:

Chairperson: José Cavaleiro

09h15 – 10h00
PL7: M. Matilde Marques
DNA-based biomarkers of potential drug toxicity: from SERMs to the HIV reverse transcriptase inhibitor nevirapine

10h00 – 10h45
PL8: Siméon Arseniyadis
Competing domino processes modulated by the substitution pattern; synthetic applications

10h55 – 11h15
Coffee break
11h15 – 12h35

Oral Communications

**Auditorium 2:**

**Chairperson:** Rocha Gonçalves

11h15 – 11h30

**OC10:** Rui G. Lopes  
A new and easy approach for the synthesis of methyl-2-deoxy-2-C[(ethoxycarbonyl)methylene]hexopyranosides

11h35 – 11h50

**OC11:** Mário M. Q. Simões  
New approaches for metalloporphirin catalised oxidation reactions

11h55 – 12h10

**OC12:** A. J. Burke  
Enantioselectivity asymmetric allylic alkylations using a DIOP analogue with a 1,4-dioxane backbone

12h15 – 12h30

**OC13:** A. L. Cardoso  
Synthesis of chiral β-amino esters

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**Meeting room:**

**Chairperson:** José Prata

11h15 – 11h30

**OC14:** M. Manuela M. Raposo  
Donor-acceptor substituted π-conjugatedheterocyclic systems: synthesis and characterization

11h35 – 11h50

**OC15:** Paulo J. Coelho  
Study of the photocromic equilibrium in spirooxazines by NMR

11h55 – 12h10

**OC16:** Arménio Serra  
Halogen atom effect on photophysical and photodynamic characteristic of derivatives of m-THPP

12h15 – 12h30

**OC17:** Ana M. Seca  
Fatty acid diterpenol esters from leaves of Juniperus brevifolia
12h35 – 14h30  
*Break for lunch*

14h30 – 15h15  
*Plenary Lecture*

**Auditorium 2:**

Chairperson: Ana Lobo

**PL9: M. J. Marcelo Curto**

*Organic chemistry in a government laboratory: ten years of research*

15h15 – 17h00  
*Poster Session (PC41-PC79)*

*Coffee break*

17h00 – 17h45  
*Plenary Lecture*

**Auditorium 2:**

Chairperson: Ana Lobo

**PL10: Jean-Marie Beau**

*Chemical glycobiology: synthesis of bioactive natural products and mimics*

18h00  
*Closing Session*
Plenary Lectures
Plenary Lectures

PL1- Allylsilanes beyond Sakurai-allylations: synthetic approaches towards (+)-alexine utilizing a novel [3+2]-annulation reaction
Peter Somfai

PL2- Ionic liquids: six years of development, applications and commercialization
Carlos Afonso

PL3- Recoverable catalysts for asymmetric synthesis
Carmen Nájera

PL4- New developments in the synthesis of imidazole-based compounds
Maria Fernanda Proença

PL5- A twisted link between chemistry, maths, molecular biology (and music)
Henry S. Rzepa

PL6- Synthesis of new derivatives of natural naphthoquinones
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PL7- DNA-based biomarkers of potential drug toxicity: from SERMs to the HIV reverse transcriptase inhibitor nevirapine
M. Matilde Marques

PL8- Competing domino processes modulated by the substitution pattern; synthetic applications
Siméon Arseniyadis

PL9- Organic chemistry in a government laboratory: ten years of research
M. J. Marcelo Curto

PL10- Chemical glycobiology: synthesis of bioactive natural products and mimics
Jean-Marie Beau
Allylsilanes beyond Sakurai-allylations: Synthetic approaches towards (+)-Alexine utilizing a novel [3+2]-annulation reaction

Peter Somfai§
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The β-amino alcohol moiety is found in a wide variety of biologically active alkaloids and peptides, it is consequently a common building block in the synthesis of natural products. The importance of vicinal amino alcohols is also well recognized in asymmetric synthesis, as many chiral auxiliaries and ligands contain this substructure. In this lecture a novel approach to vic-amino alcohols developed in our laboratory will be discussed as well as its application towards the synthesis of (+)-Alexine.1,2

IONIC LIQUIDS: SIX YEARS OF DEVELOPMENT, APPLICATIONS AND COMMERCIALIZATION

Carlos A. M. Afonso, a,b Luís C. Branco, a,b Paulo A. S. Forte, a Pedro M. P. Gois, a,b Nuno M. T. Lourenço, a Nuno M. M. Mateus, b João N. Rosa, b Andreia A. Rosatella a

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Low melting salts have long been used in electrochemistry applications due to their high electrochemical window and electrolyte properties. Since the discovery of air stable and water resistant low melting salts, later designated as room temperature ionic liquids (ILs), created during last years an impressive interest in the scientific community in different research areas such as electrochemistry, organic, inorganic, organometallic, polymer and material chemistry biotransformations, remediation, fuel and solar cells, and separation technology (biphasic, membranes, scCO2, systems and pervaporation), flotation fluids, lubricants, nanotechnology and paint additives. Perhaps the reasons for such wide research applications are due to some unique properties such as high conductivity, wide electrochemical window, near non-volatility, high thermal stability, low flammability, tunable solubility in water and in common organic solvents, insolubility in scCO2, high solubility and in some cases specific affinity for organic, inorganic, organometallic solutes, scCO2 and other gases in some ILs, and high stability of enzymes in some IL media.

Our research contribution in this area have focused mainly on the development of new ionic liquids based on the cations 1-methyl-imidazolium [mim] and tetra-alkyl-dimethyl-guanidinium [dmg] cations, including chiral ILs, and in exploring their use as an efficient reaction media for catalyst reuse, product separation, absorption of volatile compounds and selective transport by membrane technology.


Acknowledgments: We would like to thank Fundação para a Ciência e Tecnologia and FEDER for financial support.
Recoverable Catalysts for Asymmetric Synthesis

Carmen Nájera

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In the last years it has been established the enormous potential of asymmetric catalysis in asymmetric synthesis.[1] However, an important drawback for the implementation of asymmetric catalysis in industrial processes is the relative high catalysts loadings that must be used in this type of processes. Therefore, the possibility of recycling the catalyst and to be re-used is a very important task.

In our group, we have been studied the design of effective chiral organocatalysts that could be recovered using immobilization techniques but also simple separation of the catalyst from the reaction mixture. For the asymmetric synthesis of α-amino acids polymeric and dimeric Cinchona-derived ammonium salts have been prepared as recoverable phase-transfer catalysts in alkylation reactions and Michael additions of N-(diphenylmethylene)glycine alkyl esters.[2] New 2,2’-diamino-1,1’-binaphthalene (BINAM) derived prolinamides are very efficient and recoverable organocatalysts for the direct aldol condensation of ketones and aldehydes by simple acid-base extractive work-up.[3] For the Michael addition of ketones to β-nitrostyrenes we have found that prolinamides derived from (1S,2R)-cis-1-amino-2-indanol are appropriate and recoverable organocatalysts also by extractive techniques.[4] Silver metal complexes with BINAP as chiral ligand have been shown very good stability, catalytic efficiency, and recoverability in enantioselective 1,3-dipolar cycloadditon reactions of azomethine ylides.[5]

References


Acknowledgments: We thank the Dirección General de Investigación of the Ministerio de Educación y Ciencia (CTQ2004-00808/BQU), the Generalitat Valenciana (CTIOIB/2002/320, GRUPOS03/134, GRUPOS05/11 and GV05/157) and the University of Alicante for financial support.
NEW DEVELOPMENTS IN THE SYNTHESIS OF IMIDAZOLE-BASED COMPOUNDS

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The imidazole ring is an important pharmacophore in drug discovery. The skeletons of a number of bioactive natural products incorporate this structure, which is also present in a wide range of medicinally useful agents.

\[
\begin{align*}
\text{Imidazoles } & \text{3, isolated by base-catalysed intramolecular cyclization of amidine 2, proved to be versatile precursors for a number of imidazole-based heterocycles. The reaction of compounds 3 with nucleophiles (carbon, nitrogen and oxygen nucleophiles) has been used to prepare 6-substituted purines} & \text{2} \text{ or funtionalized imidazo[4,5-b]pyridines}. & \text{3} \\
& \text{The substitution pattern of the purine ring was also modified by the appropriate selection of electrophilic reagents (aldehydes and ketones, anhydrides, ethylchloroformate, orthoesters, isocyanates and electron-deficient alkenes).} & \text{2-Oxoimidazoles 5, prepared by intramolecular cyclization of urea 4, are structurally similar to imidazoles 3, and were expected to generate identical products under analogous reaction conditions. As this was not always the case, some of the research carried out on this area will be presented and the results compared with previous work developed for imidazoles 3.}
\end{align*}
\]


Acknowledgments: Thanks are due to Universidade do Minho and Fundação para a Ciência e Tecnologia (POCTI/QUI/45391/2002 and POCI/QUI/59356/2004) for financial support.
A TWISTED LINK BETWEEN CHEMISTRY, MATHS, MOLECULAR BIOLOGY (AND MUSIC)

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Both chirality and aromaticity are cornerstone concepts for organic chemistry. Both had their origins in the 1840s or thereafter in the work of Pasteur, van't Hoff and LeBel for the former and Faraday, Loschmidt, Kekule, Armstrong for the latter, this reaching its first stage of theoretical maturity with Huckel's quantum mechanical analysis in the 20th Century (the famous 4n+2 rule).

For a long period, these two concepts were thought to be exclusive; after all aromaticity manifested almost entirely in flat (achiral) benzenoid rings!

Another concept, topology, also originated in the 1840s, having been coined by the mathematician Johann Listing, who also proposed fascinating topological objects such as trefoil knots, and rings now better known by their co-discoverer, Mobius. In the 1960s, the concepts of Mobius topologies and aromaticity started merging. The chemist Heilbronner proposed aromaticity rules for Mobius cycles, although he did not identify such cycles as being chiral (this property appears to have been gradually realised only years later, although its difficult to find this expressed in print). The first such Mobius molecule was only synthesized in 2003; it was not however particularly aromatic! Meanwhile, in 1978 molecular biologists had discovered the fascinating twists and knots in cyclic DNA, via James Wang's topoisomerase enzymes. This was expressed using a concept known as supercoiling, and a new generation of mathematicians formalised this into an equation expressing a so-called linking number, which is comprised of twist and writhe;

\[ Lk = T + W \quad \ldots(1) \]

Applied extensively to the properties of cyclic DNA, these concepts did not migrate at all to organic chemists, who by and large dealt with much smaller molecules. Listing in 1847 had also introduced the concept of paradromic winding, which in modern language maps to imparting further twists to the basic Mobius topology. In 2005, we fused these various concepts from chemistry, topology and molecular biology, recognising that a new form of aromaticity based on double- and higher twisted conjugated, and importantly chiral, rings could be possible. We identified various interesting candidate molecules, but were surprised by how relatively stable they appeared (by computation), given they were at least twice as twisted as the classical Mobius rings. We found a resolution to this paradox in equation (1). The (quantum mechanical) instability we realised is associated with T and not with W. We have now computed values of T and W for a range of topologically interesting (and chiral!) systems, and approximately, those that appear the most synthetically interesting have large values of W compared to T. So W (the writhe) can be regarded as a fundamentally new property of cyclic conjugated molecules, and one moreover that might be associated with stability. This has led to our proposal that eqn (1) and the
Huckel 4n+2 rule can be combined as follows; If Lk is even (measured in units of \( \pi \)), aromaticity is implied for 4n+2 cyclic conjugated electrons ... (2)

If Lk is odd, aromaticity is implied for 4n cyclic conjugated electrons ... (3)

Intriguingly both T and W are chiral indices, and they can act together or oppose to create some fascinating novel chiral isomerisms.

In a general sense, this type of aromaticity is chiral, and benzene like systems are very much the achiral exceptions (having Lk = 0).

At the end of the talk, I will speculate on some potential real world applications of this fascinating new form of chiral aromaticity, particularly to the design of new chiral metal ligands, and perhaps even mention another interest of ours, the Semantic Web, and how this might in the future enable more efficient fusion of diverse ideas and concepts (linking is a fundamental concept there as well!).
SYNTHESIS OF NEW DERIVATIVES OF NATURAL NAPHTHOQUINONES

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Quinones have been studied for antitumor, molluscicidal, antiparasitic, anti-inflammatory, antifungal, antimicrobial and trypanocidal activities.\(^1,2\) Literature points out that the biological profiles of these molecules are centered on their ortho or para-quinonoid moiety. This group generally accepts one and/or two electrons (redox cycling) to form the corresponding radical anion or dianion species \textit{in situ}. Thus, the semi-quinone radicals accelerate intracellular hypoxic conditions by producing superoxide anion.\(^3\) Due to this mechanism, quinones may present cytotoxicity in the mammalian cells, possibly by affecting enzymes such as topoisomerase, a group of enzymes that are critical for DNA replication in cells.\(^4\)

\(\beta\)-lapachone (1) is a 1,2-naphthoquinone isolated from the bark of the Lapacho tree (\textit{Tabebuia avellanedae}). As other quinones, 1 possesses a variety of pharmacological effects, including trypanocidal activity. However, this molecule is also cytotoxic against several cell lines. Pinto e co-workers searching for new compounds with reduced cytotoxicity while maintaining the trypanocidal profile of 1 led to some derivatives modified at the redox center (2a and 2b).\(^5\)

\[ \begin{align*}
1 & \quad 2a, \ X = O \\
2b, \ X = NH
\end{align*} \]

This conference will focus our synthetic efforts in order to find new derivatives of 1 with improved pharmacological activity.


Acknowledgments: THIS WORK WAS SUPPORTED BY UFF, CNPQ, FINEP, CAPES AND FAPERJ.
DNA-based biomarkers of potential drug toxicity: from SERMs to the HIV reverse transcriptase inhibitor nevirapine

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The term biomarker [1] is increasingly becoming a synonym for molecular biomarker. Carcinogen biomarkers are usually classified in three categories, reflecting (i) exposure, (ii) individual susceptibility, and (iii) early response [2]. The role of carcinogen-DNA interactions as indicators of carcinogenicity has been recognized for over 40 years [3], and mounting evidence suggests that covalent DNA adducts can be regarded both as markers of biological effective dose and as markers of risk, taking into account individual abilities to metabolize carcinogens and repair DNA damage. A chemist’s approach to the relevance of DNA adducts as biomarkers of the potential carcinogenicity of established therapeutic regimens will be discussed with two examples selected from our studies with tamoxifen and analogues [4,5], and our more recent experience with nevirapine [6]. Tamoxifen (I), a non-steroidal selective estrogen receptor modulator (SERM), is an important adjuvant chemotherapeutic agent for the treatment of breast cancer and a chemoprotective agent for the prevention of the disease in high-risk women, but is known to increase the risk of endometrial cancer and thromboembolic events in women. Nevirapine (II), a non-nucleoside reverse transcriptase inhibitor, is used mostly in low resource countries to prevent the vertical transmission of HIV from mother to child, despite reports of severe hepatotoxicity that raise concerns about administration of the drug in the neonatal and pediatric settings.

![Chemical structures]


Acknowledgement: Financial support from Fundação para a Ciência e a Tecnologia (FCT, Portugal) and FEDER, through programs PRAXIS XXI and POCTI, is gratefully acknowledged.
Competing Domino Processes Modulated by the Substitution Pattern; Synthetic Applications

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The basis of the overview to be presented is the oxidative cleavage of unsaturated vic-diols allowing the production of high complexity in a single operation and in a modular way (Scheme 1), with the aim of ultimately developing efficient methods for the synthesis of structurally complex natural products (Scheme 2). Two or more different domino-paths can be put in competition by the judicious choice of the reaction parameters, thus rendering this methodology synthetically useful. This topic has been addressed in some detail and a regioselective profile of this domino reaction was brought to practice in which the cyclic system and the angular substituent are tethered by spacers of various lengths and nature. Noteworthy features of this domino protocol include simultaneous formation of two or three additional rings and numerous stereogenic centers with excellent stereo- and regiocontrol. The most interesting aspects in these “one-pot” transformations involve the fact that in spite of the similarities in the starting substrates, two quite different domino products can be formed by the appropriate choice of the substitution pattern, the stoichiometry or the reagent.

The presentation will focus on probing this class of domino reactions in an effort to define the origins of orienting factors and to develop a prognostic model for general use. Emphasis will be given to the mechanistic aspects of the domino process, which allowed for a modular construction of various ring systems. A brief outline will be presented establishing the synthetic utility of our domino transformations for the practical synthesis of the cyclohexane core structure of various biologically active natural products.

ORGANIC CHEMISTRY IN A GOVERNMENT LABORATORY: TEN YEARS OF RESEARCH

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An overview will be presented of the work developed in the last ten years in a government laboratory whose main mission has been to support local SMEs and help implement public policies in its areas of technical expertise, with particular emphasis in organic chemistry.
CHEMICAL GLYCOBIOLOGY: SYNTHESIS OF BIOACTIVE NATURAL PRODUCTS AND MIMICS

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The chemical synthesis of oligosaccharides, glycoconjugates and their carbon-linked analogs has been improved enormously over the past twenty years making increasingly large structures available for biological studies and applications. Improvement is still needed and in this context, we will present our recent effort to simplify the construction procedures of glycoconjugates using recombinant E. coli cells, anomeric organometallics or Dynamic Combinatorial Chemistry. Special focus will be given to a chemoenzymatic strategy that produces lipochitooligosaccharides (bacterial signaling molecules known as Nodulation Factors) and highly active aromatic analogs.\(^1\) We will also detail the scope and variations of a mild and highly stereoselective synthesis of carbon-linked analogs of natural oligomers or glycoconjugates that utilize the coupling of glycosyl samarium reagents in Barbier or Reformatsky procedures.\(^2\) We will finally show that Dynamic Combinatorial Chemistry can be successfully adapted to systems exhibiting relatively poor binding properties, for the discovery of glycoenzyme (glycosyl-hydrolases and glycosyl-transferases) inhibitors.\(^3\)


Oral Communications
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OC1- *Metal-assisted reactions in the synthesis of new fluorescent heteroaromatic systems from dehydroamino acids*
Maria João R. P. Queiroz

OC2- *O-hydroxylated 2-styrylchromones with potential antioxidant activity*
Andrea G. P. R. Figueiredo

OC3- *Biogenetically inspired enantioselective approach to indole alkaloids*
Arantxa Gómez-Esqué

OC4- *Tuberculosis: molecular targets and drug development*
Ricardo Figueiredo

OC5- *Synthesis and anticholinesterase activity of pseudo-C-nucleosides containing oxopyrimidine, tetrazole and isoxazole rings*
M. I. Ismael

OC6- *Chemical sulfation: synthesis of potential anticoagulant phenolic compounds*
Marta Correia-da-Silva

OC7- *A versatile synthetic approach for isoguanine derivatives*
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M. Lurdes S. Cristiano

OC10- *A new and easy approach for the synthesis of methyl-2-deoxy-2-C-[(ethoxycarbonyl)methylene]hexopyranosides*
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A. J. Burke

OC13- *Synthesis of chiral β-amino esters*
A. L. Cardoso
**OC14-** Donor-acceptor substituted π-conjugated heterocyclic systems: synthesis and characterization
M. Manuela M. Raposo

**OC15-** Study of the photocromic equilibrium in spirooxazines by NMR
Paulo J. Coelho

**OC16-** Halogen atom effect on photophysical and photodynamic characteristic of derivatives of m-THPP
Arménio C. Serra

**OC17-** Fatty acid diterpenol esters from leaves of Juniperus brevifolia
Ana M. L. Seca
METAL-ASSISTED REACTIONS IN THE SYNTHESIS OF NEW FLUORESCENT HETEROAROMATIC SYSTEMS FROM DEHYDROAMINO ACIDS

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A new method for the synthesis of heteroaromatic systems, initiated by Suzuki coupling of beta-bromo or beta,beta-dibromodehydroamino acid derivatives with heteroarylboronic acids and, completed by a Pd/Cu-assisted C-N intramolecular cyclization of the coupling products to form a pyrrole ring, was developed in our laboratories [1,2]. More recently we have extended the scope of our method to the synthesis of several methyl 3-arylindole-2-carboxylates. Their absorption and fluorescence were studied in several solvents and some of them may be used as solvatochromic fluorescent probes [3 and unpublished results].

\[
\begin{align*}
\text{R}^1 = & \text{R}^2 = \text{OMe, SMe, COMe, CN} \\
\text{R}^1 = & \text{COMe or OMe, R}^2 = \text{H} \\
\text{R}^1 = & \text{H, R}^2 = \text{COMe or OMe}
\end{align*}
\]

Tetracyclic systems, methyl 1-(dibenzothien-4-yl)-3H-benzothieno[2,3-e]indole-2-carboxylate and methyl 1-(dibenzofur-4-yl)-3H-benzofuro[2,3-e]indole-2-carboxylate, were also prepared by the same methodology and their DNA intercalation was studied by absorption and fluorescence. The benzothienoindole is the more promising as a potential antitumoral agent, forming a complex with ds-DNA. The intercalation is the preferred mode of binding as confirmed by the fluorescence quenching experiments using iodide anion [results submitted for publication].


