[P2.03]

Development of ERK5 inhibitors for anti-cancer therapy

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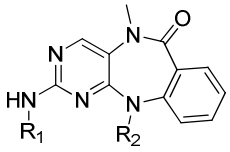
Extracellular signal-regulated kinase 5 (ERK5) is a member of the protein kinase superfamily, which plays an essential role in the transduction of extracellular signals to intracellular effectors. Activation of the ERK5 signalling pathway is associated with cell survival, proliferation, and differentiation, and thus ERK5 over-expression may have implications in carcinogenesis.[1] High levels of ERK5 are associated with poor patient prognosis and the presence of bony metastases in advanced prostate cancer.[2] It has recently been discovered that ERK5 is also involved in the development and progression of hepatocellular carcinoma (HCC).[3] Therefore, the discovery and development of small molecule inhibitors of ERK5 is a desirable therapeutic area.



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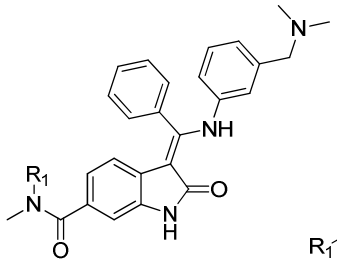

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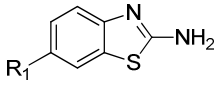

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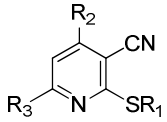

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Two potent inhibitors (**1**[4] and **2**[5]) have been described in the literature and provide insight into the therapeutic effect caused by ERK5 inhibition and further guide our structure activity relationship studies. High throughput screening of chemical libraries conducted by Cancer Research Technology identified a number of hit compounds showing good to moderate activity. Benzo[*d*]thiazole (**3**) and 3-cyanopyridine (**4**) based inhibitors were chosen for validation by re-synthesis. The syntheses of these small libraries will be discussed.

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Keywords: ERK5, High throughput screen (HTS), Cancer, Kinase

[P2.05]

Novel asymmetric catalytic intramolecular approach to bioactive chiral cycloalkanols: comparison of batch and flow-techniques

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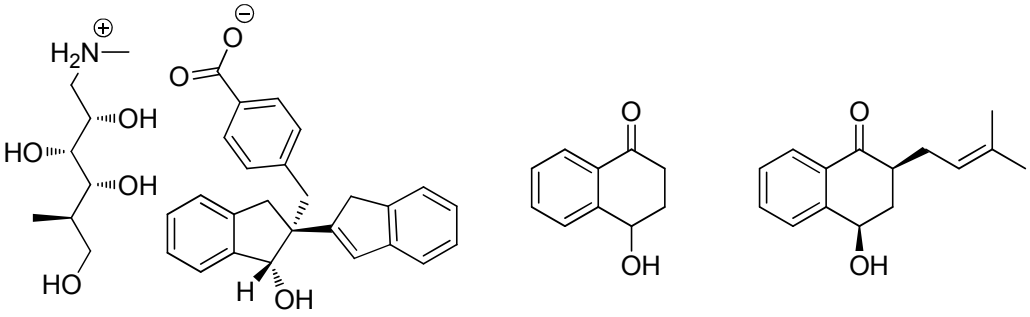
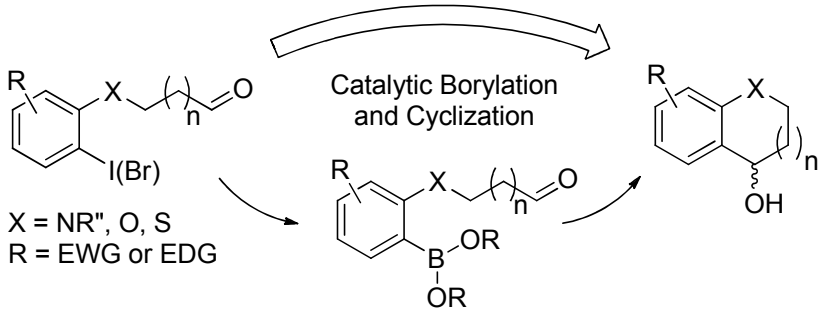
Cycloalkanols are a sought-after group of organic molecules, many of which exhibiting important biological activity.[1, 2, 3, 4] Some examples include compound PH46A, currently under clinical trials for inflammatory bowel diseases,[5] and 4-hydroxy-1-tetralone, a natural product obtained from Ampelocera edentula showing activity against cutaneous leishmaniasis.[6] We are presently investigating a novel asymmetric catalytic route to access chiral cycloalkanol cores via boronic ester derivatives.[7] As flow chemistry has been shown to be a very effective method for conducting organic synthesis,[8] we have investigated the stepwise and telescoped in-flow borylation/cyclization synthesis and compared these results with the corresponding batch processes.





Acknowledgements: This work is supported by the project: INMOLFARM - Molecular Innovation and Drug Discovery (ALENT-57-2011-20) financed from the FEDER-INALENTEJO program ALENT-07-0224-FEDER-001743, as well as PEst-OE/QUI/UI0619/2011 (CQE-UE) and the Max Planck Society.

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Keywords: Asymmetric, Catalysis, Batch, Flow

[P2.06]

Tandem ATRP-Diels Alder synthesis of polyHEMA-based hydrogels

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2-Hydroxyethyl methacrylate (HEMA) is an important functional monomer which is used in materials for contact lenses, drug delivery and hydrogels. [1] Furfuryl methacrylate (FMA) is an interesting monomer because of the presence of its reactive furfuryl group, able to take part in Diels Alder reactions. [2] Hydrogels are hydrophilic networks formed by crosslinking polymer chains. They have the ability to absorb large amounts of water without losing their structure due to its chemical or physical crosslinks. Hydrogels are materials that may display relevant biomedical applications such as drug and cell carriers, and as tissue engineering matrices. Depending on their structures, selected solutes can be released from their swollen matrices. [3]

One of the aims of this work was obtaining random copolymers of HEMA and FMA, via atom transfer radical polymerization (ATRP). Next, the formation of hydrogels *via* Diels-Alder reaction was attempted.

So, a batch of poly(HEMA-*random*-FMA) was synthesized and fully characterised. The chemical compositions of the copolymers were determined by ^{1}H NMR and FTIR and their thermal properties (thermal decomposition and crystallinity) were investigated. Kinetics studies were carried out to confirm the incorporation of FMA. Under the studied polymerisation conditions, FMA was integrated into the polymer structure within the first five hours and no side reactions were observed.

Polymer hydrogels were obtained by means of Diels-Alder reaction between the various poly(HEMA-*random*-FMA) prepared and a hydrophilic bisdienophile (which was also synthesized and characterised).The gelification of each copolymer depends on, not only the crosslinking temperature but also the polymer composition. Further data will be disclosed in the presentation.

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Keywords: ATRP, Diels-Alder, polyHEMA-based hydrogels, FMA

[P2.07]

Sugar dienes as novel building blocks for synthesis of bicyclic systems *via* olefin-nitrile oxide cycloaddition reaction

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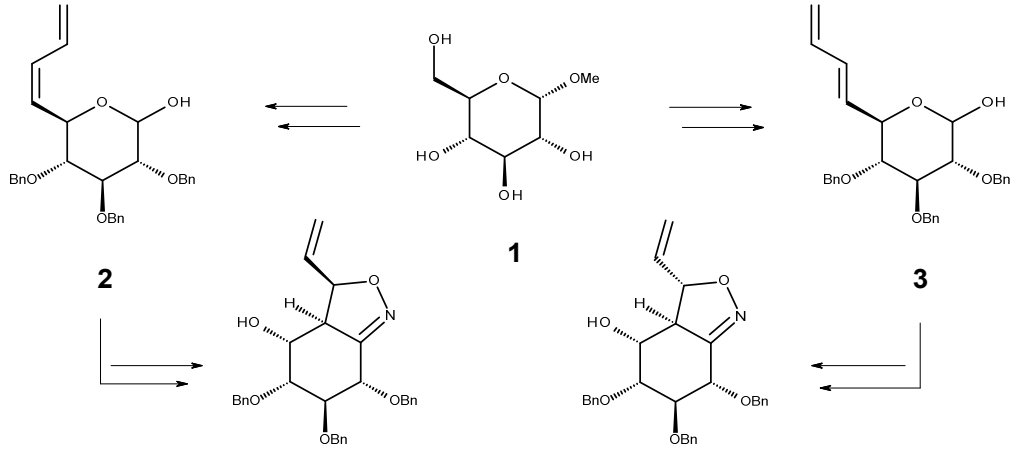
Some of polyhydroxylated bicyclic derivatives can act as inhibitors of glycosidases; in optically pure form such compounds can be conveniently prepared from sugars.[1] The important category of these bicycles is represented by derivatives with decalin skeleton.[2] Synthesis of this system is relatively underexplored, since most of the reported methods lead to racemic products.