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O-HYDROXYLATED 2-STYRYLCHROMONES WITH POTENTIAL ANTIOXIDANT ACTIVITY

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2-Styrylchromone (2-SC) derivatives are a small class of natural chromones (only two have been found), which show important biological activities [1]. Certain synthetic 2-SC possess potent antitumor, antiallergic, antioxidant and hepatoprotective activities [2]. Recently, we proved that polyhydroxy-derivatives show potent antiradical activity and act as a xanthine oxidase inhibitors [3]. The presence of hydroxyl groups in 3’,4’-positions seems to be very important to increase the antioxidant activity [4].

Following our work on the synthesis of compounds with antioxidant activity, we report the synthesis of 2-SC 3 by the Baker-Venkataraman method using 2’-hydroxyacetophenones 1 and cinnamic acids 2 as starting materials. Once 2-SC 3 were obtained, the protective groups were cleaved to yield the expected di- and tetra-hydroxylated 2-SC 4 (Scheme). Experimental details and structural characterization of the new compounds will be presented and discussed.

![Scheme](image)


Acknowledgements: Thanks are due to the University of Aveiro, FCT and FEDER for funding the Organic Chemistry Research Unit and the project POCTI/QUI/59284/2004. One of us (A. G. P. R. Figueiredo) is also grateful to FCT for a PhD grant (SFRH/BD/18387/2004).
BIOGENETICALLY INSPIRED ENANTIOSELECTIVE APPROACH TO INDOLE ALKALOIDS

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Secologanin is a secoiridoid glucoside of extraordinary significance because it is a key intermediate in the biosynthesis of monoterpenoid indole alkaloids many of them possessing considerable pharmacological and therapeutic interest. A condensation of secologanin with triptamine (or tryptophan) constitutes the initial step of the biosynthesis of these natural products. The pivotal role of secologanin in alkaloid biosynthesis has stimulated the development of biomimetic synthesis of alkaloids using this compound as the starting material.

We present here an efficient approach to indole alkaloids in which the key step consists of a cyclocondensation reaction of racemic aldehyde diester 1, which can be envisaged as a synthetic equivalent of secologanin, with (S)-tryptophanol affording enantiopure lactam 2 in 62% yield. Three stereogenic centers with a well-defined configuration have been generated in a single synthetic step. Subsequent closure of the C ring from lactam 2 through the corresponding thioamide afforded compound 3 which embodies the tetracyclic framework of Corynanthe alkaloids.

Recent progresses on the enantioselective synthesis of Dihydrocorynantheine from compound 3 will be discussed.


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TUBERCULOSIS: MOLECULAR TARGETS AND DRUG DEVELOPMENT

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In the year that marks the 125\textsuperscript{th} anniversary of \textit{Mycobacterium tuberculosis} discovery, the Tuberculosis (TB) numbers\textsuperscript{1} are more concerning than ever. Far from being eradicated as many foresaw in a not so distant past, HIV&TB coinfection and extensive drug-resistant tuberculosis (XDR-TB), imply the need for new drugs with different mechanisms of action against TB.\textsuperscript{2}

Currently we witness a disinvestment in anti-infectives R&D by Big Pharma, motivated by economic and risk factors.\textsuperscript{3} Antibiotics discovery & development is nowadays made mostly by “Biotech” companies. Diseases like TB that affects almost exclusively populations that cannot afford necessary medicines, from a commercial perspective, present little financial incentive for pharmaceutical companies to invest in R&D.

In this presentation a point of situation on tuberculosis is made. Tuberculosis molecular targets and new anti-TB drugs against those in TB R&D pipeline will be disclosed.\textsuperscript{4,5,6,7}


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SYNTHESIS AND ANTICHOLINESTERASE ACTIVITY OF
PSEUDO-C-NUCLEOSIDES CONTAINING OXOPYRIMIDINE,
TETRAZOLE AND ISOXAZOLE RINGS

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Pseudo-C-nucleosides have a wide variety of biological activities and ongoing research
on this group of compounds is likely to yield new applications in critical areas of
medicine and other fields. Compounds of this type containing a thiazolidinone ring have
been reported to inhibit butyrylcholinesterase, one of the enzymes involved in
neurotransmission in the brain [1], possibly implicated in Alzheimer’s disease
progression. As part of our ongoing search for new cholinesterase inhibitors, which may
be valuable in ameliorating Alzheimer’s disease, we now report the synthesis of
compounds with tetrazole, oxo- and thioxopyrimidine rings in their structure linked to
the sugar moieties presented in 1-6, starting from sugar precursors containing a reactive
carbonyl group. In addition, acetylcholinesterase and butyrylcholinesterase inhibition
promoted by these compounds and those with isoxazole rings in their structure [2] will
be discussed. \textit{In vitro} toxicity studies for the evaluation of acute cytotoxicity or
genotoxicity caused by exposure of lymphocytes to the bioactive compounds will be
presented.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure}
\caption{Chemical structures of the synthesized compounds.}
\end{figure}

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Ferreira, C. Rajendran, R. Wilkins, P. D. Vaz, M. J. Calhorda, \textit{J. Carbohydr. Chem.},
2005, 24, 275.
CHEMICAL SULFATION: SYNTHESIS OF POTENTIAL ANTICOAGULANT PHENOLIC COMPOUNDS

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Anticoagulant and antithrombotic activities are among the most widely studied properties of sulfated macromolecules [1]. In light of recent anticoagulant results concerning two glycosilated flavonoids [2] sulfated diosmin (I) and sulphated hesperidin (II), the sulfation of other commercial available glycosyalted phenolic compounds is described: two flavonoids, rutin (1) and trihydroxyethylrutin (2), one cumarin, esculin (3), one xanthone, mangiferin (4), and one hydroxycinnamic acid, chlorogenic acid (5).

Sulfation was carried out with triethylamine-sulphur trioxide adduct, in dimethylacetamide at 65°C [1,2]. The purification step was optimised using a Snakeskin Pleated Dialysis Tubing. The structure of the compounds was established by IR, 1H and 13C NMR, HSQC, HMBC and HRMS.

Since random screening is one of the strategies for drug discovery, sulfated compounds were first evaluated for antifungal activity against dermatophytes, yeasts and Aspergillus species with clinical relevance, using microdilution broth method [3,4]. Compounds did not show any activity against all the species tested.


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Purine-based compounds find potential application as chemical and biological tools and/or therapeutic agents due to their wide range of biological activities. Their potency and selectivity depends on the position and nature of the substituent on the ring. [1]

In our research group, 5-amino-4-cyanoformimidoyl imidazoles 1 have been used as versatile synthons for the preparation of different 6-substituted purines, usually under mild reaction conditions. Now, we present a versatile synthetic method for the preparation of isoguanine derivatives 4-8, which involve a common imidazole intermediate 3. [2] An easily accessible substituted imidazole (2) was used as the precursor of imidazole 3, formed in the presence of ammonia and primary alkyl amine at room temperature after 10 minutes to 18 hours. Compound 3 was cyclized either to a 6-amino-N¹-alkyl (4) or to a 6-alkylamino-N¹-H (5) isoguanine, depending on the reaction conditions used. In the presence of aromatic amines and hydrazides, the nucleophilic displacement of the cyano group requires more vigorous conditions, which prevent the isolation of intermediate 3.

These compounds, which are not easily prepared by other methods, were isolated in very good yields from this common intermediate.

The rearrangement of isoguanines 4 to the thermodynamically favoured isoguanines 5 was also investigated, as an alternative pathway for the preparation of compounds 5.

References


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In the last few years, our phytochemical research is being focused on the characterization of bioactive natural products from medicinal plants of diverse origin [1]. In the present communication we report the identification of cytotoxic, antileukemic, antimicrobial, and antioxidant metabolites isolated from plant species collected in Guinea-Bissau (*Ozoroa insignis*), Tunisia (*Moricandia arvensis, Rantherium suaveolens, Ebenus pinnata, Salsola tetrandra*), and Cuba (*Pedilanthus tithymaloides, Talipariti elatum*). Examples of representative structures are shown below.


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INVESTIGATION INTO THE REACTIVITY OF TETRAZOLES
AND BENZISOTHIAZOLES

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Tetrazoles are extremely relevant compounds, for instance in medicinal chemistry (as antihypertensive, antiallergic, antibiotic and anticonvulsant agents and in cancer and AIDS treatments),[1] agriculture (pesticides, growth regulators)[2] and photoimaging.[3] Benzisothiazoles are also economically important heterocyclic compounds. Saccharin is the oldest artificial sweetener, and is used industrially as a key structural element for the synthesis of biologically active compounds. Saccharyl derivatives show herbicidal, antimicrobial and antifungal activity, potential in enzymatic inhibition and anti HIV-1 activity.[4]

The relevance of both classes of compounds boosted fundamental research in their structure and reactivity. Tetrazoles and benzisothiazoles are versatile starting materials for the synthesis of related heterocyclic derivatives.[5]

Both tetrazolyl and benzisothiazolyl ethers are excellent intermediates for selective palladium-catalysed reductive cleavage of phenols, allyl, benzyl and naphthyl alcohols.[6] However, the reactivity of both heterocycles towards nucleophiles differs considerably, as does their thermal- and photo-reactivity.

The presentation will address some aspects of the reactivity of tetrazolyl and benzisothiazolyl derivatives in relevant reactions. Observed reactivity will be rationalised on structural grounds.


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A NEW AND EASY APPROACH FOR THE SYNTHESIS OF METHYL 2-DEOXY-2-C-
[(ETHOXYCARBONYL)METHYLENE]HEXOPYRANOSIDES

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In this communication a simple and direct method permitting an easy access to compounds derived from 2-keto sugars, starting from the easily prepared 3-keto templates, will be presented.

The direct oxidation of carbohydrates at position 2 leads mostly to keto sugars in low yield. Therefore, alternative methods to access this type of compounds are needed. 3-Keto sugars were used as scaffolds for the Wittig type olefination at C-2 with [(ethoxycarbonyl)methylene]triphenylphosphorane in the appropriated solvent to give compounds type 1 and 2 in good yield. The stereochemistry of the reaction products was assigned by NMR experiments, being the stereoselectivity of the reaction discussed in terms of the protecting groups used.

Acknowledgments: The authors thank Fundação para a Ciência e Tecnologia for the PhD grant SFRH/BD/30699/2006.
NEW APPROACHES FOR METALLOPORPHYRIN CATALYSED OXIDATION REACTIONS

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An important challenge for green chemistry is the finding of alternatives to the common oxidation synthetic methodologies, based on stoichiometric oxidants that lead to large amounts of non-biodegradable by-products [1]. The use of H$_2$O$_2$ as a cheap, environmentally clean and easy to handle oxidant [2], in conjugation with robust and easily obtainable metalloporphyrins as catalysts, led to efficient procedures to perform many oxidative reactions [3-5]. In some cases the role of a co-catalyst has shown to be essential [4], either by speeding up the reaction or by changing the stereoselectivity [6]. However, the potentiality of these systems can be highly increased by anchoring the catalyst to a solid support, thus allowing its easy recovery and reuse. Moreover, the local environment of the support can bring higher selectivity and prevention of catalyst self-oxidation [7]. Efficient supported metalloporphyrin catalysts use organic or mineral supports; silica is being recognized as a very attractive material, due to its stability towards drastic catalytic oxidation conditions [8]. The most recent results dealing with homogeneous and heterogeneous metalloporphyrin catalysed oxidation reactions currently in progress in our laboratory will be presented.

Acknowledgments
Thanks are due to the University of Aveiro and FCT for funding the Organic Chemistry Research Unit. R. De Paula also thanks FCT for his PhD grant (SFRH/BD/25666/2005).

References
ENANTIOSELECTIVITY ASYMMETRIC ALLYLIC ALKYLATIONS USING A DIOP ANALOGUE WITH A 1,4-DIOXANE BACKBONE

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Presently, catalytic asymmetric synthesis (CAS) is finding considerable application in providing important optically pure compounds. Asymmetric allylic alkylation (AAA) reactions [1] are powerful approaches to introduce C-C/C-X bonds in such compounds. Unfortunately, in most cases expensive ligands are required, making discovery of cheaper alternatives an important endeavour.

DIOP 1, so successful in catalytic asymmetric hydrogenation reactions (CAHR), has had only a modest impact in the reaction mentioned above [2]. After the 1,4-dioxane analogue of DIOP 2 was shown to be successful in various CAHRs [3], we became interested in screening 2 in the AAA reaction (Scheme 1). This decision was based on the premise that 2 should afford high enantioselectivities due to the presence of a rigid back-bone.

In this communications we report our preliminary results with this reaction.


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SYNTHESIS OF CHIRAL β-AMINO ESTERS

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β-Amino acids are an important class of compounds due to their unique biological properties, their occurrence in natural products and their use as precursors of biologically and medicinally important molecules. Therefore, the development of new synthetic methodologies for the asymmetric synthesis of β-amino acids is an important goal in organic synthesis.

In a previous communication we reported a highly selective two step approach to chiral β-amino esters via the reductive amination of 2,3-allenoates bearing a chiral auxiliary in the ester moiety. The nature of the chiral auxiliary determines the chirality of the β-amino esters: (1R)-(-)-10-phenylsulfonylisobornyl gives β-amino esters with S configuration whereas the (15)-(+)10-phenylsulfonylisobornyl leads to β-amino esters with R configuration.

The work was now extended to the synthesis of new chiral β-amino esters via reaction of chiral allenes 1 and 2 with α-amino esters (methyl esters of L-alanine, L-phenylalanine, L-leucine, L-tryptophan and L-proline) followed by reduction. The stereochemistry of 5a was confirmed by X-ray crystallography. Details of this study will be disclosed.

\[
\begin{align*}
\text{SO}_2\text{Ph} & \quad \text{R}^1
\end{align*}
\]


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DONOR-ACCEPTOR SUBSTITUTED $\pi$-CONJUGATED HETEROCYCLIC SYSTEMS: SYNTHESIS AND CHARACTERIZATION

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Donor-acceptor substituted $\pi$-conjugated heterocyclic systems find extended applications in several important research and technological fields, including organic conductors, solvatochromic and fluorescence probes, sensors with analytical, environmental and medicinal applications, organic electroluminescent and nonlinear optical (NLO) materials.

The synthesis of different types of push-pull heterocycles constituted by oligothiophene, arylthiophene and thiénylpyrrole as $\pi$-conjugated spacers, functionalized with several donor and acceptor moieties will be presented. Using different methods of synthesis (combination of Friedel-Crafts and Lawesson reactions, palladium catalyzed cross-couplings, electrophilic substitutions, metatation followed by reaction with electrophiles, Knoevenagel condensations, cyclocondensation reactions, etc.) it was possible to synthesize and functionalize oligothiophenes [1-2], thiénylpyrroles [3-5] and benzothiazoles [6-7]. More recent results regarding the synthesis of thiénylpyrrolyl-benzothiazoles [8] and benzimidazole derivatives will be also discussed. Studies to evaluate the potential applications of some of these compounds as nonlinear optical chromophores, solvatochromic probes and organic light emitting diodes (OLEDs) will be also described [5-8].

References
Study of the photochromic equilibrium in spirooxazines by NMR

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Among photochromic compounds, spirooxazines constitute one of the most studied families. These uncoloured compounds are of interest due to their ability to give intense photocoulouration, fast thermal relaxation and good fatigue resistance. Absorption of UV light causes the cleavage of the spiro carbon-oxygen bond, leading after rearrangement to coloured quasi-planar conjugated forms (photomerocyanines) that revert to the initial uncoloured state in the dark. The electronic conjugation appears to play an important role in the stabilisation of the photomerocyanine, giving rise to permanent open forms or to thermal equilibrium between closed and open forms [1,2]. In the course of developing novel permanent photomerocyanines, we have investigated the effect of introducing an hydroxyl group in position 5' of the 1,3,3-trimethylspiro[indoline-2,3'[3H]naphtho[1,2-b][1,4]oxazine], to induce stabilization by intramolecular hydrogen-bonding with the C=O of the coloured open form [3].

Heating a methanolic yellow solution of 1,8-dihydroxy-2-nitrosonaphthalene and 1,3,3-trimethyl-2-methyleneindoline under reflux for one hour, yielded a deeply coloured blue solution. 1 and 2D NMR spectra of the blue product in CDCl₃ at 295K revealed the presence of two structures, identified as the closed spirooxazine (~25%) and one open isomer (~75%) of the photomerocyanine in equilibrium.

At 243 K, five different structures are distinguished: the closed spirooxazine and four transoid coloured open forms TTC, CTC, TTT and CTT.

HALOGEN ATOM EFFECT ON PHOTOPHYSICAL AND PHOTODYNAMIC CHARACTERISTICS OF DERIVATIVES OF m-THPP

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The use of porphyrins as photosensitizers in photodynamic therapy for clinical uses is well known. Two porphyrin derivatives, Photofrin and Foscan, are approved for the treatment of a variety of cancers\cite{1}. Photofrin is a purified form of hematoporphyrin derivatives consisting of a mixture of porphyrins. This has encouraged an active search for novel (“second generation”) photosensitizers with improved properties over the last 20 years. At the present time, Foscan, 5,10,15,20-tetrakis(3-hydroxyphenyl)chlorin is one of the second-generation photosensitizers approved for cancer treatment. Instead of Photofrin, the well defined structure of Foscan allows the study of the relationship between modifications on the structure and the photodynamic activity.

Using the structure of 5,10,15,20-tetrakis(3-hydroxyphenyl)porphyrin (m-THPP) as a basic model, we synthesised several derivatives\cite{2} strategically modified in order to improve the photophysical properties more directly related to photodynamic activity, namely, the inclusion of halogen atoms\cite{3}.

The different synthetic methodologies followed in order to obtain the compounds with the required structures, photophysical properties, amphiphilic characteristics, and the \textit{in vitro} studies of the photodynamic activity of these compounds against WiDr human colon adenocarcinoma cells and melanoma A375 cells will be presented.

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FATTY ACID DITERPENOL ESTERS FROM LEAVES OF JUNIPERUS BREVFOLIA

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In the study on the chemical characterization of endemic plants of the Azores archipelago, we have examined Juniperus brevifolia. We become interested to analyze this plant due to the wide range of biological activity reported from other species of this genus and of their constituents [1]. Previous studies on this plant described the components of its essential oil [2-3], and of the hexane extract [4]. We report herein on the isolation and structural elucidation of seven new natural diterpenes (1-7) from the dichloromethane extract of leaves of J. brevifolia. Three of these new compounds, four abietanes (1-3,7) and three pimaranes (4-6), are esters of the long-chain fatty hexadecanoic acid and two esters of formic acid. Compounds 1, 2 and 5 represent the first examples of diterpenes possessing at C-18 an esterified fatty acid. Studies on the isolated new compounds showed those possessing a diterpenol ester of a long-chain fatty acid present lipophilicity very distinct from other diterpenoid compounds. All the structures were established by spectroscopic methods, including mass spectrometry and NMR spectroscopy (by using several 1D and 2D techniques—1H, 13C, DEPT, COSY, HSQC, HMBC, NOESY).

\[ R_1 = \text{CH}_2\text{OCO(CH}_2\text{)}_{14}\text{CH}_3; R_2=R_3=R_4= H \]
\[ R_1 = \text{CH}_3\text{OCO(CH}_2\text{)}_{14}\text{CH}_3; R_2= H; R_3=R_4= =O \]
\[ R_1 = \text{CH}_3; R_2= \text{OH}; R_3=R_4= =O \]
\[ R_1 = \text{CH}_2\text{OCHO}; R_2=R_3=R_4= =O \]


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ORGLIST Symposium
ORGLIST Symposium - Lectures

**OL1** - COMPUTACIONAL MODELS TO AID SAFETY-DIRECTED DRUG DESIGN  
Scott Boyer, Ph.D.

**OL2** - DERIVING STRUCTURE-ACTIVITY RELATIONSHIPS IN HETEROGENEOUS DATASETS  
Valerie J. Gillet

**OL3** - TWO-PARAMETER CLASSIFIER FOR PREDICTION OF PKC-ζ MODULATING BEHAVIOUR OF XANTHONES  
Bruce F. Milne, Madalena M.M. Pinto

**OL4** - REGIOSELECTIVITY OF THE CATECHOL-O-METHYLTRANSFERASE CATALYZED REACTION: COMBINED THEORETICAL AND EXPERIMENTAL STUDIES  
Nuno Palma, Maria L. Rodrigues, Margarida Archer, Maria J. Bonifácio, Ana I. Loureiro, David A. Learmonth, Maria A. Carrondo, Patricio Soares-da-Silva

**OL5** - FROM MESTREC TO MNova: A REVOLUTIONARY APPROACH TO NM  
Nikolay Larin, Stan Sykora, Santiago Domínguez, Carlos Cobas
Access to metabolism and toxicology data is critical to effective decision making in early drug discovery projects. Often in such projects little is known about the therapeutic target and usually even less is known about potential metabolism or adverse effects of the chemical series being investigated. Simply providing unstructured metabolism- and safety-related information on targets and chemical series to project teams trying to make decisions is not adequate due to the varied nature and quality of metabolism and toxicology data. This presentation gives examples of how relevant data can be structured, mined and in some cases modelled to enhance decision-making. Project examples will be presented of QSAR models and their interpretation, including characterization of the underlying assay error for better interpretation of the model results, development of SAR systems that support decision-making and enhance awareness around such endpoints as metabolism/P450 activation, mutagenesis, hERG and reactive intermediates. In general, metabolism and toxicology data should be structured depending on, 1) its intended use, 2) its overall quality and 3) its internal data structure (text vs. numerical) to assure its optimum use. Brief examples of the varying data types and their usage in project decision making will be presented along with some strategies for hypothesis generation around adverse events using a combined approach of molecular modelling/virtual screening and text mining. Together, these tools, built to be appropriate to the various data types, represent a basic toolkit for the toxicologist and drug metabolism scientist needing to make meaningful contributions to the myriad decisions made in early drug discovery projects.
DERIVING STRUCTURE-ACTIVITY RELATIONSHIPS IN HETEROGENEOUS DATASETS

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Machine learning algorithms such as Binary Kernel Discrimination and Support Vector Machines have become popular methods for the analysis of high-throughput screening data. While they have been shown to be effective ways of deriving predictive models they suffer from the disadvantage that the models are not easily interpretable. Here we describe a new method based on genetic programming. A training set of active and inactive molecules are represented as reduced graphs and genetic programming is used to evolve reduced graph queries (subgraphs) that are best able to separate the actives from the inactives. The classification rate is determined using the F-measure which combines recall and precision into a single objective. The resulting queries are validated on datasets not used in deriving the queries, for proof of their predictive power. As well as being useful models for prediction, the queries contain interpretable structure-activity information encoded within the reduced graph nodes. Results are presented for the well known MDDR dataset and also for GSK in-house screening data.
TWO-PARAMETER CLASSIFIER FOR PREDICTION OF PKC-ζ MODULATING BEHAVIOUR OF XANTHONES

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Protein kinase C ζ (PKC-ζ) occurs in many tissues in the body and is associated with numerous cellular processes including differentiation, mitogenesis, migration and apoptosis. PKC-ζ is implicated in the progression of a variety of disease states including colon cancer, inflammatory bowel conditions, leukaemia, melanoma and T-cell mediated hepatitis. Studies in our research group [1, 2] have identified a number of simple xanthone derivatives displaying varying levels and types of PKC-ζ modulating activity. Although structurally very similar, this group of compounds includes both potent activators and inhibitors of PKC-ζ and therefore it is desirable to have a method with which to attempt to predict which region of the activity spectrum new derivatives might fall into.

In an attempt to rationalize the behaviour of these compounds a computational QSAR study was undertaken and a two-parameter decision tree developed that successfully classifies all of the xanthones previously tested as either activators, inhibitors or inactive. In addition, a small selection of non-xanthone PKC-ζ inhibitors have been appended to this study and these are also correctly classified by the decision tree developed for the xanthones.


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REGIOSELECTIVITY OF THE CATECHOL-O-METHYLTRANSFERASE CATALYZED REACTION: COMBINED THEORETICAL AND EXPERIMENTAL STUDIES

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This work presents combined theoretical and experimental studies [1,2] of the regioselectivity of O-methylation of nitrocatechol-type inhibitors of the enzyme Catechol-O-methyltransferase (COMT).

As a case study, two simple regioisomeric nitrocatechol-type inhibitors of COMT, containing a benzyol substituent attached at the meta- or at the ortho-position, respectively, relative to the nitro group, were studied with regards to their interaction with the catalytic site of the enzyme and the in vitro regioselective formation of their mono-O-methyl ether metabolites. It is shown that the particular substitution pattern of the classical nitrocatechol pharmacophore has a profound impact on the regioselectivity of O-methylation.

In order to provide a plausible interpretation of these results, a comprehensive analysis of the protein-inhibitor interactions and of the relative chemical susceptibility to O-methylation of the catechol hydroxyl groups was performed by means of docking simulations and molecular orbital calculations. The major structural and chemical factors that determine the enzyme regioselectivity of O-methylation are identified and the X-ray structure of the complex of COMT with one of the two inhibitors (BIA 8-176) is disclosed. This is the first reported structure of COMT complexed with a nitrocatecholic inhibitor having a bulky substituent group in ortho position to the nitro group. Structural and dynamic aspects of this complex are analyzed and discussed, in the context of the present study.


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From MestReC to Mnova: A revolutionary approach to NMR

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High Resolution NMR spectroscopy is undoubtedly one of the most important methods used in organic chemistry for structure determination. Traditionally, organic chemists used to spend considerable time processing their NMR data to get the best experimental NMR as starting material for the lengthy and non trivial task of spectral analysis. Furthermore, recent years have witnessed dramatic improvements in high-throughput NMR in such a way that spectral processing and analysis have emerged as a new bottle neck due to the large amount of spectral data available.

In this work we present Mnova, the new incarnation of MestReC as a novel software solution offering an innovative paradigm for the unattended NMR data processing and new tools such as spectral prediction, simulation and fitting algorithms to facilitate structure verification and elucidation for organic chemists.
Poster Communications
Cardiovascular diseases are associated to high values of mortality and morbidity all over the world. The coronary dysfunctions are prominent and related to ischemic and reperfusion phenomenon (I/R) in the heart, leading to the release of large amounts of biogenic catecholamines, namely adrenaline (1), and to a sustained generation of reactive species of oxygen (ROS). Adrenaline is a redox reactive molecule. It’s oxidation leads to the formation of ROS and reactive products, as semi-quinones, quinones and aminochromes.

The quinones in the presence of a nucleophile (secondary amines or thiols) react by a 1,4-Michael addition reaction. The resulting compounds (amines and thio substituted catechols) are more easily oxidized than the parent starting molecule by virtue of the presence of an extra electron-donating group.

Herein we report for the first time the formation of compound 2 resulting from intramolecular conjugated addition of the glutathione glycine residue to the adrenaline backbone, after a second catechol oxidation. The structure was completely elucidated by FD-MS and bidimensional NMR.

A NEW APPROACH TO THE SYNTHESIS OF BENZOACRIDONE DERIVATIVES

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Acridone derivatives are a group of nitrogen heterocyclic compounds possessing important biological activities. They are known to present important citotoxic, antiviral and anti-malarial activities and also to inhibit Epstein-Barr virus activation [1,2]. It is also worthy to mention other important potential applications of acridones, the potent and selective inhibition of human immunodeficiency virus type 1 (HIV-1) replication in chronically HIV-1-infected cells [3] and also their use as labels for fluorescence detection of target materials [4].

Taking into account the potential applications of acridones, we started a programme to prepare new derivatives and to develop new synthetic methods for their synthesis. One of the explored synthetic routes considered the Diels-Alder of 3-formyl-1-methyl-4-quinolones 2 with ortho-benzoquinodimethane [5]. Since our results were not satisfactory, we decided to use other N-protecting group. In this communication, we will describe the synthesis and reactivity of 1-ethoxycarbonyl-3-formyl-4-quinolone 3 as dienophile in a Diels-Alder reaction with ortho-benzoquinodimethane, generated in situ from the corresponding sulfone. New tetrahydrobenzoacridones derivatives 4 and 5 have been obtained in good overall yield (56%) (Scheme 1). The experimental procedures and the structural characterisation of all synthesised compounds will be presented and discussed in this communication.

![Scheme 1](image)


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A NEW APPROACH TO THE SYNTHESIS OF [4,4’]-BI-1H-IMIDAZOL-2-ONES

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The chemistry of imidazole compounds has been of much interest due to the presence of these heterocycles in a large variety of biologically important molecules. For example, some imidazole derivatives have shown interesting antifungal and antitumour properties. Also, the antimicrobial activities of a series of 4-diazoimidazole-5-carboxamides bearing lipophilic substituents have been evaluated recently and these compounds have been found to possess antifungal activity. The present work describes the reaction of urea 1 with orthesters which occurred in acetonitrile and in the presence of a catalytic amount of sulfuric acid affording the corresponding imidates 2.

This compound cyclized in acetonitrile, in the presence of DBU, to generate the substituted imidazole-2-one 3. Compounds 2 and 3 were reacted with different primary aliphatic amines affording bi-imidazoles 4 under mild experimental conditions. This method allows the regioselective synthesis of acyclonucleoside analogues incorporating an imidazolone substituent. All compounds were fully characterized by elemental analysis and spectroscopic data and the mechanism of these reactions will be discussed.

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ACTIVITY OF $\beta$-SUBSTITUTED PORPHYRINS WITH PROPIONATE GROUPS IN PHOTODYNAMIC THERAPY

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Photodymanic therapy (PDT) is a mode of treatment oncological and other clinical conditions based in the light activation of a molecule inside the cell for producing harmful amounts of singlet oxygen. One of the few drugs currently used in PDT is Photofrin® which is structurally a complex mixture of oligomers derived from hematoporphyrin (1). Another drug commercially available, 5-Aminolevulinic acid (ALA) which is the precursor of the sensitizer protoporphyrin IX (2) produced endogenously by the cells.

![Structure of hematoporphyrin (1) and protoporphyrin IX (2)](attachment:image)

Protoporphyrin IX and hematoporphyrin shows very similar structures with two propionate chains in the $\beta$-positions of the macrocycle. This structural resemblance is likely an important structural characteristic for interaction with the cells worth to be included in mimetic structures.

In this work we prepared porphyrins derivatives with different number of propionate chains in the $\beta$-positions of the macrocycle (3-5) and bromo-substituted phenyl groups in the meso positions. Their anti-tumoral activities against colorectal cancer cell line (WiDr) were determined and compared with Photofrin®.

![Structures of porphyrins derivatives (3-5)](attachment:image)

[1] Osterioh, J.; Vicente, M. G. H. J. Porphyrins Phthalocyanines, 2002, 6, 305-324. Acknowledgments: The authors thank to Chymiotechnon, Ministério da Economia/POE/Prime/Proj 3/293/CLARO, Faculdade de Medicina de Coimbra and CIMAGO for financial support and Serviço de Gastroenterologia dos HUC for equipment facilities.
AN EFFICIENT SYNTHETIC APPROACH TO A NOVEL CYCLIZED 4-(PORPHYRINYLAMINO)PHTHALONITRILE

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Porphyrins have a wide range of applications in distinct fields, such as medicine, catalysis and materials for advanced technologies [1]. Several studies have been focused on the functionalization of easily accessible meso-tetraarylporphyrins in order to modulate the properties of the porphyrin macrocycle [2]. Recently, our group developed a new methodology to synthesize 4-(porphyrinylamino)phthalonitriles, which are precursors to porphyrin-phthalocyanine dyads [3].

This communication describes an efficient synthetic approach to the novel cyclized 4-(porphyrinylamino)phthalonitrile 2, that involves reflux of 4-(5,10,15,20-tetraphenylporphyrin-2-ylamino)phthalonitrile 1 in nitrobenzene. The synthetic procedure and the structural characterization of the novel compound will be discussed.


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APPLICATION OF AMIDE BOND ACIDOLYSIS AT THE C-TERMINUS OF \( \alpha,\alpha \)-DIALKYL GLYCINES TO THE FORMATION OF A NEW AMIDE BOND

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In the past years, we have been involved in a study of the application of Ugi’s reaction to the synthesis of several \( \alpha,\alpha \)-dialkylglycines. Using 4-methoxybenzylamine (Pmb-NH$_2$) as the amine component, we were able to remove the N-alkyl group by TFA cleavage and, during this process, the C-terminal amide bond of the resulting Ugi adducts (1) was cleaved by a mechanism involving an oxazolinium-type intermediate (2).\(^1\) This intermediate allows in situ functionalization of the C-terminus by reaction with nucleophiles (HO-, MeO-), thus affording different derivatives such as free acids and esters.\(^2\)

Our previous results suggested that an amide or dipeptide could be obtained if an amine or amino acid ester was used as the nucleophile. Nevertheless, preliminary results indicated that although a small amount of the required dipeptide is formed (3), 5,5-dialkyl-imidazolin-4-ones (4) are also obtained. These results from competitive attack at the less hindered C-2 of the oxazolinium intermediate, followed by rearrangement.\(^3\)

We now present new results in the optimization of the reaction conditions in order to maximise amide bond formation.

\[ \text{R} = \text{Et, Pr, } \text{iBu, Bn} \]
\[ \text{NH}_2-\text{R'} = \text{benzylamine or Phe-OrBu} \]

AZA-DIELS-ALDER APPROACH TO THE SYNTHESIS OF PIPERIDINE AZASUGARS

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In 1966, Inouye \textit{et al.}\textsuperscript{1} discovered the first natural polyhydroxylated alkaloid, nojirimycin (NJ). Isolated from a \textit{Streptomyces} filtrate, it was shown to actively inhibit $\alpha$- and $\beta$-glucosidase and was therefore the first glucose mimic. Since then there has been a growing interest towards the synthesis of azasugars analogues. We wish to report a versatile strategy for the synthesis of piperidine azasugars using anaza-Diels-Alder approach. We emphasise that compounds $1a$, $1b$, $2a$-$b$ are optically pure and obtained in good to moderated yields. All compounds were spectroscopically characterized.

References:
AZA–MICHAEL REACTIONS WITH VINYL SULPHONES

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In recent years, fluorescent molecules with reactive functional groups have received considerable interest due to their potential applicability in biomolecular systems.

Dyes containing substituted ethyl sulphonyl groups which β-eliminate to form the reactive vinyl sulphone species [1], can be important due to their fluorescent properties [2].

Vinyl sulphones became generally accepted as useful intermediates in organic synthesis and serve efficiently as Michael acceptors [3].

The aza-Michael reaction involving the conjugate addition of nitrogen nucleophiles to an α,β-unsaturated carbonyl constitutes an important reaction in organic synthesis.

Several compounds were prepared in high yields by direct treatment of a series of primary and secondary amines with vinyl sulphones in presence of Amberlyst-15 (Scheme 1) [4].

\[
\begin{align*}
R^1\text{SO}_2\text{CCH}_2 + \overset{\text{NH}}{\text{R}}^2\text{R}_3\text{NH} & \rightarrow R^1\text{SO}_2\text{CCH}_2\text{N} \overset{\text{R}}^2\text{R}_3^2 \\
R^1=\text{CH}_2\text{CH}_3 , \overset{\text{NH}_2}{\text{C}} & \\
\end{align*}
\]

Scheme 1

The products were purified by flash chromatography and/or recrystallization and characterized by the usual analytical methods (\(^1\)H and \(^13\)C NMR, MS, elemental analysis). Details on the preparation and characterization of the compounds will be presented.

References:
BACILLAMIDE – A TOOL FOR CONTROL OF ALGAL GROWTH?

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In recent years there has been reports of harmful algal blooms (HABs) causing large scale red tides and mass mortality of cultured fish and bivalves in many coastal parts of the world[1]. It has been demonstrated that many genera of marine bacteria have algicidal effects and are associated with the termination of HABs in natural coastal environments[2,3]. In 2003 the structure of a novel algicide from a marine bacteria Bacillus sp. SY-1, active against the harmful dinoflagellate Cochlodinium polykrikoides, revealed bacillamide (1) (Figure)[4]. Having synthesised 1 (and several derivatives), from tryptamine (and derivatives thereof) and 2-aceetylthiazole-4-carboxylic acid,[5] we disclose here our results with several algal strains. The toxic cyanobacteria Microcystis aeruginosa and Aphanizomenon gracile are relatively more sensitive to bacillamide than the unharmful chlorophytes Ankistrodesmus sp. and Scenedesmus sp. However, other cyanobacteria (Anabaena sp. and Anabaenopsis sp.) presented higher tolerances, similar to the ones presented by different non-toxic algae (Tetraselmis sp., Nanochloropsis sp. and Pheodactilum sp.). Thus, the use of bacillamide to control the growth of harmful cyanobacteria must take into account the composition of the phytoplankton community in natural environments.


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BROMOALKYLOXYXANTHONES AS PROMISING ANTITUMOR AGENTS: SYNTHESIS AND BIOLOGICAL ACTIVITY

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In a study involving the synthesis of bis-intercalators with a xanthonic scaffold as potential inhibitors of solid-tumour growth, especially CNS cancer [1,2], a symmetric bisxanthone (1, 50%) and a minor product 1-[(6-bromohexyl)oxy]-xanthone (2, 30%) were obtained from 1-hydroxyxanthone (3) and dibromohexane (Scheme 1A). Being the investigation of secondary products a strategy in drug discovery, both derivatives 1 and 2 were evaluated for their effect on the in vitro growth of the human tumor cell lines MCF-7 (breast cancer), NCI-H460 (non small lung cancer), and SF-268 (central nervous system cancer) using the sulforhodamine B (SRB) method [1]. Although no capacity to inhibit the growth of the human tumor cell lines tested was observed for the symmetric xanthone 1 (GI$_{50}$>100 µM), compound 2 revealed inhibition of the growth of human tumor cell lines with GI$_{50}$ values in the range of 22<GI$_{50}$<30 µM, even higher than the parent compound 3.