We have proposed a stereoselective route to optically pure, highly functionalized *cis*-decalins *via* intramolecular Diels-Alder reaction of sugar derived trienes.[3] Configuration at the ring junction is dependent on the configuration across the internal double bond of the precursor; the *E*-diene gives the *cis*-decalin. We reason that the *Z*-isomer should cyclize to *trans*-decalin. Our methodology, however, provides only the *E*-dienes.[3]

In this presentation we will show the access to both: *E*- and *Z*-dienes with sugar scaffold.



Methyl glucoside (**1**) was transformed into dienes **2** and **3**. The key step of this methodology is allylboronation of appropriate sugar aldehyde followed by Petersen elimination of resulting *β*-hydroxysilyl moiety. Such elimination, carried out in acidic medium, provided only the *E*-diene, while elimination induced by base yielded the alternative *Z*-diene. Removal of the protecting group from anomeric position afforded the free sugars (**2** or **3**), useful building blocks in the synthesis of bicyclic systems *via* cycloaddition reactions.

To demonstrate the applicability of synthetized molecules, they were subjected to intermolecular olefin-nitrile oxide cycloaddition. Dienes **2** and **3** were transformed into oximes, which - in reaction with *N*-chlorosuccinimide - gave appropriate oxazolines **4** or **5** *via* corresponding nitrile oxides. Only one diastereoisomer was obtained.

Acknowledgments:

The support from Grant: POIG.01.01.02-14-102/09 (part-financed by the European Union within the European Regional Development Fund) is acknowledged.

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Keywords: Sugars, Cycloaddition, Stereoselective synthesis, Chiral pool

[P2.08]

Electrospray ionization tandem mass spectrometry analysis of a broad spectrum of nucleotides and their synthetic analogs including potential therapeutic agents

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University of Warsaw, Poland

Electrospray ionization (ESI) belong to so-called soft ionization methods, because it does not cause the premature degradation of a sample. This makes this method universal and applicable to a wide range of compounds. ESI, in conjunction with triple quadrupole analyzer, enables the performance of the controlled fragmentation of molecules. We have applied the above mentioned techniques to the study of nucleotides, which are very important for biochemical processes taking place in living organisms. Taking advantage of a unique collection of nucleotide analogs that have been synthesized over the years in our laboratory, we created a library of fragmentation spectra of nucleotides and analogs, many of which have been tested for the first time. In our work we focused on the analysis of compounds that contain modifications in phosphate bridge and within ribose (Fig 1.). The modifications involved the substitution of hydroxyl groups and/or the introduction of the additional groups such as phosphorothioate, phosphoroselenoate, phosphoroamidate, boranophosphate, fluorophosphate, methylenebisphosphonate and imidodiphosphate. We have also tested compounds containing 2' and 3' ribose linkers. Many of our compounds are mono-, di-, tri- nucleotides and dinucleotides which are mRNA cap analogs. In the course of our studies we have concluded that the analysis of nucleotides by means of tandem mass spectrometry, especially in a negative ion mode, is a valuable source of the following information: the presence, the type and the position of a modification. In some cases we could discern isomers and isobars. We used labelling with ^{2}H, ^{18}O and ^{13}C isotopes in order to determine fragmentation pathways and to establish methods for the quantitative examination of nucleotidede degradation products. The results of our research can be applied for testing drug and prodrug metabolism, as many of the tested compounds are the present or potential therapeutic agents. Moreover, the results have relevance to the disease diagnosis and quantitative analysis, especially MRM experiments.

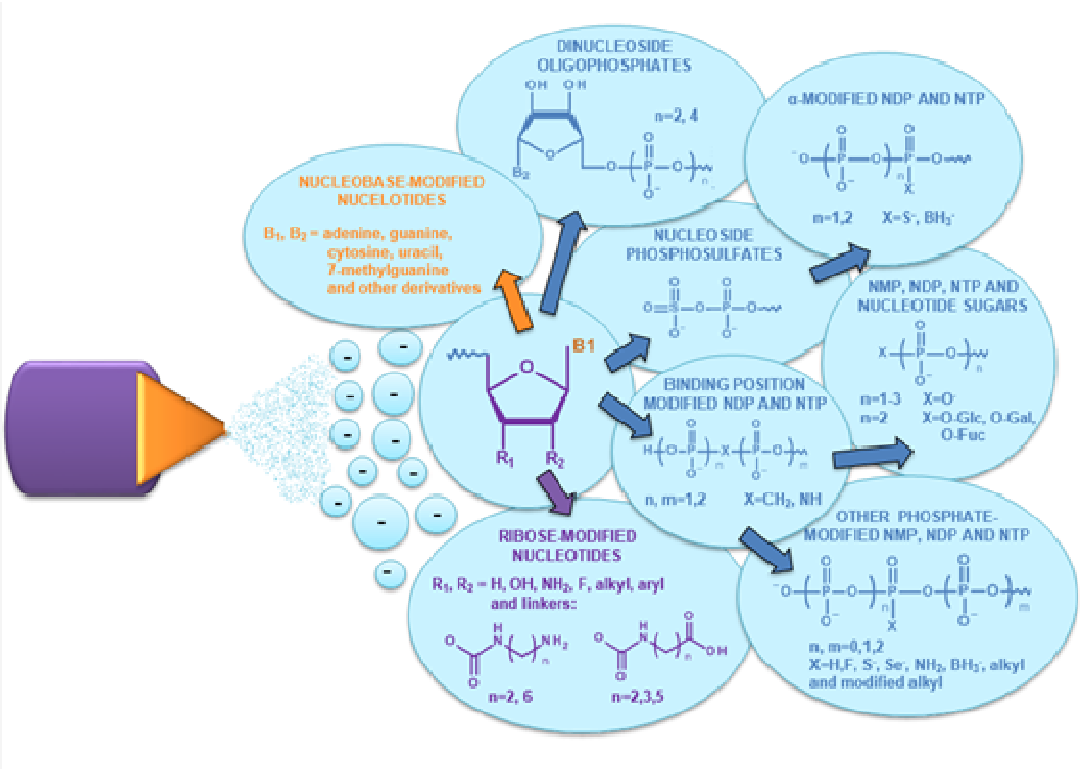

Fig. 1. Overview of the compounds investigated using MS/MS

Keywords: tandem mass spectrometry, nucleotide fragmentation, nucleotide analogs, therapeutic agents

[P2.09]