Scheme 1

In light of this results we proceed with the bromoalkylation of the hit compound, 3,4-dihydroxyxanthone (4) that revealed a potent inhibitory effect on the human tumor cell lines growth [1]. Two bromohexyloxyxanthones, 3-[(6-bromohexyl)oxy]-4-hydroxyxanthone (5, 50%) and 3,4-bis[(6-bromohexyl)oxy]-xanthone (6, 10%), were obtained (Scheme 1B) and both derivatives will be investigated for their effect on the in vitro growth of human tumor cell lines MCF-7 (ER+, breast cancer), MDA-MB-231 (ER-, breast cancer), NCI-H460 (non small lung cancer), and SF-268 (central nervous system cancer). These results revealed bromoalkyloxanthones as interesting scaffolds to look for potential anticancer drugs.


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BULK THERMAL POLYMERIZATION OF PHENYLETHYNYL-CALIX[4]ARENE COMPOUNDS

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As part of an ongoing project aiming to study the polymerizabilities of calix[4]arene compounds having phenylethynyl groups appended at the calixarene lower rim, the bulk thermal polymerization of compounds 1 and 2 was studied. The bulk polymerization of 1 was undertaken in a sealed vessel under argon at 205ºC (15 min.). Contrary to our initial expectations, the polymerization of 1 did not yield an insoluble polymer. Indeed, a completely soluble (THF) brownish-orange residue was obtained which contained less than 15% of starting 1, 7% of dimer, 5% of trimer and 75% of a polymer from which a yellow polymer was isolated in 49% \((M_n = 5700 \text{ g mol}^{-1}; M_w/M_n = 2.9; \text{GPC analysis})\). Its infra-red spectrum resembles that of a polymer obtained under Rh(I) catalyzed polymerization.\(^1\) In addition, a rather small ethynylic stretching frequency at 2110 cm\(^{-1}\) (-C≡C-) was also discernible, probably accounting for the linear dimeric/trimeric products (from Glaser and/or Strauss type couplings) found in the isolated polymer.

Polymerization of 2 on the other hand did produce an insoluble material which, due to the monomer structure, could not result from direct cross-linking reactions. In order to better understand the polymerization processes involved, a TG/DSC study was performed. When heated under N\(_2\); (7ºC/min) up to 230ºC, the DSC thermogram of 1 shows an endothermic event peaking at 160ºC which correspond to the melting of 1, immediately followed by an exothermic transition peaking at 186ºC. This event corresponds to the thermal polymerization of melted 1, for which an enthalpy of 110±10 kJ mol\(^{-1}\) was calculated. The GPC composition of the brownish-red residue thus obtained was very similar to that referred above. The DSC trace of 2 (when heated up to 255ºC) shows the same observable trends as in the case of 1, that is, an endothermic transition at 158ºC (melt), followed by polymerization (peaking at 234ºC) with an associated enthalpy of 220 kJ mol\(^{-1}\). Most of the residue (73%) was insoluble in THF which has an IR spectrum identical to the polymer obtained under catalysis.

The dissimilar and unexpected behavior of calixarenes 1 and 2 as well as the main underlying mechanisms involved in their thermal induced reactions, will be discussed in this communication.


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C-H CARBENE INSERTION OF \( \alpha \)-DIAZO ACETAMIDES BY PHOTOLYSIS IN NON-CONVENTIONAL MEDIA

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More than a half century has passed since the discovery of \( \alpha \)-diazo carbonyl compounds as excellent candidates for the construction of new and interesting molecules. However, in the last two decades, they gained special notoriety with the upring of catalysis due to the ability of some metals to coordinate with carbenes that can be generated from the decomposition of the diazo moiety [1-3]. In the absence of catalyst, this decomposition can be induced by thermolysis or photolysis, generating a high reactive carbene species that usually leads to a complex mixture of products.

In the sequence of our work in synthesising \( \alpha \)-diethoxyphosphoryl-\( \beta \)- and \( \gamma \)-lactams by C-H insertion of dirhodium stabilized carbenes[4], in non-conventional media such as ionic liquids[5] or water[6], we observed that the mild photolysis of \( \alpha \)-diazo acetamides allows similar transformations. Mercury vapour high pressure light was used to induce the photoytic decomposition of several families of \( \alpha \)-diazo acetamides in non-conventional media such as water, hexane or neat film. The correspondent \( \beta \)-or/and \( \gamma \)-lactams were obtained in reasonable yields and in some cases with good diastereoselectivities, abolishing the need of a metallic catalyst.

\[
\begin{align*}
X & = PO(OEt)_2, Ac, CO_2Et \\
n & = 0, 1
\end{align*}
\]


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COMPUTATIONAL DESIGN OF XANTHONE DERIVATIVES SHOWING ENHANCED BINDING AFFINITY FOR ESTRONE SULPHATASE

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In the current work we have attempted to design novel derivates of the compound xanth-9-one displaying significant binding affinity for the enzyme estrone sulphatase (ES), which is implicated in the development of breast cancers through its role in maintaining high levels of estrogens in the tumour cells (1). Computational protein-ligand docking was used to evaluate the ES-binding properties of the xanthenes and interaction energy grids were used to score the different docked poses. The results obtained for the xanthone derivatives were evaluated using those of the natural ligand, estrone sulphate, as a control. The presence of a doubly-branched group containing terminal electron donating groups, and a shorter electron donating group in positions 3 and 6 of the xanthone scaffold, respectively, seem to be important for optimal binding of the ligand to the receptor.


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Dissolution of mono- and di-saccharides in ionic liquids

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Carbohydrates are readily available chiral organic molecules from natural resources. Due to the large number of hydroxyl groups present, carbohydrates have a low solubility in most common solvents. Even the low molecular weight and neutral carbohydrates, such as glucose are only soluble in a small number of polar non-protic and protic solvents such as pyridine, dimethylsulfoxide, dimethylformamide and water. This property of carbohydrates prevents their use in various applications and complicates their functional manipulation and structural determination \cite{1}.

Ionic liquids (ILs) have been recognized as a possible environmentally benign alternative to classic organic solvents, mainly due to their negligible vapor pressure and highly thermal and chemical stability. They are versatile compounds due to the possibility to tune the desired property such as polarity, conductivity, thermal and chemical stability, density, viscosity, melting point, and their solvent capacity just by combination of different anions and cations. \cite{2}. ILs are solvents able to dissolve numerous polar and non-polar compounds, including carbohydrates \cite{3}. Ether-containing ILs are called “sugar-philic ILs” mainly because they have favorable solvating interactions with carbohydrates \cite{4}.

We have performed a comparative study of dissolution of mono- and di-saccharides in imidazolium \cite{5} and guanidinium \cite{6} type cations ILs containing five different anions as described in figure. The combination of cation and anion ILs strongly influence the dissolution of mono- and di-saccharides behavior. In the same way, the water content in the ILs also affects the solubility of the saccharides studied.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{lls.png}
\caption{ILs used in the study of dissolution of carbohydrates.}
\end{figure}

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The synthesis of well-defined calixarene-based polymers as new materials for sensing devices, together with its characterization and properties evaluation are current research topics in our laboratory. The synthesis of conjugated calix[4]arene polymers comprising 1,3-(4-ethynyl)benzylxoxy-p-t-butylcalix[4]arene units along the main-chain was recently described. The aforementioned monomer underwent a smooth polymerization when [Rh(nbd)Cl]$_2$ was used as catalyst and PPh$_3$ as an additive. Under appropriate conditions, high conversions were obtained and the resulting polymers, isolated in high yields, showed monomodal MWD and less than 5% of dimeric and oligomeric materials. On the contrary, when the polymerization of tri-O-propyl-(4-ethynyl)benzylxoxy-p-t-butylcalix[4]arene (I) was attempted, under the very same general conditions used for the difunctional counterpart, huge amounts of dimeric, trimeric and oligomeric materials were obtained, whatever the particular conditions tested. We now report that a highly efficient polymerization of 1 has been accomplished by Rh-based ternary catalytic systems. In one case, the initiator was prepared in situ from [Rh(nbd)Cl]$_2$, 1,1-diphenyl-2-phenylvinyl lithium (TPVLi) and PPh$_3$ in toluene, adapting a reported procedure by Masuda et al. for the living polymerization of monosubstituted phenylacetylenes (PA). After 1h at 30ºC, monomer 1 was quantitatively converted (GPC analysis) affording poly 1 in high yield, with virtually no oligomeric materials. A second ternary catalytic system, firstly developed by Noyori et al. for PA, was similarly prepared, using PhC≡CLi instead of TPVLi as the rhodium alkylating agent. It also proved effective in the polymerization of 1, albeit in a less efficient way, requiring extended reaction times for complete conversion of the monomer and producing a polymer with a larger polydispersity under the conditions used. The underlying features of these polymerization systems will be reported.


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Electrochemical Epoxidation of Geraniol

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Introduction
Terpenes are natural compounds widely distributed in nature and their epoxides are important starting materials for the industrial synthesis of more complex molecules like flavours, fragrances or pharmaceuticals.

Materials-methods
Two platinum electrodes (2.5\times2.5\text{ cm}^2) parallel each other were placed in a beaker with MeCN/H$_2$O (4:1), geraniol (40mM) and NaBr (40mM) as mediator. A constant density current (3.3 mA/cm$^2$) was produced in a DC source. After the electrolysis, sodium metabissulfite (1%) was added to the reaction mixture which was extracted with chloroform. The crude residue was submitted to flash chromatography and the pure compounds were identified by NMR ($^1$H and $^{13}$C).

Results
From geraniol (1), 6,7-epoxigeraniol (2) and 2,3:6,7-epoxigeraniol (3) were obtained.

\[
\text{NaBr} \quad \text{MeCN:H}_2\text{O (4:1)} \quad \rightarrow \quad 2 \quad 3
\]

Discussion
Compounds 2 and 3 were obtained in 43\% and 6\% yields, respectively, in the same run after 594 C. However, after 891 C compound 2 was obtained with a yield of 36\% and compound 3 with a yield of 24\%. Using a chemical procedure [1], only compound 2 was obtained in 67\% yield. Electrochemical approach can be used to produce epoxides that could not be obtained by chemical methods or were difficult to obtain. Once the electrochemical parameters are established the reaction can afford the required products in an optimized way.

References:

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ENANTIOSELECTIVE APPROACH TO THE SYNTHESIS OF MEDICINALLY IMPORTANT DIHYDROXYLATED PYRROLIDINES

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Dihydroxylated indolizide alkaloids are a very important group from the pharmacological and medical point of view, given that in general they exhibit strong biological activities. Compounds like, Swainsonine and derivatives [1] that exhibit anti-tumor activity, (+)-lentiginosine, with potent amyloglucosidase inhibitory activity [2] and (-)-anisomycin [3] that shows strong and selective activity against pathogenic protozoa and fungi (Figure 1).

Figure 1

In this communication we report the development of a novel synthetic route to these compounds.

ENANTIOSELECTIVE SYNTHESIS OF INDOLO[2,3-a]QUINOLIZIDINES

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Due to the wide range of biological activities associated to indole alkaloids, these compounds constitute important synthetic targets.

We report here a cyclocondensation reaction of (L)-tryptophanol 1 with racemic aldehyde 2. In this reaction two stereogenic centres with a well-defined absolute configuration are formed with excellent stereoselectivity in a process involving a dynamic kinetic resolution. The resulting enantio pure lactam 3 was converted to the 6,12b-trans indoloquinolizidine 4a by treatment with HCl, which after removal of the hydroxymethyl substituent gave the indoloquinolizidine 5.

Remarkably, cyclization of 3 with BF$_3$·OEt$_2$ resulted in a dramatic change in the stereoselectivity as the major product obtained was 6,12b-cis indoloquinolizidine 4b. [1]

Reagents and Conditions:
(i) toluene, reflux;
(ii) BF$_3$·OEt$_2$, anh CH$_2$Cl$_2$, reflux;
(iii) HCl (1.2 M in EtOH), rt;
(iv) IBX, then Boc$_2$O;
(v)NaClO$_2$;
(vi) (PhSe)$_2$, n-Bu$_3$P;
(vii) AIBN, Bu$_3$SnH, then Bu$_4$NF.


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EVALUATION OF $A_2B_2$ HYDROXYLATED PORPHYRINS AS SENSITIZERS FOR PHOTODYNAMIC THERAPY

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Photodynamic therapy (PDT) is presently a well established treatment for oncological and non-oncological diseases. It is a minimal invasive procedure based on the destruction of cells by the destructive action of singlet oxygen ($^{1}\text{O}_2$) generated through the combined action of a sensitizer and light. PDT has attracted a lot of interest due to the selectivity shown by malignant tumours for the sensitizers relatively to healthy tissues. The sensitizer which is not a therapeutic agent becomes active when irradiated with low power light, developing a reaction cascade that produces apoptotic pathways leading to cell death.

The capacity of the sensitizer to absorb visible light of the red region of the electromagnetic spectrum and its ability to go inside cancer cells are key elements in order to get anti-tumoral activity. Besides good absorption properties, porphyrins have shown particular affinity for tumor cells$^1$ if macrocycles present some hydrophilicity, being mainly efficient in the presence of hydroxyl groups. Also, the existence of halogens in the structure can increase the efficiency of the sensitizer for $^{1}\text{O}_2$ generation.$^2$

Porphyrins with $A_2B_2$ structures (1-4) with hydroxyl groups and halogens in different positions were prepared. Their anti-tumoral activities against colorectal cancer cell line (WiDr) were determined and compared with the tetrahydroxyl symmetrical porphyrin 5.


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INVESTIGATION OF 2-HYDROXY-NEVIRAPINE AS A POTENTIAL GENOTOXIC METABOLITE FROM THE ANTI-HIV DRUG NEVIRAPINE

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The non-nucleoside reverse transcriptase inhibitor nevirapine (11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, NVP, I) is one of the most commonly prescribed antiretrovirals worldwide [1]. Its chronic use against the human immunodeficiency virus (HIV), e.g., in post-exposure prophylaxis, is currently not recommended, due to consistent reports of severe hepatotoxicity of the drug [2]. Nonetheless, NVP is still widely used in low resource countries to prevent the vertical transmission of HIV from mother to child [1]. Despite its efficiency in this last context, and the decreased risk of single-dose administration, concerns about the safety of the drug remain, particularly when given to children. Although the reasons for NVP toxicity are currently unknown, it is plausible that metabolic activation to reactive electrophiles may be involved in the initiation of genotoxic responses, through DNA adduct formation. NVP metabolism entails Phase I oxidation to 4-hydromethyl-NVP (II) and ring hydroxylation to phenol-type derivatives (III-V) [3]. Subsequent metabolism, either through further oxidation of the phenols to quinoid derivatives or Phase II esterification of the hydroxymethyl group of II, could conceivably produce electrophiles capable of binding to DNA.

We have previously demonstrated DNA adduct formation in vitro by the O-mesyl derivative of II, used as a surrogate for a Phase II metabolite [4]. We are now conducting a comprehensive evaluation of the phenolic NVP metabolites regarding oxidation and subsequent reaction with (bio)nucleophiles. We report herein the synthesis of 2-hydroxy-NVP (III) and the analysis of its oxidation products, generated under mild conditions from reaction with Fremy’s salt or silver(I) oxide. The significance of similar transformations in vivo will be discussed.

![Diagram of molecules I, II, III-V](image)

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MECHANISTIC STUDIES ON RADICAL OXIDATIVE DEMETHYLATION OF PYRAZOLONE DERIVATIVES

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Antipyrine (AP, I) and 4-Dimethylaminoantipyrine (4-DMAAP, II) are pyrazolone derivatives, with therapeutical effects, which have been attributed to their analgesic, antipyretic and anti-inflammatory properties. This family of compounds has also been appointed as potential antioxidants. Previous results of this group showed a much higher antioxidant activity of 4-DMAAP as compared to AP,¹ which was attributed to the 4-DMAAP capacity to undergo oxidation followed by demethylation in the reaction with free radicals,²,³ giving rise to 4-methyl-aminoantipyrine (4-MMAAP, III), which can be further demethylated to 4-aminoantipyrine (IV).

![Chemical Structure](image)

To validate this mechanistic proposal 4-dimethyl-aminoantipyrine (4-DMAA, II), 4-methyl-aminoantipyrine (4-MMAAP, III) and 4-aminoantipyrine (4-AAP, IV) were submitted to the Fenton reaction conditions. The final products analysis (HPLC-DAD, GC-Ms and NMR) enabled their identification. The reaction of 4-DMAAP (II) with the hydroxyl radical involves benzene ring hydroxylation to phenolic derivatives (ortho, meta and para positions) and demethylation on the amino group with formation of 4-MMAAP (III). The 4-MMAAP is further demethylated to 4-AAP (IV). The 4-aminoantipyrine is oxidized to final products which are also identified in the reactions of II and III.

In order to characterise the transient radicals involved the ESR spectra of the radical cations obtained by one-electron oxidation of II and III were recorded.


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MERRIFIELD SUPPORTED PORPHYRINS AS EFFICIENT OXYGEN SINGLET GENERATORS

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The efficient use of molecular oxygen as oxidant is very attractive from the economical and environmental perspectives, and photochemical activation a good approach to achieve this purpose. On the other hand, some porphyrins proved to be good sensitizers for singlet oxygen generation especially if they have halogen atoms in the structure.¹

If the objective is to develop photosensitizers for use in large scale processes, attachment of the porphyrin to polymeric materials is essential. The polymeric structure can give some protection against degradation of the sensitizer and allows for the easy recovery of the catalyst.

Commercial Merrified resins seemed to be good polymeric supports because they can be easily modified to attach the porphyrin structure.

In this work we attached several halogenated porphyrin macrocycles to a Merrifield polymer using a spacer containing a twelve atom carbon chain (1-3). The evaluation of the efficiency of the polymeric catalysts was made by photochemical oxidation of α-terpinene and citronellol using air as oxygen source.

The reactions are efficient using substrate/catalyst ratio from 600/1 up to 15000/1. Results for consecutive reactions with recovered catalysts will be presented.


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MICROWAVE-ASSISTED SYNTHESIS OF ASYMMETRICAL PORPHYRINS LINKED TO PEG$_{2000}$ AND THEIR PHOTODYNAMIC ACTIVITY

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The use of microwaves as a thermal energy source affords a set of reaction conditions unattainable by conventional heating and has already undoubtedly demonstrated to be a widely successful technology in organic chemistry. It allows significant improvements of several types of synthetic reactions [1-4], including the synthesis of symmetrical porphyrins and metalloporphyrins[5].

This study reports the extension of our methodology for the microwave-assisted synthesis of porphyrins to the preparation of 5,10,15-tris(ortho-halogenophenyl)-20-(3-hydroxyphenyl)porphyrins. The poor amphiphilic character of these compounds was improved by covalently bonding to PEG$_{2000}$. The photodynamic activity of the corresponding derivatives was tested against WiDr human colon adenocarcinoma cell lines and compared with Photofrin, approved for PDT of cancer in Portugal.

\[\begin{align*}
N &\quad N \\
\text{Y} &\quad \text{Y} \\
\text{Y} &\quad \text{Y} \\
\text{Y= H, Cl or Br}
\end{align*}\]


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MICROWAVE ASSISTED SYNTHESIS OF XANTHONES: 1-HYDROXANTHONE, 1-METHOXYXANTHONE AND ONE DIHYDROPYRANOXANTHONE

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The use of microwaves (MW) as an energy source for chemical reactions and processes has been extensively investigated during recent years [1]. Microwave assisted organic synthesis (MAOS) provides faster reactions, with greater selectivity and better yields, when compared to classical reactions. Moreover, it can be used in conjunction with solid catalysts, which allows even higher yields in milder conditions [2].