Design and synthesis of CrtM transition-state mimetic inhibitors

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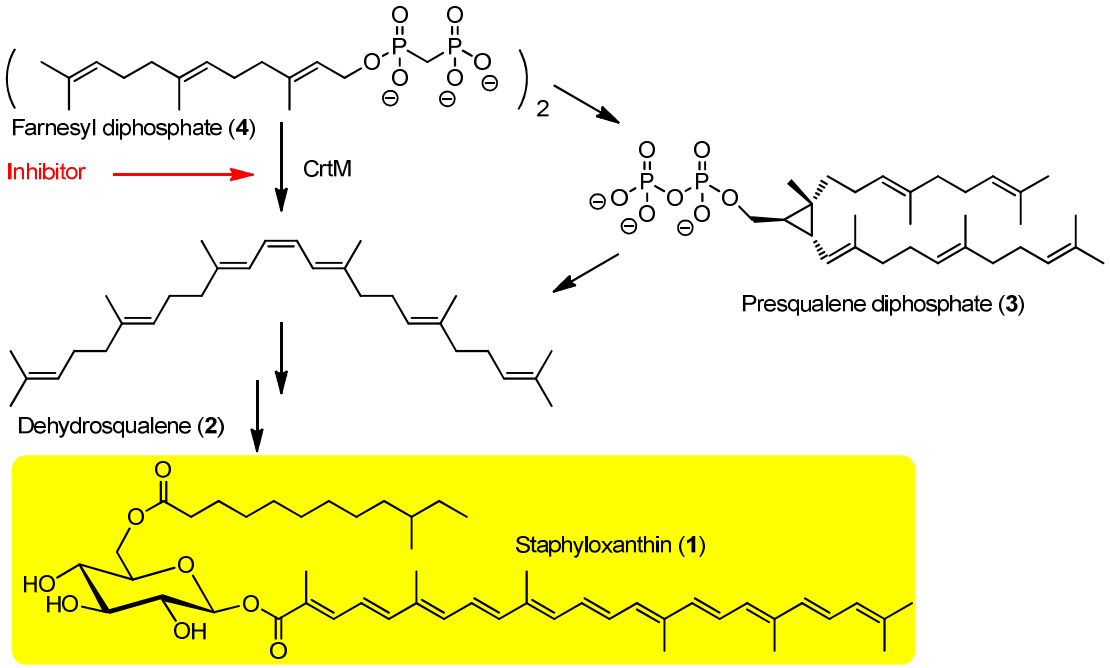
Staphyloxanthin (STX, **1**) is the yellow pigment produced biogenetically from dehydrosqualene (**2**) in *Staphylococcus aureus* (SA), including the methicillin-resistant strain (MRSA). STX is a toxin and functions as an antioxidant of SA. Dehydrosqualene synthase (CrtM) is an essential enzyme in the biosynthetic pathway of STX. In 2005, Nizet and coworkers have shown that interference of the STX biosynthesis will weaken bacteria for facile eradication by host immune system. The cocrystal structure of CrtM was published in 2008 to provide useful information for design of the enzyme inhibitors. To construct the inhibitors by mimicking native substrate is a widely applied strategy for development of antibacterial. In another approach, we aimed to design and synthesize a series of benzoic acid derivatives to mimic the transition state in formation of presqualene diphosphate (PSPP, **3**) by the CrtM-catalyzed coupling reaction between two farnesyl diphosphonate (FPP, **4**) molecules. We also evaluated the bioactivity (IC_{50} and MIC) of these potential CrtM inhibitors which blocked the STX production. It is interesting to observe that the combined use of the CrtM inhibitor with antibiotics, e.g. ampicillin, has shown moderate additive effect to suppress the growth of MRSA.



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Keywords: Staphyloxanthin, MRSA, CrtM inhibitors

[P2.10]

Zanamivir conjugated with anti-inflammatory drugs for enhanced anti-influenza activity

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Influenza is a respiratory infection that may cause severe pneumonia, cytokine storm, and even multiple organ failures. The high mortality of human infected by avian influenza A/H5N1 has been partly attributed to uncontrolled virus-induced cytokines. Monotherapy for influenza is limited due to the rapidly developed drug-resistance. The combination therapy with two or more drugs that target different viral proteins or host immune response may overcome the problem of drug-resistance. Zanamivir is an effective influenza drug targeting neuraminidase. The hydroxyl group on C7 does not form direct hydrogen bonds with influenza neuraminidase because it is directed away the active site.[1] The C7-modified analogue of zanamivir may retain good inhibitory activity. Our previous study has revealed a new type of dual-targeted conjugates of zanamivir with anti-inflammatory agents to inhibit both influenza virus and inflammation. Zanamivir conjugated with anti-inflammatory agents, e.g. caffeic acid, showed enhanced inhibition against influenza virus.[2] In this symposium, we shall report a series of dual-targeted conjugates of zanamivir containing more hydrophobic moiety of anti-inflammatory drugs. We wonder if the bioavailability and efficacy of such zanamivir conjugates will be improved by increase of lipophilicity.

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Keywords: anti-influenza, zanamivir conjugates, anti-inflammatory drug

[P2.11]

Synthesis of antroquinonol

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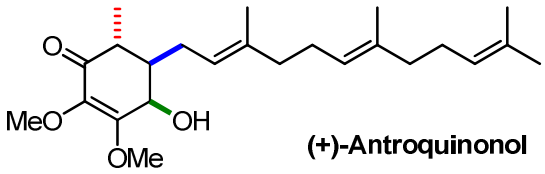
[1]*National Taiwan University, Taiwan,* [2]*Academia Sinica, Taiwan*

Antroquinonol, a natural ubiquinone derivative, was isolated from *Antrodia camphorate*, a parasitic fungus indigenous to Taiwan. Antroquinonol has been reported to have antitumor effects against various cancer cells, such as hepatocellular carcinoma (HCC). Antroquinonol displays anticancer activity against HCCs through AMPK activation and inhibition of mTOR translational pathway, leading to G1 arrest of the cell-cycle and subsequent cell apoptosis.[1]

In this symposium, we would like to report the synthesis of antroquinonol using a sequential three-component coupling reaction. We also prepared a series of derivatives to determine the absolute configuration of natural antroquinonol.



(+)-Antroquinonol

Reference:

Lee T.-H.; Lee C.-K.; Tsou W.-L.; Liu S.-Y.; Kuo M.-T.; Wen W.-C. *Planta Med.* **2007**, *73*, 1412–1415.

Keywords: Antroquinonol, hepatocellular carcinoma, a sequential three-component coupling reaction

[P2.12]

Synthesis, characterization, antitumor activity and safety testing of novel aminophosphonate derivatives

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Aminophosphonic acid derivatives attract continuous attention because of their unusual capacity for medicinal and pharmaceutical applications, especially, for the treatment of several metabolic disorders and cancer. Numerous publications focus on their synthetic routes, structure and biological activities, as well as on the development of new original approaches for their use. Here we report novel aminophosphonate derivatives, synthesized on the basis of polymeric H-phosphonates and azomethines. By varying the reaction conditions, the products were prepared with different content of the active substance and the hydrophilic H-phosphonate unit, which was determined on the basis of their $^{31}P\{^{1}H\}$ NMR spectra. The aminophosphonate derivatives were characterized by IR, NMR (^{1}H, ^{13}C and ^{31}P), fluorescence and mass spectrometry. The NMR spectral data confirm the structure of the products. The fluorescence spectra revealed emission maxima in the blue – blue-green spectral range. The mass spectra showed a break of the C-P bond of the aminophosphonate moiety and a formation of a $C_{22}H_{18}N^{+}$ ion. Two of the synthesized products were tested for *in vitro* antitumor activity on a panel of seven human epithelial cancer cell lines. Safety testing was performed both *in vitro* (3T3 NRU test) and *in vivo* on IRC mice for genotoxicity and antiproliferative activity. One of them showed excellent antiproliferative activity to HBL-100, MDA-MB-231, MCF-7 and HepG2 cell lines. All products exhibited low or moderate clastogenicity *in vivo* and slightly inhibited bone marrow cell division, compared to Mitomycin C. The subcellular distribution of the substances was studied in model cell culture systems. The obtained results showed, that the tested substances are promising for the development of active antineoplastic agents for chemotherapy of malignant breast and liver disease.

Acknowledgments: Thanks are due to Polinnova, Project funded under the FP7 Grant Agreement No 316086 and to the Bulgarian National Science Fund; Contract DCVP 02-2/2009 for the financial support.