Recently, our group has been focusing on prenylated and dihydropyran xanthones that have demonstrated interesting results for their effect on the in vitro growth of human tumor cell lines [3]. For that reason, we have used several methodologies to obtain xanthone derivatives including classical, MW, heterogeneous catalysis (Montmorillonite K10 clay) and the combination of MW and heterogeneous catalysis, either with or without solvent. So, in this work, we report the synthesis of 1-hydroxanthone (1) and 1-methoxyxanthone (2) under MW irradiation [4, 5]. We also report the synthesis of dihydropyranoxanthone (3) from 1-hydroxanthone, using MW with heterogeneous catalysis (Montmorillonite K10 clay).

![Chemical Structures](image)

The coupling of MW irradiation with clays, under solvent conditions, provided enhanced reaction rates, higher yields and selectivity in the synthesis of dihydropyranoxanthones just in one step from hydroxyxanthones. The method using MW and Montmorillonite K10 clay was applied for the first time, by our group, to the synthesis of xanthone derivatives.


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MOLECULAR GASTRONOMY

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Molecular Gastronomy is the scientific discipline devoted to the study of culinary transformations and gastronomical phenomena in general. Molecular gastronomy can have important technological and educational applications and in the last 6 years we have been working in the exploration of its potentials at these levels.

The European Union has been committed to raising public awareness of science and bridging the gap between science and the public. This is why scientists in Europe are increasingly asked to communicate their work to a wider audience. In this context, under the initiative of Ciência Viva and Pavilhão do Conhecimento, we started using molecular gastronomy and food and cooking to attract the interest of the public to science and scientific activities. The activities named “The Kitchen is a Laboratory” were very successful and in the last 6 years we have undertaken them for the general public and also in schools. Food and cooking is a topic with widespread appeal and importance and we consider that the interest and excitement it generates can make a positive contribution to a better understanding of the role of science and scientists in everyday life and in our present living standards.

Following the success of these activities, and in parallel with them, the next step was to start developing work on the technological applications of molecular gastronomy. In the last three years, we have been working with professional cooks that want to enlarge their knowledge, and particularly benefit from scientific developments to improve traditional cooking techniques and introduce new ones. In fact, gastronomy has an important role in the tourism industry and the necessity to keep up with the most recent developments in this area is widely recognized and considered crucial from an economic point of view. In this context, we have mainly focused on the study of several hydrocolloids, analyzing their properties and devising innovative ways of using them in a gastronomical context.

NEW BIO-ORGANOMETALLIC BENZOTHIOPHENENE
DERIVATIVES AS POTENTIAL ANTICANCER DRUGS

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The incorporation of organometallic moieties into the structure of known active drugs to improve their therapeutic properties has gained considerable interest in recent years [1]. The benzothiophene derivative raloxifene (I) is a selective estrogen receptor modulator (SERM) with estrogen-agonistic effects on bone and lipid metabolism and estrogen-antagonistic effects on endometrium and breast tissue. Preliminary results from a large scale clinical trial (STAR), designed to evaluate the relative ability of raloxifene and the widely used antiestrogen tamoxifen to reduce breast cancer incidence, suggest that raloxifene may have the benefits of tamoxifen with fewer side effects [2].

Based upon these observations, we have undertaken the synthesis of a series of bio-organometallic benzothiophene derivatives (II) containing a ferrocenyl unit and several terminal amino groups (e.g., HNR₂=morpholine, piperidine, pyrrolidine, piperazine, and dimethylamine), expected to insure affinity to the estrogen receptor (ER). These species have been designed to combine SERM properties associated with a raloxifene-type backbone with potential cytotoxicity, provided by the organometallic fragment.

The synthetic strategies towards II and the full structural characterization of the novel benzothiophene derivatives will be presented. Moreover, properties of these new prospective SERMs (e.g., partition coefficients and redox potentials), expected to determine their bioactivity, will also be reported. Further studies, involving binding measurements to the ER and cytotoxicity evaluation in breast cancer cell lines, are planned in order to assess the potential therapeutic properties of the new organometallic benzothiophene derivatives against breast cancer.


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NEW ORGANIC LIGANDS FOR NONLINEAR OPTICAL COMPLEXES

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The search for organometallic compounds with nonlinear optical (NLO) properties has becoming a field of considerable interest due to their potential as materials with technological applications in the area of nonlinear optical phenomena [1]. In the organometallic push-pull systems, the metal center behaves as an electron-acceptor or electron-donating center bonded to an organic delocalized π-electron system. Organic compounds could present themselves NLO properties due to the high electronic polarizability of their π-system [1]. The ability to introduce subtle changes in the chemical structures, leading to improvements in their properties, and to build structure-property relationships, make the organic compounds still good candidates for electronics and optical phenomena investigation area [1,2].

Here, we present the synthesis and spectroscopic characterization of electron-withdrawing organic ligands, suitable for coordination to electron donating Fe or Ru metal centers. These ligands present a two aromatic rings backbone linked by a spacer (double, triple or hydrazone bond) with one or two electron withdrawing nitro groups on para and ortho positions of the second aryl ring (Figure 1). The substitution with a nitrile or alkyne groups provide an available site for coordination to the metals. The structures of several compounds were confirmed by X-Ray diffraction studies.

![Figure 1](image)

**FIGURE 1**


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NOVEL BENZISOTHIAZOLE-TETRAZOLYL DERIVATIVES AS POTENCIAL NITROGEN LIGANDS

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In the last few years, the design of new bridging ligands for controlling the molecular architectures required for the desired physical properties of the resulting coordination compounds has been a topic for many research groups, in important fields such as supramolecular chemistry[1] and molecular magnetism.[2]

The 5-substituted tetrazolate group, isosteric with the carboxylate group, and with good coordination capacities, has scarcely been explored in building coordination frameworks, mainly because no effective method for synthesizing 5-substituted tetrazoles in high yields was known. In the past few years, Sharpless and Demko have developed a convenient route to 5-substituted tetrazoles by addition of azide to organic nitriles catalyzed by zinc salts in water.[3] Since then, studies on 5-substituted tetrazolate-bridged coordination frameworks have been slowly emerging.[4]

To the best of our knowledge, tetrazoles have not been investigated as a ligand function of saccharin, though they demonstrate the ability to bind cations of transition metals.[5] In this communication, we report the synthesis and characterisation of three new benzisothiazole-tetrazolyl derivatives (see Structure 1), differing on the spacer-group used for linkage of the two heterocycles, as potential nitrogen ligands in coordination reactions with transition metal complexes.[6]

\[
\text{SO}_2\text{N}^{-} \quad \text{Spacer} \quad \text{N}^{-} \quad \text{N}^{-} \quad \text{N}^{-} \\
\text{H} \quad \text{M} = \text{metal}; \text{L} = \text{ligand}; \quad \text{L} \quad \text{L}
\]


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NOVEL METHODOLOGY TO SYNTHESIZE BIOLOGICALLY ACTIVE BISPHOSPHONATES BASED ON ORGANOCATALYSIS

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Several bisphosphonates are used nowadays for the treatment of bone diseases such as osteoporosis, Paget’s disease of the bone, bone metastasis and multiple myeloma.[1] They are taken up by the skeleton and inhibit osteoclast mediated bone resorption. A and B are examples. In addition, some bisphosphonates containing a carbonyl function, such as C, have been found to have potent anti-inflammatory activities too.[2]

![Structures of Clodronate (A) and Etidronate (B)]

Here we present new methodology to synthesize analogs of the carbonyl-containing bisphosphonates, for example C, based on organocatalysis.

![Structure of analog C]


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“ONE-POT” PALLADIUM-CATALYZED SYNTHESIS OF BENZOTHIENOQUINOLINES FROM 3-BROMOBENZO[b]THIOPHENE-2-CARBALEHYDE AND 2-(PINACOLBORONATE)ANILINE

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For some years now we have been interested in the synthesis of tetracyclic planar compounds derivatives of benzo[b]thiophenes as potential antitumors, using palladium-mediated reactions [1]. Recently we have prepared tetracyclic lactams in a “one pot” three steps reaction of borylation, Suzuki coupling (BSC) and intramolecular cyclization, from alkyl 3-bromobenzo[b]thiophene-2-carboxylates and o-haloanilines, and their interaction with DNA was studied by fluorescence [2]. Here we present the palladium-catalyzed “one pot” synthesis of two benzothienoquinolines from 3-bromobenzo[b]thiophene-2-carbaldehyde and 2-(pinacolboronate)aniline. In the synthesis of the benzothieno[2,3-c]quinoline, a Suzuki coupling and a nucleophilic attack of the amino group on the carbonyl of the aldehyde occur. In the synthesis of the benzothieno[3,2-b]quinoline a palladium-catalyzed C-N coupling followed by an intramolecular cyclization with loss of H2O, seems to occur.

The compounds obtained are fluorescent and their intercalation with DNA and interaction with biological membranes will be studied.


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4-OXO-\(\beta\)-LACTAMS AS INHIBITORS OF ELASTASE

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Elastase is a serine protease implicated in many inflammatory diseases.\(^1\) Recently, 3-oxo-\(\beta\)-sultams, 1, were reported as potent inhibitors of elastase.\(^2\) We now report that 4-oxo-\(\beta\)-lactams, 2, are novel potent inhibitors of porcine pancreatic elastase PPE, while decreasing the reactivity towards non specific nucleophiles when compared to the highly reactive isosteric analogues 1.

![Structural formulas of 1 and 2](image)

Both alkaline and enzymatic hydrolysis of N-aryl-4-oxo-\(\beta\)-lactams 2 occur with endocyclic C-N ring fission, yielding respectively 3 and 4 and the ratio varies with the aryl substituent. A good amide leaving group seems to be an important requisite to increase chemical reactivity and to achieve enzyme irreversible inhibition by 2. We found that the most reactive derivatives were also the most actives ones against PPE, which supports the use of \(k_{\text{OH}}\) value for the alkaline hydrolysis of potential serine enzymes inhibitors as a crude indicator for their ability to be useful acylating agents.\(^3\)

![Reactions of 2](image)

Fig.1 – Hydrolysis of 4-oxo- \(\beta\)-lactams: a) by hydroxide ion; b) by PPE


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Prenylflavonoids are compounds naturally occurring in plants showing a large diversity of pharmacological activities, namely antitumor [1-3]. Due to these interesting biological effects recently our research group has been focusing on the study of this class of compounds.

In this work we describe the synthesis of prenylated derivatives using 3,7-dihydroxyflavone (1) as building block by two synthetic strategies: a classic one, based on refluxing with prenyl bromide in the presence of K$_2$CO$_3$ and acetone anhydrous [4] and the other protocol developed for the first time performing reactions assisted by microwave. With both procedures two prenylated derivatives 2 and 3 were obtained. However, microwave irradiation technique showed to be a better way to obtain these prenylated derivatives, as it affords better yields (35% vs. 44% for compound 2 and 2% vs. 18% for compound 3) in shorter reaction times. Structures were established by IR, UV, MS and NMR ($^1$H, $^{13}$C, HSQC and HMBC) techniques.

The effect of the compounds on the in vitro growth of three human tumor cell lines, MCF-7 (breast), NCI-H460 (non-small cell lung) and SF-268 (central nervous system) are understudy.


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PREPARATION AND CHARACTERIZATION OF IONIC LIQUIDS CONTAINING HYDROPHOBIC CATION AND HYDROPHILIC ANION

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Ionic Liquids are emerging very fast as an alternative solvent for the volatile organic compounds various chemical processes, particularly in the area of applied chemistry. It is principally due to their essential properties over the conventional solvents, such as non volatility, non flammability, large liquid range & high thermal stability. These features of ionic liquids offer numerous opportunities for modification of the existing and for the development of green technologies [1].

A novel class of ionic liquids based on imidazolium and guanidinium cations and dicyanamide and thiocyanate anions have been prepared and characterised. The important physico-chemical properties of these ionic liquids including viscosity, glass transition and degradation temperature were studied. The present hydrophilic anions have shown very unusual chemical properties in comparison with the previously reported routine ionic liquids containing hydrophobic anions. Therefore, their properties were compared with the representative hydrophobic anions such as bis(trifluoromethanesulfonyl)imide and trifluoromethanesulfonate [2]. Additionally, the study of applications of these ionic liquids as an absorbent is reported [3].

\[
\begin{align*}
\text{Scheme 1: Basic structures of the ionic liquids prepared and characterized.}
\end{align*}
\]


Acknowledgement: We thank Fundação Para a Ciência e Tecnologia (POCI 2010) and FEDER for the financial support (Ref. SFRH/BPD/14848/2003).
Neurotransmitters are of particular interest as they are implicated in neurodegenerative and neuropsychiatric disorders such as Alzheimer disease [1], schizophrenia [2], Down’s syndrome [3] and Parkinson’s disease [4]. As a result, the quantification of neurotransmitters, such as amino acids, nucleotides and physiological amines, in biological samples may offer valuable mechanistic insight into disease cause and progression as well as possibly providing a diagnostic tool. Most of the neurotransmitter amino acids are small aliphatic molecules with neither strong absorbance nor fluorescence in the ultraviolet/visible region. Thus derivatisation of such analytes is necessary to enhance the sensitivity of detection. Fluorescent labelling is a widely applied methodology, as it is the most suitable for analytical purposes.

Bearing this in mind, a strongly fluorescent pyrene moiety was linked to several model amino acid neurotransmitters, such as glycine, alanine, β-alanine, glutamic acid and γ-aminobutyric acid, through an ester bond at their carboxylic functions at the main and side chain (in the case of glutamic acid). The derivatisation was carried out with potassium fluoride in DMF, at room temperature, and the resulting fluorescent conjugates were obtained in excellent yields. Full characterisation by the usual spectroscopic techniques, including UV-vis and fluorescence, was performed and the data will be presented.

![Chemical Reaction](image)

\[ Z\text{-HN-(CHR)}_n\text{-CO}_2\text{H} + \text{Cl-H}_2\text{C} \xrightarrow{\text{KF/DMF, r.t.}} Z\text{-HN-(CHR)}_n\text{-CO}_2\text{CH}_2 \]

\( R = \text{H, CH}_3, \text{CH}_2\text{CH}_2\text{COOH} \)

\( n = 1, 2, 3 \)


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REACTION OF NITROSOAROMATICS AND 2-(1’-HYDROXYETHYL)-THIAZOLIUM SALTS

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Thiamine diphosphate (1) (Figure 1) is a coenzyme of importance in mammalian carbohydrate metabolism as it is involved in vital non-oxidative and oxidative processes. It catalyses the enzymatic cleavage of C—C bonds in α,β-dicarbonyl and α-hydroxycarbonyl compounds [1].

Figure 1

In a preliminary account of the work [2] it was reported that 2-(1’-hydroxyethyl)-thiazolium salts 3 (R=CH₃), modelled on the coenzyme 1, reacted with nitrosobenzene 2 in the presence of base to give a major phenylhydroxylamine derivative 4 (Scheme 1).

Scheme 1

Concerning the reaction mechanism various possibilities were considered, such as hydride transfer or electron transfer from 3 to 2. Herein we present our recent results towards the elucidation of this reaction mechanism.


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Reactivity of Bsmoc derivatives with nucleophiles

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The Bsmoc (1,1-dioxobenz[b]thiophen-2-ylmethylcarbonyl) amino-protecting group was recently suggested as a novel scaffold for double-hit inhibitors for clan CA proteases. Cyclic vinyl sulfones derived from Bsmoc, were shown to be irreversible inhibitors of papain and cathepsin B [1]. The rate of thiolysis, aminolysis and alkaline hydrolysis of ester and carbamate derivatives (1) were measured in aqueous solutions. The obtained Hammett values for thiolysis ($\rho \approx 0.3$) and alkaline hydrolysis ($\rho \approx 1$) revealed the importance of substituent inductive effect on the leaving group and the existence of different mechanisms for these nucleophiles. These results are consistent with thiol addition at the ring C-3, rather than at the carbonyl carbon or other exocyclic positions and indicate thiolate anion addition to the cyclic vinyl sulfone moiety as the rate-limiting step ($\beta_{ \text{nuc} } \approx 0.3$). The second order rate constant for the reaction of Bsmoc derivatives with N-acetyl-cysteine is ca. 15 times greater than the corresponding value for the reaction with piperidine, the reagent recommended for removing the Bsmoc protecting group. Additionally, in contrast to the reaction of Bsmoc protected amino acids with piperidine already described, which leads to a rearrangement (2), these derivatives give exclusively Michael addition products with thiols (3).


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Di-rhodium(II) complexes are bi-metallic complexes highly popular among organic chemistry community due to their remarkable efficiency in the generation of carbenoids from diazo compounds.[1]

In this work was found that di-rhodium (II) tetrafluorobutyrate can catalyze arylation of aromatic aldehydes in presence of in situ generated N-heterocyclic carbenes (NHC). The interesting spacial complementarity between the NHC ligand and the di-rhodium (II) structure allowed the formation of an extremely efficient catalyst especially in arylation of aldehydes containing electro-donating substituents and alkyl aldehydes.[2]

\[
\begin{align*}
\text{R} & \quad \text{H} \quad \text{R}'' \quad \text{Cl} \\
\text{OH} & \quad \text{OH} \\
\text{B(OH)₂} & \quad \text{Rh₂(pfb)}₄, 3 \text{ mol %} \\
\text{ligand, 3 mol %} & \quad \text{KO'Bu, 1 eq.} \\
\text{t-amyl alcohol} & \quad 40 - 80 \degree C
\end{align*}
\]

**yields up to 99 %**


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REARRANGEMENT REACTION OF ENEHYDROXYLAMINES DERIVED FROM DIOXIMES

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Enehydroxylamines (R = alkyl, Z = O) are useful compounds, and suitable derivatives 2 can be involved in 3,3-sigmatropic rearrangement providing a means of functionalisation of the α-carbon (Scheme) [1]. For the purpose of expanding the ambit of this reaction it would be of interest to be able to remove the N-substituent R at the end of the rearrangement [2]. We present in this communication our results with the oxime derivatives of type 1 (R = H, Z = NOH) and the thermal rearrangements of their acyl derivatives 4. Possible routes for final deprotection are discussed.


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SCREENING FOR ANTIBACTERIAL ACTIVITY OF PLANTS USED IN TRADITIONAL MEDICINE

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Infectious diseases are the leading cause of death world-wide. The recent increase of multidrug resistant organisms to the major classes of antibiotics has created an urgent need for new antibacterial agents. Natural products, either as pure compounds or as standardized extracts, provide unlimited opportunities for new drug leads because of their unmatched structural diversity. [1] In the last 25 years, 98 chemical entities have been developed as new antibacterial drugs being 10 of them from natural origin and 64 natural compounds derivatives. [2] Plant-derived compounds have traditionally played a significant role in the treatment of human diseases; about 80% of the world population in developing countries is almost completely dependent on plant products for their primary health care.

The aim of this study was to evaluate the antibacterial activity of n-hexane and methanol extracts obtained from seven plants used in traditional medicine: Anacardium occidentallis, Gomphocarpus fruticosus, Tecomaria capensis, Salvadora australis, Salvadora persica, Litogyna gariepina and Cassia abbreviata. The in vitro antibacterial activity was examined against Gram-negative (Klebsiella pneumoniae) and Gram-positive (Staphylococcus aureus, Enterococcus faecalis) strains by using agar diffusion methods (discs and wells). Anacardium occidentalis, Litogyna gariepina and Cassia abbreviata extracts showed activity against Staphylococcus aureus and Enterococcus faecalis.

SEPARATION AND IDENTIFICATION OF ATROPISOMERS OF A₂B₂ TYPE PORPHYRINS

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The rotational process of the aryl groups in meso aryl porphyrins was reviewed in 1970s [1,2]. However, research in this field expanded enormously in the last thirty years [3] because atropisomers found applications in several fields, such as chiral and molecular recognition in asymmetric catalysis [4-9], membrane carriers in PVC membrane electrodes [10], models for biological systems such as photosynthetic centers or hemoproteins [11]. These applications take advantage of the different sides of the porphyrin, either to incorporate an exogenous molecule or to deliver an axial ligand to the metal inside the porphyrin [12] and for many of these applications was establish the importance of have tetrapirrolic systems with mixed hydrophobic/hydrophilic substitution pattern. One way of achieve these combination of properties is the synthesis of A₂B₂ substituted porphyrins such as 5,15-diarylsubstituted porphyrins but there is a very few reports about atropisomers of these porphyrins [13,14].

In this work the HPLC separation, LC-MS and ¹H-RMN characterization of atropisomers of 5,15-bis(2-bromo-5-hydroxyphenyl)porphyrin and Ni(II)-5,15-bis(2-bromo-5-hydroxyphenyl)porphyrinate will be presented.

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It is known that in Michael additions, the kinetic product resulting from attack on a triple bond is the \textit{cis} olefin [1]. The last tends to isomerize to the more stable \textit{trans} olefin (scheme). In the present work, the \textit{cis} addition product 3, obtained by Michael addition of 1 on the triple bond 2 undergoes at room temperature a \([3,3']\)-sigmatropic rearrangement to the allene 5, while the \textit{trans}-addition product 4, resulting from isomerization, accumulates intact. The reaction is found to be dependent upon the substituents \(R_1, R_2\) and \(R_3\). Discussion of its mechanism will be presented.

\[\begin{align*}
\text{R}_1 & - \text{adamantyl, 1-methylcyclohexyl, tert-butyl or benzyl} \\
\text{R}_2 & - \text{H or Me} \\
\text{R}_3 & - \text{H or Me}
\end{align*}\]


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Fast accurate predictions of $^1$H NMR spectra of organic compounds play an important role in structure validation, automatic structure elucidation, or calibration of chemometric methods.

Ensembles of Feed Forward Neural Networks (FFNNs) were trained [1] with >3000 experimental chemical shifts of protons to predict chemical shifts from the molecular structure. Empirically calculated physicochemical, geometrical and topological proton properties were used as descriptors [2]. An additional memory of >15000 protons and their experimental chemical shifts was used to correct the predictions, on the basis of the observed errors for the most similar examples in the memory – Associative Neural Network (ASNN) [3]. In the memory, each proton is represented by an output profile, which is the series of outputs produced by the set of FFNNs in the ensemble [4].

For the prediction of coupling constants a second memory is linked consisting of coupled protons and their experimental coupling constants. The output profiles generated for chemical shift prediction are re-used to form profile pairs that describe pairs of coupled protons. An ASNN finds the pairs of coupled protons most similar to a query, and these are used to estimate the coupling constant [5].

Predictions were obtained for independent test sets with mean average errors of 0.2-0.3 ppm for chemical shifts, and 0.6-0.8 Hz for coupling constants.

The methods for predicting chemical shifts and coupling constants were mounted together in a $^1$H NMR full-spectra prediction tool – SPINUS. A web-based implementation is available at http://neural.dq.fct.unl.pt/spinus. It makes use of ChemAxon’s Marvin applet to draw the query structure, and MDL’s Chime plugin for visualization of the spectra and 3D structures.

In this communication statistics will be presented, and the ability for full-spectra generation will be demonstrated.

References:

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STRUCTURAL CHARACTERIZATION OF A NEW DYE OBTAINED FROM 1-HYDROXY-2-ACETONAPHTHONE AND 2-FLUOROBENZOPHENONE

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The reaction between 1-hydroxy-2-acetonaphthone and benzophenone in the presence of sodium ter-butoxide is known to give, after reflux in HBr/HOAc, mainly 2,2-diphenylnaphthopyran-4-one a useful compound for the synthesis of photochromic naphthopyrans [1,2].

In an attempt to prepare some fluoro substituted photochromic naphthopyrans substituted in position 4 we tried the reaction of 1-hydroxyl-2-acetonaphthone 1 with 2-fluorobenzophenone 2 in the presence of potassium ter-butoxide in toluene at reflux. The reaction gave a red suspension that after solvent evaporation was treated with HCl/HOAc. After heating for 10 min a deeply red solution was obtained. Hydrolysis and CH$_2$Cl$_2$ extraction gave a deep blue solution. After column chromatography a blue dye was isolated in low yield. When dissolved in CH$_2$Cl$_2$, the blue dye 3 was not extracted by a basic solution of NaOH (aq) indicating that it was not a phenol. Spectroscopic characterization of this new compound, using mono and bi-dimensional NMR techniques (DEPT, COSY, HMBC, HSQC, NOESY) proved structure 3:

STUDIES IN SULFAMOYLATION OF HYDROXYXANTHONES AND INVESTIGATION OF BIOLOGICAL ACTIVITIES

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Steroid sulfatase (STS) is a new therapeutic target in oncology. Attempts to design nonsteroidal STS inhibitors have revealed benzomate (1) as a potent STS inhibitor with IC\textsubscript{50}=190 nm [1]. Aiming the investigation of more rigid derivatives, 3,6-dihydroxyxanthone (2) was synthesized and submitted to treatment with sulfamoyl chloride, which was obtained from the chlorosulfonyl isocyanate. Due to limitations concerning both sulfamoyl reagents stability, the raw material 2 almost didn’t react. Thus, the coupling reagent, TBTU \((O-(\text{benzotriazol-1-y})-N,N,N',N'\text{-tetramethyluronium tetrafluoroborate})\), often used in the peptide synthesis, was applied to activate chlorosulfonyl isocyanate in the sulfamoylation of the following compounds, 3,6-dihydroxyxanthone (2), 1,2- dihydroxyxanthone (3), 3,4-dihydroxyxanthone (4), and 2,2’,4,4’-tetrahydroxybenzophenone (5), in triethylamine and anhydrous THF.

Since one of the main strategies in drug discovery is the evaluation of synthetic intermediates, xanthones 2-4, 2,2’,4,4’-tetrahydroxybenzophenone (5) and its acetylated derivative 6 were investigated for their effect on the \textit{in vitro} growth of human tumor cell lines using the sulforhodamine B (SRB) method [2] and showed an inhibitory effect in the \(\mu\text{M}\) range on the growth of NCI-H460 (non small lung cancer) and SF-268 (central nervous system cancer). Also, compounds 2-6 were screened for their antifungal activity against \textit{Candida albicans}, \textit{Aspergillus} species and dermatophytes with clinical relevance, using the microdilution broth methods [3]. Compounds 2, 5 and 6 were found to be active against the complete range of five representative dermatophyte species tested. Regarding \textit{C. albicans} and the \textit{Aspergillus} species no activity was registered.


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STUDIES TOWARDS THE SYNTHESIS OF K-252d

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One of the major difficulties associated with the synthesis of structurally interesting and biological active alkaloids such as K-252d (1) is the regiocontrol required for the glycosilation step [1]. In relation with our previous work in the synthesis of biologically active indole alkaloids such as K-252d and staurosporine [2,3], we herein present our results in the N-glycosilation of 2,2’-biindole with different sugars. Our synthetic approach started with treatment of 2,2’-biindole (2) and rhamnosyl bromide (3) with Ag₂O. After chromatographic separation and characterization of the products, the N-glycosilated orthoester 4 was identified (Scheme 1).

Scheme 1

The next step consisted of a rearrangement achieved by subjecting 4 to basic conditions. Thus, the desired rearrangement product 5 could be isolated in moderate yield (Scheme 1). This contains the correct stereochemistry for the synthesis of 1, constituting a valuable alkaloid precursor. A similar protocol was adopted for other glycosil donors. The pertaining results and discussion will be presented in this communication.


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SYNTHESIS AND CHARACTERIZATION OF AMINOACID AND PEPTIDE ADDUCTS FROM THE ANTI-HIV DRUG NEVIRAPINE

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Nevirapine (11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, NVP, I) is a non-nucleoside reverse transcriptase inhibitor used against the human immunodeficiency virus (HIV), mostly in combination with other antiretroviral agents. NVP is also administered to prevent the vertical transmission of HIV from mother to child. Among the drawbacks of NVP use are its severe hepatotoxicity and its association with skin rash development which raises concerns about chronic administration of the drug, particularly in the perinatal, neonatal, and pediatric settings. NVP metabolism involves oxidation of the 4-methyl substituent to 4-hydromethyl-NVP (12-hydroxy-NVP, II), or ring hydroxylation to phenolic derivatives. Further metabolism, either through oxidation of the phenols to quinoid derivatives or Phase II esterification of the hydroxymethyl substituent of II, may produce electrophilic species capable of reacting with proteins to yield covalent adducts which could be involved in the genesis of toxicity processes.

As a model electrophile derived from 12-hydroxy-NVP, we synthesized 12-O-mesylnvirapine (III) and investigated its reactivity towards the nucleophilic amino acids (AA), N-acetyl-cysteine and Nα-Boc-histidine, and the peptide glutathione. We report herein the isolation and characterization of covalent NVP-AA adducts, typically formed with significant yields. Our results suggest that NVP metabolism to 12-hydroxy-NVP could potentially be a factor in NVP toxicity.


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SYNTHESIS AND CHARACTERIZATION OF NOVEL HYDROXY- AND AMINOBISPHOSPHONATES

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Bisphosphonates (BPs) are a family of drugs that are successfully used in the treatment of various calcium-related disorders such as Paget’s disease, osteoporosis and bone metastases. In addition, functional BPs have been also used in the treatment of metal intoxication and as novel ligands for well-defined radioactive metal complexes that can be used in imagiology, scintigraphy and radiotherapy applications [1,2].

The indazole derivatives are pharmacologically important compounds and the indazole ring system forms the basis of a number of drug molecules. Condensed pyrazoles are also known as pharmacophoric elements in numerous active compounds. However, in comparison with other heteroaromatic compounds, the chemistry of indazole and condensed pyrazoles remains less studied [3].

The present work is to extend the previous studies in indazolebisphosphonates [4] in order to obtain new BPs derived from indazole and condensed pyrazole with potential biological/therapeutical activities. Herein, we report the synthesis and characterization of a series of new 1-hydroxybisphosphonates (1) and aminobisphosphonates (2) (substituted at different C- or N-positions of the indazole ring - N-1, C-5, C-6, C-7) (Figure 1). Crystal structure of an aminobisphosphonate was determined by X-ray crystallography.

hydroxybisphosphonate 1
aminobisphosphonate 2

Figure 1


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SYNTHESIS AND CHARACTERIZATION OF TWO MACROCYCLIC COMPOUNDS CONTAINING SULPHUR AND NITROGEN AS DONOR ATOMS

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Nowadays there is a critical need of ligands with the right architecture for the selective complexation of metal ions in solution. The design of ligands as therapeutic agents for the treatment of metal poisoning [1] is one of our goals. Following our previous studies [2] and taking into account this proposal, we have synthesized two macrocyclic compounds, L1 and L2.

The synthesis were performed using high dilution procedures involving a previous esterification of thiodiacetic acid or thiodipropionic acid respectively, followed by the cyclization reaction between the esters and triethylenetetramine. The cyclization reaction was done by two addition-elimination steps: the first one based on the reaction of an ester and the amine (intermolecular) and a second one involving an intramolecular reaction.

The compounds L1 and L2 were obtained upon purification using chromatographic and recrystallization techniques.

Characterization of the macrocyclic compounds were performed by NMR ($^{1}$H NMR, $^{13}$C NMR, $^{1}H$-$^{1}H$ COSY, DEPT, HMQC and HMBC) and I. R. spectroscopies.


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SYNTHESIS AND CONFORMATIONAL ANALYSIS OF β-HAIRPIN MIMICS CONTAINING BIFUNCTIONAL DIKETOPIPERAZINE SCAFFOLDS

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In the field of peptidomimetics much effort has been focused on the design and synthesis of conformationally constrained compounds that mimic or induce specific secondary structural features of peptides and proteins. A common motif in protein structure is the reverse-turn. Reverse-turn mimics are generally cyclic or bicyclic dipeptide analogues which, as a result of their constrained structure, force a peptide chain to fold back upon itself.1

Herein, we report the synthesis of a new bifunctional DKP-scaffold 1, derived from L-aspartic acid and (S)-2,3-diaminopropionic acid, bearing an amino and a carboxylic functionalities. As a consequence of the absolute configuration of the two α-amino acids forming the cyclic dipeptide unit, the two reactive functionalities are locked in a cis-configuration and, when inserted into an oligopeptide sequence, the DKP scaffold acts as a reverse-turn inducer. In addition, the DKP-scaffold 1, while being derived from α-amino acids, can be seen as a constrained dipeptide formed by two β-amino acids2 and in particular a β3- and a β2-amino acids (following Seebach’s nomenclature).3

A tetrapeptide (AA1-DKP-AA2) and a hexapeptide (AA1-AA2-DKP-AA3-AA4) incorporating the DKP-scaffold 1 were synthesized, and their conformations studied by NMR and molecular modelling showing the formation of a β-hairpin mimic.

3. The superscripted number after β specifies the position of the side chain on the corresponding β-amino acid; see Hintermann, T.; Seebach, D. Synlett 1997, 437-438.

Acknowledgements: We thank the European Commission (Marie Curie Early Stage Research Training Fellowship "Foldamers" MEST-CT-2004-515968) for financial support and for a PhD fellowship to A. R. We also like to thank MIUR (PRIN 2006) for financial support.
SYNTHESIS AND CRYSTAL STRUCTURE OF Fe AND Pd COMPLEXES OF 4-CYANOBENZENEDITHIOLATE. CHARGE TRANSFER SALTS WITH TTF.

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The transition metal bis(dithiolene) complexes have been widely used in the last years as versatile building blocks for conducting and magnetic molecular materials. In this communication we report the preparation and characterisation of a new series of [M(cbdt)]\textsuperscript{2} complexes based on less symmetric ligand, cbdt = 4-cyanobenzenethiol with different transition metals (M = Au, Ni, Co, Fe, Cu, Pd). All the complexes were obtained as tetrabutylammonium or tetraphenylphosphonium salts in the monoanionic oxidation state, with the exception of Pd that was obtained in the dianionic oxidation state.

They show either cis or trans configurations depending on the coordination geometry; dimerised complexes with 4+1 coordination geometry such as Fe prefer a cis configuration while the square planar complexes such as Pd prefer a trans configuration. As expected their cyclic voltammetry data reveals lower oxidation potentials when compared with the dcbdt analogs, previously described\cite{1-3}.

The magnetic properties of these compounds, were studied by EPR and temperature dependent magnetic susceptibility measurements.

These metal complexes were used as acceptors to prepare charge transfer salts with the donor TTF (tetraethiafulvalene), by electrocrystallisation.

Selected references

Acknowledgments:
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SYNTHESIS AND IN VITRO ANTIFUNGAL ACTIVITY OF A NOVEL CHROMENE DERIVATIVE

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The screening for new antifungal chemicals is a constant need, due to the public demand for crop protection agents with low use rates, a benign environmental profile, and low toxicity to humans and wildlife. Chromene derivatives are an important class of compounds, widely present in plants, including edible vegetables and fruits [1]. The biological activity of some natural chromene-based structures led to the development of synthetic analogues, some of them displaying remarkable effects as pharmaceuticals [2], including antimicrobial agents [3].

In the present work, a novel 2-iminochromene dimmer was prepared by the Knoevenagel condensation of salicylic aldehydes 1a e 1b with malononitrile. Compound 4 could also be prepared from chromenes 2 and 3, under appropriate reaction conditions. The activity of compounds 2, 3 and 4 on Aspergillus spp. growth and on Ochratoxin A production was evaluated.

The chromene dimmer 4a was found to be the most effective of the tested compounds. A moderate inhibitory effect was also observed for the analogous structure 4b but only for the inhibition of ochratoxin A production. No effect was registered for compounds 3a and 3b, used as synthetic precursors of the dimmeric species 4. These results suggest that the dimmeric structure is essential to the antifungal activity.


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SYNTHESIS AND REACTIVITY OF 4-HYDROXY-3-METHOXYAMPHETAMINE A “ECTASY” METABOLITE

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3,4-Methylenedioxymethamphetamine (MDMA or “Ecstasy”), is a widely abused, psychoactive recreational drug. There is growing evidence that MDMA neurotoxic profile may be highly dependent on its systemic metabolism.¹ Metabolism of MDMA involves N-demethylation to 3,4-methylenedioxyamphetamine (MDA). MDMA and MDA are O-demethylenated to N-methyl-α-methyldopamine (N-Me-α-MeDA) and α-methyldopamine (α-MeDA), respectively, both of which are catechols that can undergo oxidation to the corresponding o-quinones. The catecholic compounds can undergo subsequent O-methylation mediated by catechol-O-methyltransferase (COMT) to 4-hydroxy-3-methoxyamphetamine (3-OMe-α-MeDA) and 4-hydroxy-3-methoxyamphetamine (3-OMe-N-Me-α-MeDA). These metabolites are excreted in the urine. Nevertheless the toxicity mediated by these metabolites as also their conjugated thioethers of biological nucleophiles, remain to be completely elucidated.² Herein we report the synthesis of 3-OMe-α-MeDA and 3-OMe-N-Me-α-MeDA and their reactivity in the presence of oxidants and glutathione (vide Scheme).

SYNTHESIS OF β-BROMO AND β-IOODO β-SUBSTITUTED DEHYDROAMINO ACID DERIVATIVES

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In recent work, we have been interested in the synthesis of β-halogenated dehydroamino acid derivatives that can be used as substrates in palladium catalysed cross couplings [1,2]. The synthesis of β-bromodehydroamino acids has been carried out reacting dehydroamino acid derivatives with N-bromosuccinimide (NBS), followed by treatment with NEt₃. β-Alkyl, β-bromo and β-aryl, β-bromodehydroalanines were prepared in good yields (Scheme 1, Table 1). The stereochemistry of the β-halogenated dehydroamino acids obtained was determined using NOE difference experiments by irradiating the α-NH and the OCH₃ protons and observing the effect on the β-methyl and β-phenyl protons. A high selectivity towards the Z isomer was observed for the dehydrophenylalanine derivatives and when the 4-toluenesulphonyl group is used as protecting group. The same reaction with N-iodosuccinimide (NIS) gave the corresponding β-iodo, β-substituted dehydroamino acids in good to high yields. A higher Z stereoselectivity for the β-iododehydroamino acids was found, thus in the case of Z(NO₂)-∆Abu(β-I)-OMe and of Boc-∆Phe(β-I)-OMe only the Z-isomer was isolated.