Keywords: aminophosphonic acids, NMR, antitumor activity, genotoxicity

[P2.13]

Synthesis of novel macrocycles based on a sucrose scaffold

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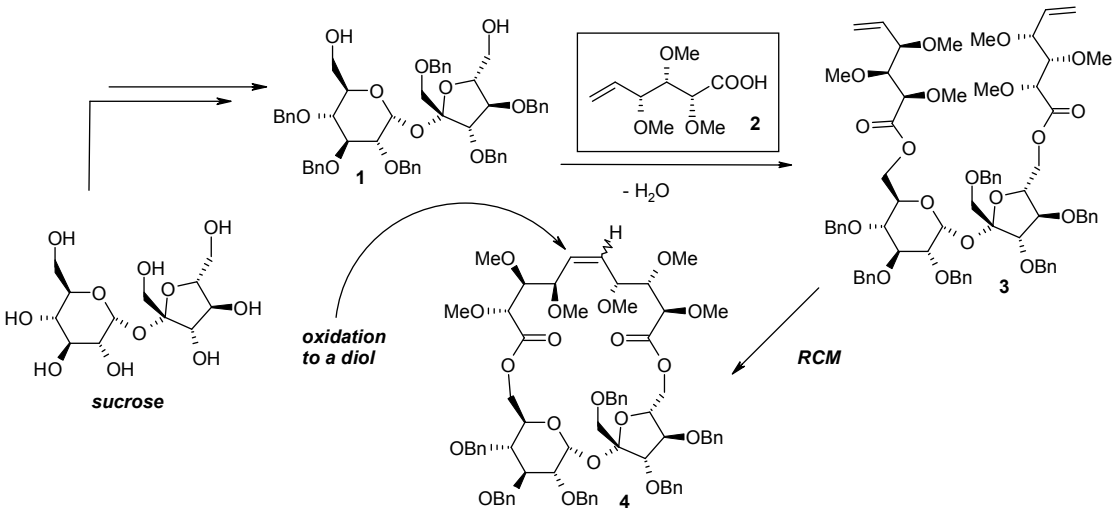
Chiral macrocyclic compounds, because of their wide application in enantioselective recognition, are important targets in organic synthesis.[1] In our group, we have proposed several approaches enabling efficient synthesis of sucrose-based macrocycles.[2] Encouraged by their promising cation-binding properties,[3] we have elaborated preparation of novel macrocyclic derivatives of type **4**. This was realized by connection of the terminal positions [C-6 (glucose) and C-6' (fructose)] in known[4] hexa-*O*-benzylsucrose **1** with suitably modified simple sugars. Building block **2** was obtained by a reductive dehalogenation of the proper chloro-glucose derivative(Vasella reaction)[5] and subsequent oxidation. Reaction of both blocks (**1** and **2**) afforded ester **3**. The desired macrocyclic framework was obtained by a ring-closing metathesis, which provided olefin **4** as a mixture of *E*/*Z* isomers. Based on our previous studies, we expect this new class of macrocycles with sucrose scaffold -based to be active receptors of organic and inorganic cations. By changing the structure of the acid **2** (which may be prepared from configurationally different sugars) a number of macrocyclic derivatives are available.



Acknowledgments: The support from Grant of National Science Centre UMO-2012/05/B/ST5/00377 is gratefully acknowledged.

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Keywords: sucrose, macrocycles

[P2.14]

Synthesis and evaluation of novel heterocyclic analogues of aminoflavone for anticancer activity

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Flavones and aminoflavones are known for its anticancer potential and lesser toxicity. The objective of the present work is to synthesise newer analogues of flavones by incorporating thiazolidinone and imidazolidinone heterocycles to the flavone nucleus in an attempt to obtain synergistic anticancer activity.

6-aminoflavone and 7-aminoflavone were used as the parent compounds for the synthesis. Imidazolidinone analogues were synthesised by treating aminoflavone with azlactone in presence of pyridine. Thiazolidinone analogues were obtained by treating aminoflavone with aromatic aldehydes in presence of thioglycolic acid. Twenty novel analogues were synthesised and characterised accordingly. The *in vitro* cytotoxic potential of these compounds were evaluated using MTT assay against HeLa and MDA MB cell lines. Apoptotic potential was tested using flow cytometry and Hoechst staining analysis. Active compounds evolved from the above screen were further tested to establish the *in vivo* anticancer activity.

Results of the MTT assay revealed that all the novel analogues were better cytotoxic agents than the parent aminoflavones. It was observed that the thiazolidinone analogues were more cytotoxic than the imidazolidinone analogues and the activity of the methoxy substituted thiazolidinone analogue was similar to that of doxyrubicin against HeLa cell line. The flow cytometry experiment resulted in histograms characteristic of apoptosis. Hoechst staining showed the nuclear condensation in the HeLa cells treated with the test compound, which points to the apoptotic potential of these analogues. The *in vivo* studies conducted on albino mice using Daltons ascites carcinoma model resulted in an increase in the life span, which was comparable to Cisplatin. Further studies are required to establish the anticancer activity against a panel of human cancer cell lines.

Keywords: aminoflavone, imidazolidinone, thiazolidinone, anticancer activity

[P2.15]

Design and development of novel T. brucei inhibitors inspired by nature

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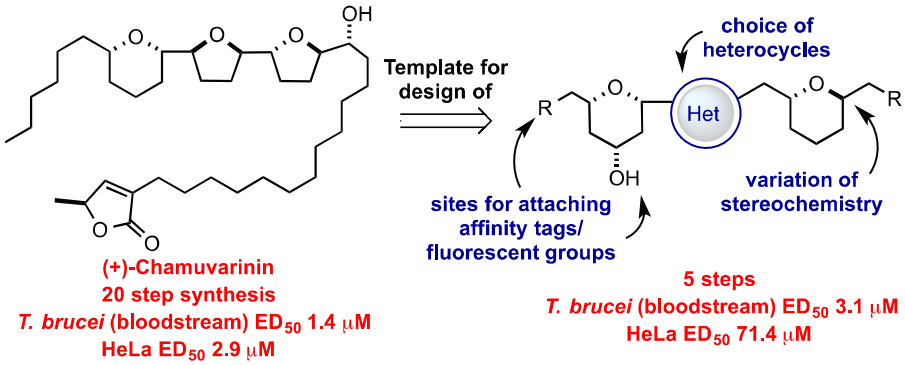
African sleeping sickness or Human African trypanosomiasis (HAT) is a disease transmitted to humans by the bite of the tsetse fly which carries the protozoan parasite *Trypanosoma brucei*. HAT affects the developing countries of sub-Saharan Africa threatening >70 million people[1] and is one of the greatest causes of social and economic hardship, as well as mortality in these countries; responsible for more deaths than HIV/AIDS. Current treatments for this Neglected disease are limited to a range of largely ineffective, highly toxic, hard to administer drugs with an ever-growing concern over drug resistance.



Chamuvarinin,[2] an acetogenin isolated from the roots of *Uvaria Chamae*, displays single figure micromolar activity towards both procyclic and bloodstream forms of *T. brucei* as well as towards HeLa cancer cells. Building on our report of the first total synthesis of chamuvarinin, new rapidly assembled THP-triazole-THP analogues were designed on the basis of molecular modeling of the central tricyclic core of chamuvarinin and these simplified analogue were found to kill *T. brucei* at micromolar levels and, significantly, are selective against mammalian cells. This paper will detail preliminary SAR studies and identification of lead compounds, as well as exploration of different heterocyclic cores and the influence of THP stereochemistry. We have identified our compounds as disruptors of the mitochondrial function in *T. brucei* and will outline our work towards identifying the protein target of these novel anti-parasitic agents, primarily through the synthesis and application of suitable affinity tags for protein identification and fluorescent labels for cell imaging.

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Keywords: Trypanosomiasis, neglected diseases, tetrahydropyrans, natural products

[P2.16]

Chemical probes to study ADP-ribosylation - focusing on the ARTD/PARP family of proteins

A.E.G. Lindgren*[1], T. Karlberg[2], T. Ekblad[2], S. Spjut[1], A-G. Thorsell[2], C.D. Andersson[1], H. Schüler[2], A. Linusson[1], M. Elofsson[1]

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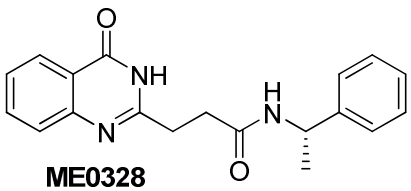
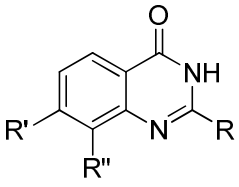
The diphtheria toxin-like ADP-ribosyltransferase (ARTD, also known as poly ARP-ribose polymerase (PARP)) family consists of 17 proteins that all share a similar catalytic ART domain. Even though ADP ribosylation was discovered more than 40 years ago it is still a relatively poorly understood mechanism. Most of these proteins are not yet fully characterized and their substrates are often unknown. However, it is believed that the members of the ARTD family have a crucial role in chromatin remodelling and DNA repair.