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield / %</th>
<th>E/Z ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boc-∆Abu(β-Br)-OMe</td>
<td>92</td>
<td>1/1</td>
</tr>
<tr>
<td>Z(NO₂)-∆Abu(β-Br)-OMe</td>
<td>80</td>
<td>1/1</td>
</tr>
<tr>
<td>Tos-∆Abu(β-Br)-OMe</td>
<td>94</td>
<td>1/9</td>
</tr>
<tr>
<td>Boc-∆Phe(β-Br)-OMe</td>
<td>97(2)</td>
<td>1/2(2)</td>
</tr>
<tr>
<td>Tos-∆Phe(β-Br)-OMe</td>
<td>78</td>
<td>Only Z</td>
</tr>
<tr>
<td>Boc-∆Abu(β-I)-OMe</td>
<td>88</td>
<td>1/3</td>
</tr>
<tr>
<td>Z(NO₂)-∆Abu(β-I)-OMe</td>
<td>96</td>
<td>Only Z</td>
</tr>
<tr>
<td>Boc-∆Phe(β-I)-OMe</td>
<td>87</td>
<td>Only Z</td>
</tr>
</tbody>
</table>

β-Halogenated dehydrodipeptides were prepared by reacting Boc-Gly-∆Abu-OMe with NBS or NIS followed by treatment with NEt₃. The β-bromo and β-iodo dehydrodipeptides were obtained in good yields, 90% and 76%, respectively. The E/Z ratio was 1/1 for bromination and in the case of the reaction with NIS only the Z isomer was isolated. Now we are extending the reaction with NIS to other dehydrodipeptides with different amino acids and different protecting groups.


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Epoxides are very useful intermediates for the synthesis of biologically active compounds, namely pharmaceuticals and agrochemicals. The asymmetric epoxidation of alkenes with chiral transition metal complexes is a very efficient method for obtaining chiral epoxides.

Our interest in asymmetric synthesis and catalysis led us to prepare a series of new chiral salen ligands, Scheme 1, derived from (1R,3S)-1,3-diamino-1,2,2-trimethylcyclopentane 2, a diamine which is easily obtained from camphoric acid 1. The reaction of this diamine with several salicylaldehyde derivatives 3a-d allowed us to obtain the chiral salens 4a-d in very good yields. Salens 4e and 4f were also obtained by reaction of 2 with 2-hydroxynaphthaldehyde 3e and acetophenone 3f, respectively.

The Mn(III) complexes of the new chiral salen ligands were prepared and tested as catalysts for the epoxidation of styrene. The synthesis of the ligands, the corresponding complexes and the results of the catalytic oxidations will be presented in this communication.

SYNTHESIS OF 4H-CHROMENES WITH POTENTIAL BIOLOGICAL ACTIVITY

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The chromene moiety often appears as an important structural component in both biological active and natural compounds like chromanes, 2H-chromenes and 4H-chromenes as well as a key intermediate in the synthesis of medicinal reagents. [1-2] Fused chromenes have a wide spectrum of biological activities namely antimicrobial, antiviral, antiproliferative among others and recently they were identified as anticancer agents. [3-4] The synthesis of 4-aryl-4H-chromenes their characterization as well as some preliminary biological studies will be presented.

\[
\begin{align*}
R \quad &+ \quad \text{EtOH} \\
\text{CHO} \quad &\rightarrow \quad \text{R} \quad \text{CN} \\
\text{R}^1 \quad &\quad \text{NH}_2 \\
\text{HO} \quad &\quad \text{CN}
\end{align*}
\]

R, R¹ = different substituents

SYNTHESIS OF 1,8-DIARYLNAPHTHALENES BY THE SUZUKI CROSS COUPLING REACTION


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The π-π stacking interaction between adjacent aromatic moieties is a very interesting concept in the fields of chemistry and biochemistry.[1] Its importance in biological systems and crystal packing is known but the nature of this interaction is yet to be completely understood. In the 1,8-diarylnaphthalenes, despite of the steric repulsion, the two parallel aromatic substituents can interact favourably by π-π stacking.[2] Using the experimental values of the standard molar enthalpies of formation on the gaseous phase, \( \Delta f^\circ H(g) \), the magnitude of this interaction can be evaluated. Once these compounds are not commercially available and the synthesis of some of them were never reported in the literature we decided to synthesize them by the Suzuki cross coupling reaction, starting from 1,8-dibromonaphthalene, using a variety of synthetic approaches. The mono-substituted analogues were also synthesized by the same reaction mechanism using 1-bromonaphthalene as the starting aryl halogenated reagent.

\[
\begin{align*}
\text{cat.} & = \text{Pd(OAc)}_2, \text{PdCl}_2(\text{dppe}) \\
\text{solvent} & = \text{H}_2\text{O}/\text{DMF, Toluene/H}_2\text{O} \\
\text{Ar} & = \text{phenyl, biphenyl, thiophene, pyridine}
\end{align*}
\]


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SYNTHESIS OF GLYCO CHLORIN DERIVATIVES AND THEIR BIOLOGICAL ACTIVITY AGAINST HSV-1

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Porphyrrins and their derivatives (e.g. chlorins) have been intensively studied due to their applications mainly in photodynamic therapy, where they can act in the elimination of microorganisms such as virus [1,2]. Herpes simplex virus type 1 (HSV-1) with the passing of the years have become resistant against the available antiviral compounds. [3]

In the present work we report a new and easy synthetic route for N-glycoconjugated pyrrolidine chlorin with MAOS approach and also for the desprotection of the corresponding cationic compound. Besides the two compounds we also synthesised another chlorins already described in literature [4,5] to be used for the assay \textit{in vitro} to look for their ability to inhibit HSV-1 infectivity. In this communication we show relevant aspects of their cytotoxicity with and without photoactivation as well as their effect against HSV-1. Studies using scanning electron microscopy are being done to evidence some possible alterations on the morphology of cell surfaces.


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**SYNTHESIS OF NEUROSTEROID RING A ANALOGUES: MODULATORS OF \( \text{GABA}\_A \) RECEPTORS**

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\( \gamma\)-Aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the brain, involved in controlling many conditions ranging from anxiety to epilepsy. The effects of GABA can be magnified by several types of compounds (e.g. benzodiazepines), which bind to \( \text{GABA}\_A \) receptors. Some metabolites of progesterone, like 3\(\alpha\)-hydroxy-5\(\alpha\)-pregnan-20-one (‘allopregnanolone’), also bind allosterically to the \( \text{GABA}\_A \) receptor and increase the inhibitory effects of GABA by opening the membrane chloride ion channel with little tolerance (1,2).

The relevance of CNS diseases has motivated intense research towards the synthesis of allopregnanolone analogues aiming longer half-lives and better solubilities in the body liquids, besides a good affinity to the \( \text{GABA}\_A \) receptor (3,4). Neuroactive steroids have drawn our attention and in this communication we report the synthesis of a library of allopregnanolone analogues, with structural modifications at the ring A, as potential modulators of the \( \text{GABA}\_A \) receptor. Chemo- and enzymatic processes developed in our lab, as ring-opening of epoxides (5,6), and lipase-catalysed reactions (7), were adapted to produce the desired steroids. The modulation of the \( \text{GABA}\_A \) receptor will be assessed by the \( ^{35}\text{S}\)TBPS test and the results will allow us to set up structure-activity relationships and to design new molecules.


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SYNTHESIS OF NEW ACRIDONES FROM DIELS-ALDER REACTIONS OF 1-METHYL-2-STYRYL-4-QUINOLONES

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Acridones and 4-quinolones are classes of nitrogen heterocyclic compounds possessing important biological activities. Acridone derivatives are known to present a significant citotoxic, antiviral and anti-malarial activities [1] and 4-quinolones has been used as antibacterial agents, having an important role in the treatment of urinary infections [2]. The search of new 4-quinolone derivatives has been carried out to improve the spectrum of antimicrobial activity against Gram-negative as well as Gram-positive bacteria [3]. Recent studies also revealed a new potential application for these types of compounds as anti-tumour agents [4,5].

In this communication, we present the synthesis of 2-styryl-4-quinolones 2a-d, from 2'-aminoacetophenone and the appropriate cinnamic acids, and the reactivity of the N-protected derivatives 3a-d as dienophiles in Diels-Alder reactions with N-methylmaleimide. New acridone derivatives 5a-d have been obtained in good yields. Synthetic procedures and structural characterization of the obtained compounds will be presented and discussed in this communication.

Acknowledgements: Thanks are due to the University of Aveiro, FEDER and FCT for funding the project POCI/QUI/58835/2004 and the Organic Chemistry Research Unit.

SYNTHESIS OF NEW CALIX[4]PYRROLE DERIVATIVES THROUGH 1,3-DIPOLAR CYCLOADDITIONS

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Calixpyrroles (meso-octasubstituted porphyrinogens) are a kind of tetrapyrrolic macrocycles, synthesized for the first time by Baeyer in the XIXth century[1]. They have recently gained significant attention due to its ability to bind small anions[2]. In this communication we describe the synthesis of new calyx[4]pyrrole derivatives using as starting material the 2-formyl-octamethylcalix[4]pyrrole 1[3]. This compound was converted into the corresponding azomethine ylide 2, which was trapped in situ with dipolarophiles to afford cycloadducts 3. Details of the synthesis, structural characterization and anion binding studies of the new compounds will be presented and discussed.


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SYNTHESIS OF NEW CORROLE DERIVATIVES VIA CYCLOADDITION REACTIONS

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Corroles continue to attract increasing interest mainly due to the development of new significant synthetic routes and also to their promising applications in catalysis and medicine. The search for functionalization procedures leading to new derivatives plays a key role in finding compounds with new potential applications. We have shown that porphyrinic macrocycles can participate in both Diels-Alder and 1,3-dipolar cycloaddition reactions. Due to structural similarities between porphyrins and corroles we have decided to look for the behaviour of the latter ones under similar reaction conditions. We also have demonstrated that corroles can participate in Diels-Alder and thermal [4+4] cycloaddition reactions.

Here we report that β-formylcorrole 1 reacts with N-methylglycine generating in situ the corresponding azomethine ylide. This 1,3-dipole participates in 1,3-dipolar cycloaddition reactions with several dipolarophiles (dimethyl fumarate, dimethyl acetylenedicarboxylate, C₆₀ fullerene, 1,4-benzoquinone, 1,4-naphthoquinone and 1,4-anthraquinone) affording the corresponding cycloadducts 2-6 and 8. In the two latter cases not only the expected 1,3-dipolar cycloadducts were obtained but also two new unexpected products (7 and 9). We believe that they result from the 1,5-electrocyclization of the azomethine ylide, giving rise to a pyrrolo[3,4-b]corrole, which then undergoes a Diels-Alder reaction with 1,4-naphthoquinone and 1,4-anthraquinone, with subsequent deamination.


Acknowledgments: Thanks are due to the University of Aveiro, Fundação para a Ciência e a Tecnologia (FCT) and FEDER for funding the Organic Chemistry Research Unit and the project POCI/QUI/57589/2004.
SYNTHESIS OF NEW DELOCALISED CATIONIC AZO DYES

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Nevertheless the enormous synthetic versatility of azo dyes, which has turn them into the most widely used dye class, they have scarcely been modified to display absorption into the near infrared. Their aptitude as sensitizers for Photodynamic Therapy (PDT) has rarely been explored and, so far, no delocalized cationic azo dyes appear to have been studied for that purpose.

Following our interest in the development of alternative sensitizers for PDT, we addressed to the synthesis of novel delocalized cationic monoazo dyes displaying absorption in the phototherapeutic window (600-1000 nm). A bathochromic thiazole ring was incorporated in the chromophoric system of the dye to shift the dye’s absorption into the long-wavelength region.

The synthetic strategy involved the formation of an intermediate azo dye (1) bearing a terminal formyl group to allow the extension of the conjugation through condensation with an active methylene benzoazolium quaternary. By this procedure several delocalized cationic monoazo dyes (2), displaying intense absorption (log ε > 5.61) in the range 650-750 nm, were obtained in rather good yields (Figure).

This methodology constitutes an alternative to that traditionally employed in the synthesis of delocalized cationic azo dyes, which generally involves the regioselective alkylation of disperse azo dyes.

Z = S, Se, CMe₂, CH=CH; R₁ = H, Cl; R₂ = H, I; R₃ = Et, Hex.

Figure


Acknowledgments: Fundação para a Ciência e a Tecnologia, POCI 2010 and FEDER are greatly acknowledged for the funding of the Project (POCI/QUI/57913/2004).
SYNTHESIS OF OLIGOTHIENYL-CROWN ETHER DERIVATIVES DESIGNED FOR METAL ION DETECTION

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Detection of cations is of great interest in several areas. The ability of crown ethers to complex cations has been exploited to produce chemosensors for cation recognition and extraction, for analytical, environmental and medical applications [1].

During the last years we have been concerned with the synthesis and characterization of several functionalized heterocyclic compounds containing the thiophene nucleus due to their potential applications as nonlinear optical chromophores, organic conductors, solvatochromic and fluorescence probes and organic light emitting diodes (OLED’s) [2-8]. We were therefore motivated to explore the potential of conjugated luminescent (oligo)thiophene units as pendant substituents on amine-crown ether derivatives as new chemosensors for cations. The tertiary amines 2a-c were synthesized by reductive amination of the corresponding macrocycles with formyl thiophene derivatives 1a-c in the presence of NaBH(OAc)₃ at room temperature (Scheme), in fair to good yields and completely characterized by the usual spectroscopic and analytical techniques.

Recent evaluation of compounds 2a-c as fluorimetric sensors for cations proved that they could be used as efficient chemosensors, especially compound 2b in the presence of H⁺, Na⁺, Pd²⁺ and Zn²⁺ [8].

Acknowledgments: Thanks are due to Fundação para a Ciência e Tecnologia (Portugal) for financial support through Centro de Química (Universidade do Minho).
SYNTHESIS OF PEPTIDES WITH $\alpha,\alpha-\text{DIALKYL}$ AND $N,\alpha,\alpha-\text{TRIALKYL}$ GLYCINES

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$\alpha,\alpha$-Dialkyl glycines are useful moieties for the synthesis of peptide mimetics. However, most of these amino acids cannot be obtained commercially and, owing to steric crowding, are difficult to synthesise and difficult to use in the synthesis of peptides by conventional methods. This can be overcome by taking advantage of the strategy developed in our laboratory based on the Ugi-Passerini reaction, which, in a two-step synthesis, allowed to obtain N-acyl-$\alpha,\alpha$-dialkyl glycines ready for further coupling at their C-terminus. These substrates include peptide acids with a C-terminal $\alpha,\alpha$-dialkyl glycine residue.[1,2]

By taking advantage of this strategy, we were able to synthesise, in fair to good yields, a series of these peptide acids having one of the following amino acid residues at their C-terminus:[3] dimethyl, diethyl, dipropyl, diisobutyl and dibenzyl glycine. These peptides were elongated by coupling with a C-protected amino acid or preformed peptide.

Taking the previous approach even further, a series of peptides having a C-terminal $N,\alpha,\alpha$-trialkyl glycine were obtained and coupled with H-Phe-OtBu.


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SYNTHESIS OF 2-QUINOLONES FROM THE METHYL ESTER OF N-BOC-β,β-DIBROMODEHYDROALANINE AND 2-(PINACOLBORONATE)ANILINE

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In our laboratories we have been interested in the synthesis of heterocyclic compounds from β,β-dibromodehydroalanines using palladium-catalyzed and assisted reactions [1]. Recently we have prepared several 3-arylindole-2-carboxylates using a bis-Suzuki coupling followed by an intramolecular Pd/Cu-assisted C-N cyclization [2]. Here we present the “one pot” palladium-catalyzed synthesis of two 2-quinolones from the methyl ester of N-(t-butoxycarbonyl)-β,β-dibromodehydroalanine and 2-(pinacolboronate)aniline. The reactions involve Suzuki couplings and lactamization by nucleophylic attack of the amino group on the carbonyl of the ester, with loss of methanol.

\[
\text{Br}_2\text{Br} \quad \text{NH}_2\text{BO} \quad \text{O} \\
\text{H} \quad \text{N} \quad \text{COOCH}_3 \quad \text{Boc} \\
\text{H} \quad \text{N} \quad \text{Boc} \quad \text{NH}_2 \quad \text{NH}_2 \quad \text{NH} \\
\text{Boc}^+ \quad \text{NH} \quad \text{O} \\
\text{H} \quad \text{N} \quad \text{Boc} \quad \text{NH}_2 \quad \text{NH} \\
\text{Boc} \quad \text{NH} \quad \text{O} \\
\text{H} \quad \text{N} \quad \text{Boc} \quad \text{NH}_2 \quad \text{NH} \\
\text{Boc} \quad \text{NH} \quad \text{O} \\
\text{H} \quad \text{N} \quad \text{Boc} \quad \text{NH}_2 \quad \text{NH} \\
\text{Boc} \quad \text{NH} \quad \text{O}
\]

i) 20mol% PdCl\(_2\)(dppe).CH\(_2\)Cl\(_2\) (1:1), 1.4 equiv. Cs\(_2\)CO\(_3\), THF/H\(_2\)O (1:1), 3h, 90 °C.

The compounds obtained were separated by column chromatography and were characterized by \(^1\)H, \(^{13}\)C NMR and HRMS.

These 2-quinolones were obtained by a new method and will be submitted to biological activity studies.


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SYNTHESIS OF SOME NOVEL PYRAZOL-[3,4-d]PYRIMIDINE DERIVATIVES WITH POTENTIAL BIOLOGICAL ACTIVITY.

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In recent years, pyrazolopyrimidines and related fused heterocycles are of interest as potential bioactive molecules. They are known to exhibit agrochemical and pharmaceutical activities such as CNS depressant, neuroleptic, and tuberculostatic.\(^1\) Pyrazolo[3,4-d]pyrimidines were identified as a general class of adenosine receptors.\(^2\) Their structures are similar to purines. Moreover, in recent years, fluorinated compounds find much importance in the pharmaceutical field.\(^3\) The introduction of a CF\(_3\) group provides compounds with increased lipophility and activity when compared to their non-fluorinated analogues.

The 5-amino-4-cyanopyrazoles 1 were reacted with triethylorthoformate to give the corresponding ethoxymethylene amino derivatives 2 which are the key compounds for cyclization using hydrazine to afford 4-imino-pyrazolo[3,4-d]pyrimidines 3 and phenylhydrazine derivatives to give a mixture of the Dimroth rearrangement products 4 together with its oxidized forms 5.\(^5\)\(^6\)

![Chemical structures](image)

To confirm the structure of compounds 4 an independent route was followed reacting 4-chloropyrazolopyrimidine with \(p\)-tolylhydrazine, and the product isolated was the pyrazolo[3,4-d]pyrimidine 4a, whose spectral characteristics were completely coincident with those found for the product which was prepared before. The structures of the compounds obtained were confirmed by IR, Mass spectrometry, \(^1\)H and \(^13\)C NMR.

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SYNTHESIS, PURIFICATION AND ANALYSIS OF PROCESS IMPURITIES IN MINOCYCLINE

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Minocycline is a potent semisynthetic derivative of tetracycline with a broad antibacterial spectrum.

Synthetic pathways, using demeclocycline as starting material, indicate that 6-deoxy-6-demethyltetracycline, 7-didemethylminocycline and 7-monodemethyl minocycline are potential by-products and constitute the main impurities of antibiotic.

We isolated each one of these compounds in two steps:
1) promoting their formation within the synthetic pathway
2) separating the compound of interest using preparative HPLC.

All these compounds were analysed by HPLC and mass spectrometry.