Our goal is to develop potent and selective small organic compounds, chemical probes, which can be used to study the biological role of individual ARTDs. Progress is being made on several of the ARTD proteins, and recently we published an ARTD3 selective chemical probe (ME0328).

The quinazolinone scaffold has proven versatile and by introducing substituents in different positions we explore if selectivity for other ARTDs can be achieved. For instance, ARTD8 selectivity is obtained by introducing amides at R' and by inverting the stereochemistry of ME0328 a selective ARTD1 inhibitor is produced.



ME0328



Keywords: ARTD, PARP, Chemical probes, Quinazolinone

[P2.17]

New synthetic route for polymer-supported preparation of benzo[1,4]-diazepin-5-ones with three diversity positions

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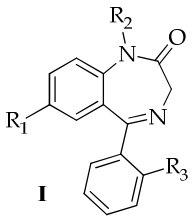
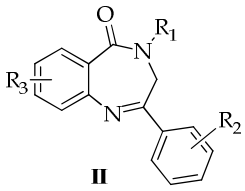
In the entire history of 1,4-benzodiazepine scaffold containing substances, 5-substituted-1,3-dihydro-benzo[e][1,4]diazepin-2-ones **I** have been studied most extensively particularly due to their influence on a central nervous system (CNS).[1] In contrast, structurally isomeric 2-phenyl-3,4-dihydro-benzo[e][1,4]diazepin-5-ones **II** have been studied rarely and only a few articles dedicated to the preparation and properties of such compounds have been published.

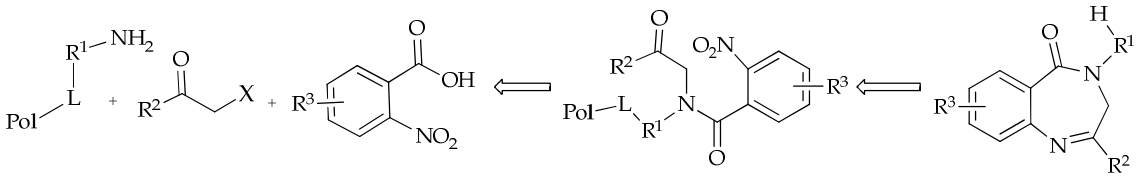


I



II

This contribution describes high-througput synthesis of 2-phenyl-3,4-dihydro-benzo[e][1,4]diazepin-5-ones from commercially available building blocks with polymer-supported α-aminoketones being the key intermediates. The solid-phase synthesis concept has been used in order to introduce the methodology applicable for the future preparation of chemical library and subsequent structure-activity relationship studies of the target substances **II** that contain three diversity positions: (i) substitution at position 2, (ii) substitution of the nitrogen atom at position 4, (iii) substitution of a benzene ring of the benzodiazepine scaffold.[2]



Trisubstituted benzodiazepinones **II** were obtained in very good crude purity, although some structural limitations were observed. Finally, model derivatives were characterized with ^{1}H, ^{13}C NMR spectrometry and HRMS. Described chemistry is applicable for (semi)automated combinatorial synthesis of chemical library to produce novel derivatives for biological screening.

This research was supported by project CZ.1.07/2.2.00/28.0184 coming from European Social Fund. The infrastructural part of this project (Institute of Molecular and Translational Medicine) was supported from the Operational Program Research and Development for Innovations (project CZ.1.05/2.1.00/01.0030).

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[2] V. Fulopova, T. Gucky, M. Grepl, M. Soural, *ACS Comb. Sci.* **2012**, *14(12)*, 651-656.

Keywords: Benzodiazepines, Solid-phase synthesis, alpha-aminoketones, nitrobenzoic acids, haloketones

[P2.18]

Progress toward the total synthesis of phomoidride D

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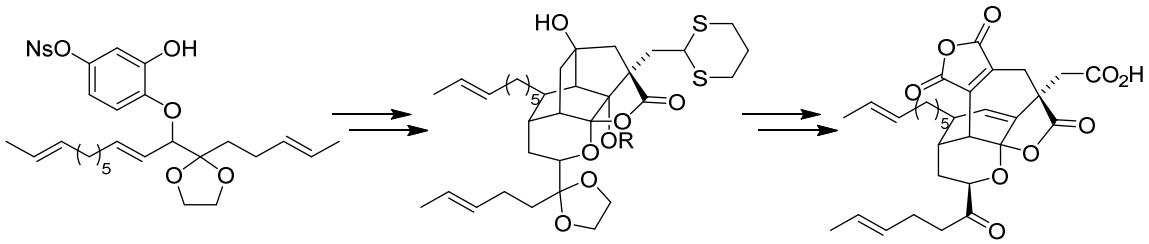
Baylor University, USA



Phomoidride D

The bicyclo[4.3.1] core architecture of the phomoidrides has attracted the interest of many creative synthetic chemists and four groups have completed syntheses of the natural product. These efforts include completed syntheses of phomoidride B by the groups of Nicolaou, Danishefsky, Fukuyama, and Shair.[1]

Our approach toward the synthesis of phomoidride D utilizes a phenolic oxidation/Diels-Alder sequence to rapidly build up complexity. A Wharton fragmentation will then be used to deliver the bicyclo[4.3.1] core inherent to the natural product. Late stage formation of the maleic anhydride substituent would then furnish phomoidride D.

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Keywords: Total Synthesis, Natural Product Synthesis, Phomoidride, Wharton Fragmentation

[P2.19]

Synthetic studies toward citrinadin a: construction of the pentacyclic core

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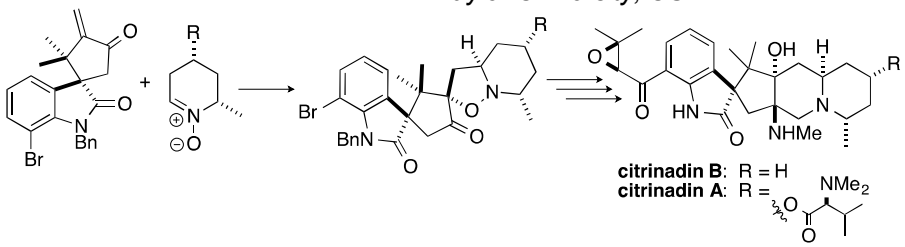

The citrinadins were isolated from the marine fungus *P. citrinum* by Kobayashi and coworkers in the early 2000s, and have subsequently inspired several synthetic approaches.[1] These efforts culminated in the total synthesis and structural reassignment of the citrinadins in the recently published work of our group on citrinadin B and that of Martin and coworkers on citrinadin A.[2] Herein we present out approach to citrinadin A, utilizing a [2+3] nitrone cycloaddition with both enantioenriched enone and nitrone for improved yields of the pentacyclic core of the citrinadins.

1. a) Kobayashi, J. *Org. Lett.* **2004**, *6*, 3087–3089. b) Kobayashi, J. *J. Org. Chem.* **2005**, *70*, 9430–9435.

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Keywords: citrinadin, total synthesis, cycloaddition, natural product

[P2.20]

S-alkylation of the terminal nucleoside thiophosphate moiety as a route to obtain modified dinucleotides

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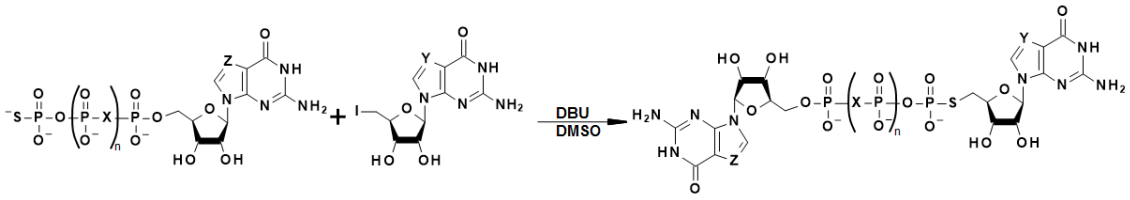
Nucleotides modified at the terminal position of the polyphosphate chain have numerous potential applications, including nucleotide labelling, design of enzymatic inhibitors, nucleic acid sequencing as well as serve as tools for investigation of cellular processes such as nucleic acid metabolism, protein phosphorylation or DNA/RNA polymerization.

Here, we report a simple method for the functionalization of the nucleotides at the terminal position of the oligophosphate chain, which employs a sulfur atom as the site of modification. We show that the sulfur atom within the terminal phosphorothioate moiety is selectively and efficiently alkylated by 5'-iodonucleosides, without side-reactions at other nucleophilic centres present in nucleotides and under mild conditions

To show the utility of this method we synthesized several dinucleoside oligophosphates bearing a 5'-phosphorothiolate moiety. (Fig. 1) Due to the presence of 7-methylguanosine these compounds are analogs of mRNA 5' end (cap), and thus potential tools to study mRNA cap-related proteins and enzymes. The starting materials for these reactions, i.e. appropriate terminal phosphorothioate-bearing nucleotides, were synthesized by the methods previously established by our group.[1],[2]. By using 5'-iodoguanosine or 5'-iodo-7-methylguanosine as the alkylating agents we synthesized several cap analogs: m^7GppS-G, m^7GpppS-G, m^7G-S-ppG and m^7G-S-pppG and an analog containing a methylene group replacing the pyrophosphate bridge oxygen atom (m^7GpCH_2ppS-G). We synthesized also two unmethylated counterparts as controls for biological studies(GppS-G and GpppS-G). Subsequently, the influence of 5'-thioester bond on the biological properties of the cap, including resistance to DcpS enzyme and the affinity to eIF4E protein was studied. The results of preliminary studies directed at applying similar methodology for chemical capping of 5'-iodooligonucleotides will be also presented.

References:

1. Kowalska, J. et al *Tetrahedron Letters* **2007**, *48,* 5475-5479
2. Strenkowska, M. et al *Org. Lett.* **2012**, *14*, 4782-4785



N°	Compound	n	X	Y	Z	N°	Compound	n	X	Y	Z
1	GppSG	0	-	N	N	**5**	m^7GpppSG	1	O	N	N^+-CH_3
2	GpppSG	1	O	N	N	**6**	m^7GSpppG	1	O	N^+-CH_3	N
3	m^7GppSG	0	-	N	N^+-CH_3	**7**	m^7GpCH_2ppSG	1	CH_2	N	N^+-CH_3
				4	m^7GSppG	0	-	N^+-CH_3	N		

Fig. 1

Keywords: thiophosphates, S-alkylation, mRNA, cap analogs

[P2.21]

Pd(II)-catalysed controlled switching between oxidative Heck and conjugate addition reactions

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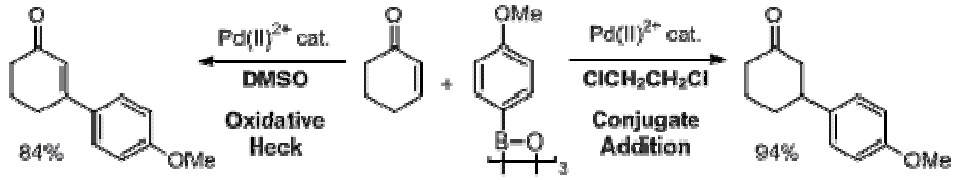
In recent years, Pd(II) catalysis has emerged as a promising new method for oxidative Heck couplings on cyclic systems, many of which fail under standard Pd(0) catalysis. The Lee Group has studied Pd(II)-catalysed conjugate addition reactions to substituted cyclohexenones[1] and discovered that the selectivity can be completely switched to the oxidative Heck product by *simply changing solvent*.

In the Pd(II)-catalysed reaction between cyclic enones and aryl boroxines, we have discovered that DMSO yields the oxidative Heck product **1**, and 1,2-dichloroethane yields the conjugate addition product **2** (Scheme 1).[2]

This protocol can be applied to a wide range of aryl boroxines and substituted cyclic alkenes yielding the desired products in moderate to excellent yields.



1 **Scheme 1** **2**

The reaction is tolerant of air and moisture and uses a ligand- and base-free cationic Pd(II) catalytic system: $(MeCN)_4Pd(OTf)_2$ or $Pd(OAc)_2$ + TfOH [*in situ* $Pd(OTf)_2$].

Our investigations have demonstrated that more polar solvents promote the oxidative Heck reaction over conjugate addition. We propose that DMSO stabilises the $Pd(II)^{2+}$ centre and is able to facilitate *β*-H elimination, thus promoting formation of the oxidative Heck product.

References:

1. James A. Jordan-Hore, James N. Sanderson and Ai-Lan Lee, *Org. Lett.*, 2012, **14**, 2508.

2. Sarah E. Walker, Julian Boehnke, Pauline E. Glen, Steven Levey, Lisa Patrick, James A. Jordan-Hore and Ai-Lan Lee, *Org. Lett.*, 2013, **15**, 1886.

Keywords: Pd(II), oxidative Heck, conjugate addition

[P2.22]

Design, synthesis, 3D pharmacophore, QSAR, and docking studies of carboxylic acid derivatives as antiproliferative agents

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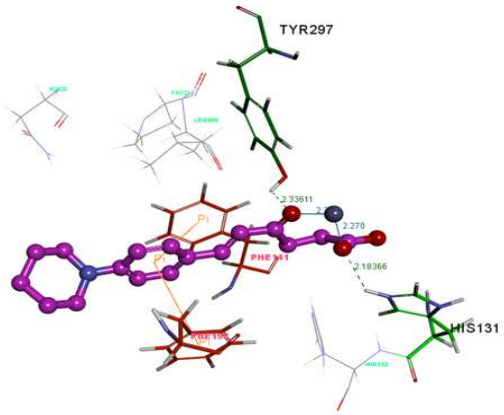
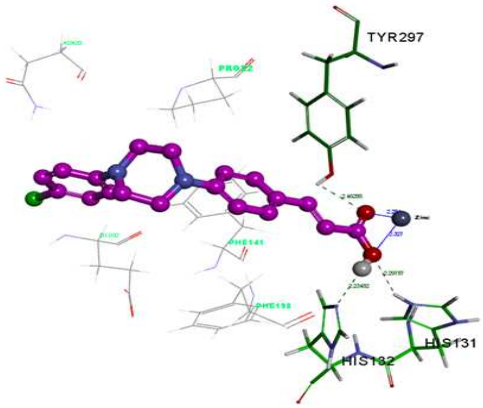
In this study, two series of (*E*) 6-(4-substituted phenyl)-4-oxohex-5-enoic acids **IVb-e,g** and (*E*)-3-(4-substituted phenyl)acrylic acids **Va-g** were designed, synthesized and evaluated *in vitro* for their antiproliferative activity on HepG2 cell line in which histone deacetylase (HDAC) is over-expressed . The design of the target compounds was based on earlier study of carboxylic acids as zinc binding functional group in HDAC metallo-enzymes. Compounds **IVc**, **IVe**, **Vb**, and **Vf** exhibited significant antiproliferative activity against HEPG2 human cancer cell with IC_{50} ranging from 2.27-10.71 µM. Molecular docking simulation was also carried out for the human HDAC8 enzyme to investigate possible binding modes of the synthesized compounds into the active site to investigate the inhibition activity and the 3D poses of inhibitor-enzyme complexes and chelation of the active compounds with zinc metal in the enzyme pocket. In addition, 3D-pharmacophore modeling and quantitative structure activity relationship (QSAR) models were combined to explore the structural requirements controlling the observed antiproliferative properties. It was found that the major structural factors affecting the potency of these compounds were related to their basic skeleton. The results indicated that these carboxylic acid derivatives could serve as promising lead compounds for further optimization.