Minocycline: R₁ = N(CH₃)₂, R₂ = H, R₃ = N(CH₃)₂
6-deoxy-6-demethyltetracycline: R₁ = H, R₂ = H, R₃ = N(CH₃)₂
7-didemethylminocycline: R₁ = NH₂, R₂ = H, R₃ = N(CH₃)₂
7-monodemethyl minocycline: R₁ = NHCH₃, R₂ = H, R₃ = N(CH₃)₂

Acknowledgments: Thanks are due to Cipan and Fundação para Ciência e Tecnologia (BDE / 15515 / 2004)
THE CAHN-INGOLD-PRELOG SYSTEM:
HISTORY AND RECENT DEVELOPMENTS

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The Cahn, Ingold and Prelog (CIP) System was originally proposed in 1951\(^1\) for the description of the relative configuration of chiral molecules. Soon after this, methods became available to determine absolute configurations\(^2\) and an adaptation of the system to this new situation was proposed in 1956.\(^3\) The system was soon widely adopted by chemists, and the experience accumulated with its use, coupled with new developments in chemistry, were the causes for its two revisions in 1966\(^4\) and 1982.\(^5\) Each of these revisions contributed to improve its logic, consistency, scope and applicability, and in fact the 1982 version enabled the specification of the great majority of the stereogenic units commonly encountered in organic molecules. Several authors have, however, reported examples of structures for which specification is impossible, ambiguous or inconsistent by using the 1982 CIP System\(^6-12\). To overcome these problems, we have proposed extensions and modifications to the CIP Sequence Rules\(^8,9,12\).

In this presentation, focusing on the specification of stereogenic centres, the history of the evolution of this nomenclature system is briefly outlined and our proposals for the modification of the Cahn-Ingold-Prelog Sequence Rules are described. The specification of a set of representative stereogenic centres is also presented in order to highlight shortcomings of the System and illustrate the strengths of our proposals.

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THE REARRANGEMENT OF C-VINYLPYRROLES TO C-ALLYLPYRROLES

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We have recently reported the reactivity of azafulvenium methides (2) generated by the thermal extrusion of sulfur dioxide from 1-methyl- and 1,1-dimethyl-1H,3H-pyrrolo[1,2-c]thiazole-2,2-dioxides. These transient 8π 1,7-dipoles undergo [1,8]H sigmatropic shifts to give vinylpyrroles. The flash vacuum pyrolysis (FVP) of sulfone 1a leads to C-vinyl-1H-pyrrole 3a and C-allyl-1H-pyrrole 4a. Under FVP conditions, 3a can also be converted into pyrrole 4a proving that 3a is an intermediate in the synthesis of compound 4a from sulfone 1a. The thermal reaction of 1,3-dimethyl-1H,3H-pyrrolo[1,2-c]thiazole-2,2-dioxide 1b affords the corresponding C-vinylpyrrole and N-vinylpyrrole via two competitive [1,8]H sigmatropic shifts, although the major product is pyrrole 4b, obtained in 58% yield.

The study was extended to the thermolysis of new 1,1-dimethyl-1H,3H-pyrrolo[1,2-c]thiazole-2,2-dioxides in order to evaluate the scope of the interesting rearrangement of C-vinylpyrroles to C-allylpyrroles. New allylpyrroles 4c-e were obtained, in the thermolysis under FVP conditions of sulfones 1c-e, through the rearrangement of vinylpyrroles 3c-e. In this communication details of this study will be presented.

\[
\begin{align*}
\text{Me} & \quad \text{R}^1 \quad \text{R}^4 \quad \text{CO}_2 \text{R} \\
\text{O}_2 \text{S} & \quad \text{R}^2 \quad \text{R}^3 \quad \text{N} \\
1 & \quad \text{FVP} \\
& \quad \text{SO}_2 \\
\end{align*}
\]


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\[
\begin{align*}
a & : R^1 = R^3 = \text{Me}; R^2 = \text{Ph}; R^4 = \text{CO}_2 \text{Me} \\
b & : R^1 = \text{H}; R^2 = R^3 = \text{Me}; R^4 = \text{CO}_2 \text{Me} \\
c & : R^1 = R^2 = \text{Me}; R^3 = \text{p-F-C}_6 \text{H}_4; R^4 = \text{CO}_2 \text{Me} \\
d & : R^1 = R^2 = \text{Me}; R^3 = \text{p-F-C}_6 \text{H}_4; R^4 = \text{Ph} \\
e & : R^1 = R^2 = \text{Me}; R^3 = \text{Ph}; R^4 = \text{CO}_2 \text{Me}
\end{align*}
\]
TRANSFORMING ORGANIC REACTIONS INTO NUMBERS:
APPLICATION TO GENOME-SCALE MAPPING OF ENZYMATIC REACTIONS

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MOLMAP descriptors can represent reactions by numbers, based on the changes occurring in the physicochemical and topological properties of chemical bonds when reactants are transformed into products.\(^1\) MOLMAPs use self-organizing maps (SOMs) to compare the bonds available in the reactants with the bonds available in the products – the difference is taken as a representation of the reaction. Such a numeric fixed-length representation enables the automatic comparison of reactions in large databases.

We explored MOLMAP descriptors for data mining databases with metabolic reactions\(^2\) (basically organic reactions), in order to identify similarities between reactions, to extract knowledge about the metabolic reactivity, and to compare reactomes of different organisms. The encoding and classification of enzymatic functions, i.e. metabolic reactions, is crucial in the reconstruction of metabolic pathways from genomes, in the comparison of reactomes, or in the design of biotechnological processes.

Here we report the latest developments of the method applied to a genome-scale database. A dataset of 3784 enzymatic reactions extracted from the KEGG database were represented in both directions by MOLMAP descriptors (yielding a dataset of 7568 reactions). These were submitted to Self-Organizing Maps (SOMs) and Random Forests (RFs) for reaction classification in terms of official Enzyme Commission (EC) numbers. The mapping of the genome-scale dataset of enzymatic reactions by a SOM provides an intuitive visualization of similarities and differences between reactions, and highlights similar reactions hidden by different EC numbers. In general, the approach showed a good compatibility with the EC numbers, allowing for accurate predictions of EC numbers from the reaction equation, at the four levels of the EC hierarchy. A web interface for automatic classification of enzymatic reactions, and retrieval of similar known reactions was developed (http://neural.dq.fct.unl.pt/metabolic).

References:


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TUNING THE REACTIVITY OF DI-RHODIUM (II) COMPLEXES WITH AXIAL NHC LIGANDS: THE ARYLATION OF ALDEHYDES


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In this study we show that NHC ligands, in particular NHC - IPr 1 (Scheme 1), can efficiently coordinate with di-rhodium(II) complexes and tune their reactivity generating a new family of complexes, with remarkably activity in the arylation of a variety of aryl and alkyl aldehydes, at considerable mild conditions (Scheme 1).

Scheme 1.

The near-perfect structural match between Rh₂(OAc)₄ and NHC IPr found in the X-ray structure of 1 and in the calculated geometry of Rh₂(OAc)₄(NHC IPr) 2, as well as the electronic structure of this species may explain the effectiveness of this system as reaction catalyst (Scheme 2). This study highlights, an unprecedented reaction mode for di-rhodium(II) dimmers.

Scheme 2.


ORGLIST – an international virtual community of organic chemists

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During the last ten years chemists from all over the world have gathered in ORGLIST (www.orglist.net) to discuss Organic Chemistry. ORGLIST is a discussion forum implemented as a free Internet mailing list (listserv). Anyone can subscribe to the list and only the members have the privilege to post (email) messages to the forum. Useful content, as well as a complex thread of personal relationships, emerged from the interaction of the members through this simple technological framework. ORGLIST is in fact a virtual community of organic chemists where many interesting problems and questions have been raised and where practicing chemists have found help for their work.

ORGLIST has currently a fluctuating size around 950 members (with valid email addresses), and an average traffic of 1 message/day. Interestingly, the current list of subscribers include 42 email addresses (scattered through four continents) that were already in the list in 1998. We also found that more than 50% of the current members were already members of the list in 2004. Geographically, in 2007 ca. 25% of the subscribers belong to European domains, ca. 40% belong to common public e-mail providers, and ca. 20% are from other US domains (including .com). Analysis of the hour of posting also reveals an overlap with work hours in Europe and US.

In one way ORGLIST can be seen as a unique resource for finding information, quite different from literature or web searching procedures. An Internet mailing list allows for fast and world wide "community searches" through the pool of diverse knowledge, intelligence, wisdom, and intuition of their members. Furthermore, the 10-years full archive of more than 4600 messages is available at the web site and is indexed by Google. ORGLIST archive has undoubtedly become a reference in Organic Chemistry.

The success of ORGLIST resides on email. Email has established itself as one of the most important ways of direct communication between scientists. Its almost universal availability, low cost, asynchronous nature, quickness, informality and the possibility of exchanging electronic documents completely revolutionized our concept of "contacting someone". It is probably the Internet tool most integrated into information processing routines of common chemists. It is a daily routine for virtually everyone in science. Based on email, ORGLIST reaches the daily lives of hundreds of subscribers, allowing for quick useful answers to posts, and making users feel part of a community. And 10 years of history deepens this sense of belonging.

In this poster, ORGLIST will be described and more detailed statistics will be presented.
UNUSUAL GAS-PHASE BEHAVIOUR OF A PYRIMIDINE-AMINOACID C\textsubscript{60} ADDUCT: A STUDY BY ELECTROSPRAY MASS SPECTROMETRY

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The synthesis of organic derivatives of fullerenes has been an area of growing interest over the past decades. In special the C\textsubscript{60} adducts with substituted pyrimidines, are potential inhibitors of the HIV protease.\textsuperscript{1} The characteristic physicochemical properties of fullerenes that makes them interesting potential pharmacophores (drug carriers)\textsuperscript{2,3} entail, on the other hand, restrictions for their analysis by ESI-MS (Electrospray Mass Spectrometry) so that C\textsubscript{60} derivatives were considered to be “ESI-inactive” compounds. Thus it is not surprising that most of the studies by ESI-MS of C\textsubscript{60} derivatives report the formation of radical cations/anions prior to mass analysis. Nevertheless the direct analysis (without performing charge transfer reactions) of C\textsubscript{60} neutral derivatives as their molecular open shell ions, M\textsuperscript{+} and M\textsuperscript{-}, in the positive and negative modes, respectively, was reported before\textsuperscript{4}.

We report here the study of a fullerene exohedral derivative (see figure) by ESI-MS and ESI-MS/MS (Electrospray Mass Spectrometry/Mass Spectrometry) in the positive mode. We have obtained the protonated closed shell species, [M+H]\textsuperscript{+}, and [M+2H]\textsuperscript{2+}, from slightly acidic solutions.

These species were mass selected and subjected to low energy collisions in the hexapole cell of a Q-Tof (Quadrupole-Time-of-Flight) mass spectrometer. The fragmentations observed showed some interesting features. Loss of the non-fullerene moiety, with formation of the [C\textsubscript{60}+H]\textsuperscript{+} is observed but it is not a predominant process. Instead ions formed by loss of C\textsubscript{60} through double retro Diels-Alder reactions are observed along with other fragments of the non-fullerene moiety. The same type of fragmentation occurs for both the singly and doubly charged ions. To our knowledge this type of fragmentation was not reported before. We have found that ESI-MS/MS is a suitable technique for the characterization of this exohedral C\textsubscript{60} derivative.

References:

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Lupinus seeds are important food and feed components with high nutrient value that is comparable to soybean. The bitter taste of the seeds is imparted by the quinolizidine alkaloids (QA) mainly lupanine that is a valuable starting material for the hemisynthesis of other alkaloids. *Lupinus albus* species is endemic in Iberic Peninsula and for consumption must be subject to extensive debittering by leaching in water. The debittering process is performed in large scale and the waste waters are discarded or finds some application in agriculture as fertilizer or in plant protection.

Concentration of debittering effluents of *L. albus* was accomplished by osmotic evaporation (OE), using a 5 M solution of CaCl₂. In this process, a porous hydrophobic membrane separates a diluted aqueous solution from a concentrated osmotic solution. A membrane contactor (0.23 m²), with hydrophobic polypropylene fibres was used to evaporate water from the effluent to the osmotic solution. The experiment was carried out during 45 h due to the low membrane area employed compared to the volume processed (3 L). The concentration factor obtained was 16. The time can be reduced using a contactor with a higher area. A 1 m² contactor can accomplish the same concentration factor in only 9 h. The initial flux obtained in the concentration process was 8x10⁻⁸ m³/(m² s), however due to presence of other components in the effluent (oligosaccharides, amino acids and proteins) the flux was reduced to 4x10⁻⁸ m³/(m² s) in the last 10 h.

Lupanine occurs in both enantiomeric forms and the proportion of each enantiomer is different between Lupinus species. In the leaching waters that we have studied lupanine is present in a proportion of 1 g / L and (-)-lupanine is the predominant enantiomer. The enantiomeric excess is near 33 % of the *levo* enantiomer. The enantiomers were resolved by crystallization of their dibenzoyltartrate derivatives.

\[\begin{align*}
\text{(-)-(6S,7R,9R,11S)-lupanine} & \quad \text{(+)-(6R,7S,9S,11S)-lupanine}
\end{align*}\]

SYNTHESIS OF CATIONIC AND PERMETHYLATED CHLORINS

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Tetrapyrrolic macrocycles constitute a large family of natural compounds in Nature [1-3] of which common examples are the hemoproteins, cytochromes, vitamin B\textsubscript{12} and chlorophylls. Uses of tetrapyrrolic compounds in Medicine (e.g., in cancer treatment and detection) are of great significance [3], but novel and efficient compounds are required. Also water-soluble compounds are more attractive for medical applications [3]. Chlorins (dihydro-type porphyrins) are good candidates since their electronic spectra present a good absorption band in the so-called “therapeutic window” (λ\textsubscript{abs}>600 nm). As it was shown by the Aveiro group, an easy way for obtaining chlorins is the cycloaddition reaction of porphyrins with azomethine ylides (Scheme 1) [4,5]. Here we describe the synthesis of a water-soluble tetracationic, permethylated chlorin and a few of its metallocomplexes. The synthetic methodology, spectroscopic and photophysical analysis will be discussed.

![Scheme 1. Synthesis of permethylated cationic chlorin (free-base (\(M=H\)) and metallated (\(M=Zn^{(II)}\))](image)

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OXIMES OF GLYOXYLATES AS DIENOPHILES IN AZA-DIELS-ALDER REACTIONS

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In the last years, our research group has been interested in the synthesis of 2-azabicyclo[2.2.1]heptenes and its derivatives as synthetic intermediates in the preparation of a great variety of compounds of chemical, pharmaceutical and biological interest. In particular, 2-functionalized 3,5-bis(hydroxymethyl)pyrrolidines (glycomimetics) can be obtained through bis-hydroxylation of the C₅-C₆ bond of 2-azabicyclo[2.2.1]hept-5-ene-3-carboxylates followed by oxidative cleavage of the corresponding diols and in situ reduction of the resulting intermediates (dialdehydes).

In this work we describe the synthesis of 2-azabicycloalkenes from aza-Diels-Alder reaction between cyclopentadiene and oximes of glyoxylates. These compounds represent an important group of sytonns useful in the preparation of aminoalcohols derived from pyrrolidine necessary for the synthesis of azanucleosides and/or iminosugars.

References:


SYNTHESIS, CONFORMATIONAL ANALYSIS AND METAL CATION BINDING PROPERTIES OF A NEW HOMOOXACALIX[3]ARENE TRIKETONE DERIVATIVE BY PROTON NMR STUDIES

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In the field of host-guest chemistry, many studies have focussed on the binding ability of calixarenes bearing carbonyl groups at their lower rims towards metal ions [1]. For some years we have been synthesising dihomooxacalix[4]arene derivatives containing carbonyl groups at the lower rim and studying their binding properties towards alkali, alkaline earth, transition and heavy metal cations [2-4]. In the course of these studies, we have now extended our research to the study of hexahomotrioxacalix[3]arenes [5]. We present in this work the synthesis, the conformational analysis and the binding properties towards alkali and alkaline earth metal cations of adamantylketone 2.

Ketone 2 was synthesised for the first time. Treatment of p-tert-butylhexahomotrioxacalix[3]arene (1) with 1-adamantyl bromomethyl ketone and NaH in THF at reflux for 24 h furnished compound 2. Proton and carbon-13 NMR spectra were carried out in chloroform at room temperature, indicating a cone conformation for ketone 2. The binding properties of 2 have been assessed by proton NMR titration experiments. Variable amounts of the metal salts (Na+, K+, Ca2+, Sr2+ and Ba2+) were added into the NMR tubes containing the ligand, and the spectra recorded after each addition. These titrations indicated 1:1 complexes with all cations.

The results are compared to those obtained with other homooxacalixarene analogues.

NEW APPROACHES FOR METALLOPORPHYRIN CATALYSED OXIDATION REACTIONS

Mário M.Q. Simões, Domingos M.A. Silva, Rodrigo De Paula, Augusto C. Tomé, M. Graça P.M.S. Neves, José A.S. Cavaleiro

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An important challenge for green chemistry is the finding of alternatives to the common oxidation synthetic methodologies, based on stoichiometric oxidants that lead to large amounts of non-biodegradable by-products [1]. The use of \( \text{H}_2\text{O}_2 \) as a cheap, environmentally clean and easy to handle oxidant [2], in conjugation with robust and easily obtainable metalloporphyrins as catalysts, led to efficient procedures to perform many oxidative reactions [3-5]. In some cases the role of a co-catalyst has shown to be essential [4], either by speeding up the reaction or by changing the stereoselectivity [6]. However, the potentiality of these systems can be highly increased by anchoring the catalyst to a solid support, thus allowing its easy recovery and reuse. Moreover, the local environment of the support can bring higher selectivity and prevention of catalyst self-oxidation [7]. Efficient supported metalloporphyrin catalysts use organic or mineral supports; silica is being recognized as a very attractive material, due to its stability towards drastic catalytic oxidation conditions [8].

The most recent results dealing with homogeneous and heterogeneous metalloporphyrin catalysed oxidation reactions currently in progress in our laboratory will be presented.

Acknowledgments

Thanks are due to the University of Aveiro and FCT for funding the Organic Chemistry Research Unit. R. De Paula also thanks FCT for his PhD grant (SFRH/BD/25666/2005).

References

PREPARAÇÃO DE N-ÓXIDOS POR OXIDAÇÃO DIRECTA DE DERIVADOS DA PIRIDINA

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As propriedades electrónicas únicas do grupo funcional N-óxido, que lhe permitem activar os anéis heteroaromáticos, quer para ataque por nucleófilos, quer para ataque por electrófilos, conferem aos N-óxidos heteroaromáticos possibilidades sintéticas que dificilmente se conseguiriam por outros métodos. Para além disto, os N-óxidos heteroaromáticos têm-se revelado úteis como grupos protectores, oxidantes, ligandos em complexos metálicos e catalisadores¹. As suas propriedades biológicas são também reconhecidas. Muitos têm propriedades antibacterianas, antivirais, anticancerígenas, antifungícas ou antielmintícas². São também utilizados em cosmética, na regulação do crescimento de plantas, na síntese de medicamentos, etc³.

Os N-óxidos são tradicionalmente preparados por oxidação directa da respectiva base com ácidos percarboxílicos. Contudo, com substractos activados por grupos dadores de electrões, a protonação da base nas condições acídicas em que a oxidação decorre, impede a sua oxidação. Nos últimos anos, outros oxidantes foram introduzidos de modo a que a reacção decorra em meio não acídico: dioxiranos e, fundamentalmente, sistemas catalíticos envolvendo complexos metálicos³.

Neste trabalho, descrevemos a oxidação directa de piridinas activadas com substituintes electrodadores com peróxido de hidrogénio, utilizando como catalisador o MTO (metiltrioxorénio – CH₃O₃Re). Este complexo que já havia tido muito sucesso como catalisador noutras reacções de oxidação⁴, em particular em N-oxidações, permitiu também obter resultados muito satisfatórios com este tipo de substractos.

³ V.V. Prezhdo et al., 1998, 127.
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