Compound IVc

IC_{50} = 2.27 µM



Compound Vf

IC_{50} = 10.63 µM

Keywords: Histone deacetylase, antiproliferative agents, HDAC 8

[P2.23]

Synthesis and reactions of sulfone-substituted dihydropyridones

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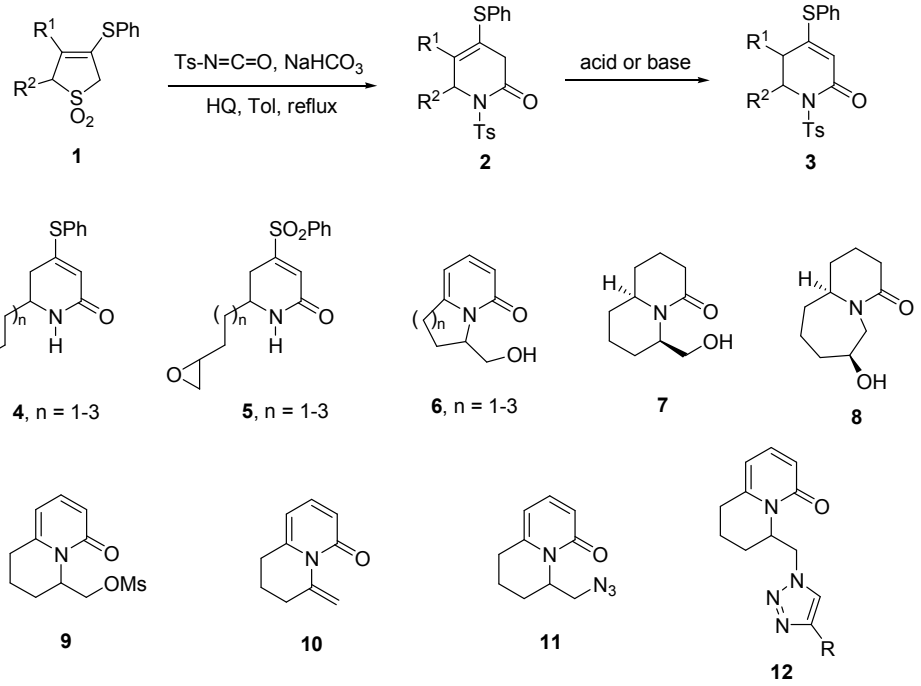
Fu Jen Catholic University, Taiwan

We have previously shown that 3-phenylthio-3-sulfolenes **1** can undergo [4+2] cycloaddition reactions with *p*-toluenesulfonyl isocyanate (PTSI) to yield dihydropyridones **2**, which upon treatment with acid or base can lead to the conjugated products **3**.[1,2] We now report that the reaction of compounds **4** with excess of *m*-CPBA gave the corresponding epoxysulfones **5**, which upon treatment with base yielded the bicyclic compounds **6**. The reaction of compound **6b** (n = 2) with H_2 at high pressure gave a mixture of products **7** and **8**. Compound **6b** was also converted to the mesylate **9**, which could undergo the elimination reaction to give product **10**, or the substitution reaction to give the azido product **11**. Further reaction of compound **11** with terminal acetylenes provided the triazoles **12**.



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2. Chou, S. S. P.; Hung, C. C. *Synthesis* **2001**, 2450.

Keywords: cycloaddition, dihydropyridones, sulfones, triazoles

[P2.24]

Synthesis of homologated amino acid derivatives containing three vicinal fluorine atoms placed stereospecifically along the backbone

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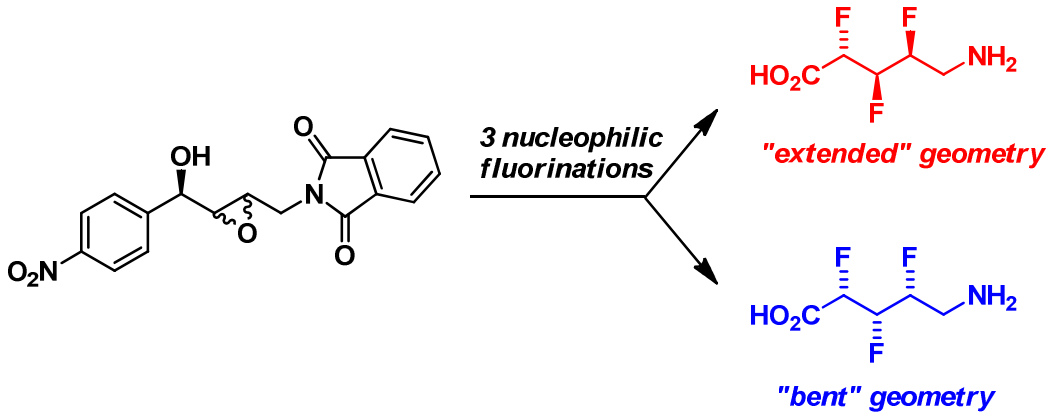
The incorporation of fluorine atoms into organic molecules can have a dramatic impact on the substances' physical and chemical properties.[1] For example, fluorine substituents can lead to higher hydrophobicity and greater metabolic stability, and they can affect the p*K*a of nearby functional groups. These effects have been put to good use in the pharmaceuticals area. Fluorination can also affect the conformations of organic molecules,[2] since the highly polarised C–F bond participates in a variety of stereoelectronic interactions with adjacent functional groups. This concept has potential applications in medicinal chemistry, because bioactive molecules need to adopt the correct conformation for optimal potency. In this project, we are exploring this idea in the context of amino acids.

As a part of an ongoing research programme concerning backbone fluorinated amino acids,[3] we recently became interested in the □,□,□-trifluoro-□-aminopentanoic acid structure (see below). In this project we have synthesized two novel δ-amino acids, each of which contains three vicinal fluorine atoms placed stereospecifically along the backbone.[4] Notable features of our synthetic approach include the successful stereochemical control throughout, and an expedient method for converting a nitroaryl moiety into a carboxylic acid group. The conformations of two precursor trifluoro compounds have been compared in the solution and solid states, and it emerges that different diastereoisomers have strikingly different conformations, consistent with known stereoelectronic effects associated with C–F bonds.[2]

These □-amino acids are suitable for incorporation into natural peptides as a replacement for two □-amino acids. For example, we are now investigating the anti-malarial cyclic peptide pohlianin C,[5] with the hypothesis that incorporating shape-controlled fluorinated amino acids will improve the anti-malarial potency.



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Cheerlavancha, R.; Lawer, A.; Cagnes, M.; Bhadbhade, M.; Hunter, L. *Org. Lett.* **2013**,*15*, 5562.

Auvin-Guette, C.; Baraguey, C.; Blond, A.; Xavier, H. S.; Pousset, J. L.; Bodo, B. *Tetrahedron* **1999**, *55*, 11495.

Keywords: Fluorinated amino acids, Sequential deoxyfluorination, Organo Fluorine, C-F Bond conformational analysis

[P2.25]

Total synthesis of neuraminic acid via an anti,syn-oxazine as a chiral building block

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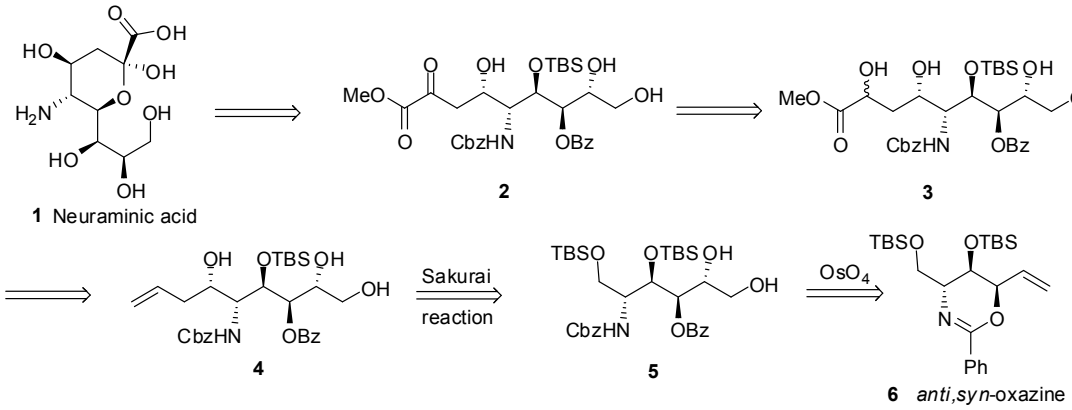
Sungkyunkwan University, Republic of Korea

Neuraminic acid and its derivatives have important roles in influenza infection. An influenza virus infection on the respiratory system produces severe cold like symptoms. Neuraminidase, a surface glycoprotein of the influenza virus membrane, assists disintegration between virus and host cell. And its inhibitors, for example, Relenza®(zanamivir) that was firstly identified as a potent neuraminidase inhibitor in 1989 and Tamiflu®(oseltamivir phosphate), are widely prescribed for effective treatment of influenza. Despite the significance of synthesis of neuraminic acid was recognized, the investigations have not been entirely published. Here we report the total synthesis of neuraminic acid **1** based on our previously described strategy.

On the basis of our previous research, we anticipated that the palladium(0)-catalyzed oxazine formation of a γ-allyl benzamide with a benzoyl substituent as the *N*-protecting group from D-serine in the presence of $Pd(PPh_3)_4$, NaH, and n-Bu_4NI might procced with high stereoselectivity. The bulkiness of the protecting group of the secondary alcohol is responsible for controlling the diastereoselectivity in the oxazine ring formation.

The synthetic utility of *anti,syn*-oxazines as chiral building blocks has been demonstrated by their successful application to the synthesis of biologically active natural products especially glucosidase inhibitors such as phytosphingosines and deoxynojirimycins. As part of the expansion of the synthetic utility of chiral *anti,syn*-oxazines, we have also been exploring the development of a novel strategy for the concise total synthesis of neuraminic acid. We envisioned neuraminic acid **1** could be generated by acid catalyzed *O*-cyclization of α-keto ester **2** transformed from α–hydroxy ester **3**. α–Hydroxy ester **3** would be induced via lithiated methoxyallene and subsequent ozonolysis of homoallylic alcohol **4**. Homoallylic alcohol **4** would come from chelation controlled Sakurai reaction of diol **5**. Diol **5** could be prepared by stereoselective OsO_4 dihydroxylation of *anti,syn*-oxazine **6**.



Scheme 1. Retrosynthetic analysis of neuraminic acid

Keywords: neuraminic acid, anti,syn-oxazine, Osmium tetroxide, sakurai reaction

[P2.26]

Novel pyrrolobenzodiazepine derivatives from a soil actinomycetes iaolate, Streptomyces sp.11A057

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[2]*Unversity of Science and Technology (UST), Republic of Korea*

The secondary metabolites produced by microorganisms have proven to be a valuable repository of bioactive compounds. Traditionally, a lot of bioactive molecules have been reported from actinomycetes strains. In the course of screening to discover novel secondary metabolites from microorganisms, we found three novel pyrrolobenzodiazepine (PDB) derivatives together with a known PDB usabamycin B from a culture broth of *Streptomyces* sp.11A057. This strain was isolated from a soil sample collected in a green-tea field of Boseong in Korea. PDBs are a family of naturally occurring antitumor antibiotics such as anthramycin, sibiromycin and neoanthramycin produced by actinomycetes strain. Their cytotoxic activities were exerted by covalently bonding to the C-2 amino group of guanine residues within the minor groove of DNA. The chemical structures of three new compounds were constructed by the basis of extensive spectroscopic analysis using 1D-(1H and 13C), 2D-NMR (COSY, HSQC, HMBC and NOESY) techniques and MS experiment. Cell growth inhibition effect of these compounds was evaluated against Jurkat, K-562, HL-60 and HepG2 tumor cell lines. Here we report the isolation, structural determination, and biological activities of these PDBs.

Keywords: novel pyrrolobenzodiazepine derivatives, Streptomyces isolate, isolation and chemical structures determination, biologicla activity

[P2.27]

Design and synthesis of 8-quinolinamine as antimalarial agents

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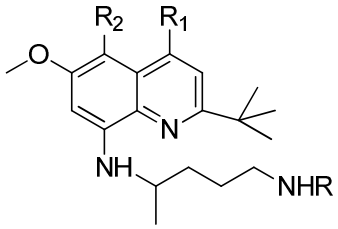
National Institute of Pharmaceutical Education and Research, India

Despite more than a century of efforts to eradicate or control malaria, the disease remains a major and growing threat to the public health and economic development because of prevalence, virulence and drug resistance of the parasite in tropical and subtropical countries. None of the antimalarial drugs act on all stages of parasite life cycle and development of resistance against them created a need to urgently develop new agents.

8-Quinolinamines represent the typical tissue-schizontocidal agents, and the most important drug of this class primaquine exerts its action against the primary and secondary tissue forms of the *Plasmodium* but suffers from serious side effects and toxicity limiting its use in both prophylactic and therapeutic applications. We have already shown that placement of metabolically stable bulky *tert*-butyl group at the C-2 position of the quinoline ring in primaquine offers analogues with tremendous improvement in their blood schizontocidal antimalarial activity. The resulting compound 2-*tert*-butyl-primaquine is free of almost all toxic manifestations due to their inability to undergo C-2 position metabolic pathway observed in primaquine. In continuation of our research work to develop 8-quinolinamines with enhanced blood-schizontocidal activities and other biological activities. We have synthesized various D- and L-amino acid conjugates of 8-quinolinamines and modification of primaquine at the C-4 and C-5 positions, which exhibited potent *in vitro* and *in vivo* blood-schizontocidal activities.



R- Aminoacids, R_1- Me, Et, R_2- Alkoxy C_4-C_8

Keywords: Antimalarial, 8-Aminoquinoline, Primaquine, 2-tert.butylprimaquine

[P2.28]

Towards the total synthesis of escobarine B; building the ring C

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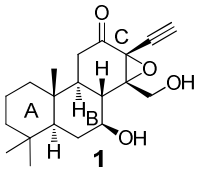
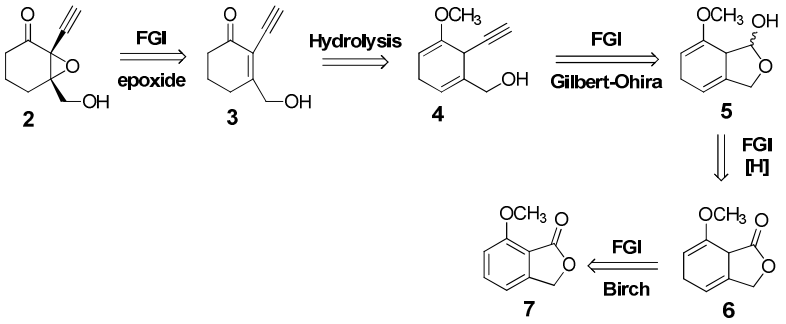
Escobarine A and B 1, two cassane-type diterpenes, were isolated from the root of Calliandra californaica, a perennial endemic shrub distributed over some regions of Baja California Sur, México. These compounds showed promising activities against two Mycobacterium tuberculosis strains. Moreover, until now no synthetic efforts through the synthesis of escobarines have been reported in the literature.



1 escobarine B

We believe that ring C, because of its vast number of functional groups, is the key structure that provides the biological activity against tuberculosis. In this scenario, the starting point in escobarine's total synthesis is the construction of ring C, not only to put these functionalities in the same ring as a synthetic challenge, but to evaluate its plausible biological activity as well. The retrosynthetic analysis proposed in our research group is shown herein.



The starting material **7** was treated under Birch reduction conditions to provide the enol ether **6**, which under appropriate conditions, the ester functionality is selectively reduced to lactol **5**. Followed by a Gilbert-Ohira reaction, the alkyne and primary alcohol moieties are installed to provide compound **4**, which is then hydrolysed to form the □.□-unsaturated carbonyl compound **3**. An asymmetric epoxidation process (Sharpless) as the last step yields ring C **2** of escobarine B.

Keywords: total synthesis, biological activity, tuberculosis, natural products synthesis

[P2.29]

An enzyme-responsive photodynamic nanoparticle for cancer therapy

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The Catholic University of Korea, Republic of Korea

In order to design an enzyme-responsive photodynamic nanoparticle (EPN) for cancer therapy, the EPN was prepared from a cationic polymer conjugated photosensitizer (PS) and an anionic polysaccharide conjugated quencher. EPNs have a unimodal size distribution with about 100 nm. Photoactivity of EPN was controlled with the weight ratio of PS and quencher. The EPN was very stable in a salt-condition, indicating that the EPN is not active in the normal blood stream of the body. However, the quenched photoactivity was rapidly restored by the enzyme treatment. In human colon cancer cells, the rapid cellular internalization of EPN without any other ligands was observed by confocal microscopy imaging. Upon light irradiation after internalization, phototoxicity was observed via colorimetric assay. Also, when the EPN was subcutaneously injected in both tumoral and normal regions of tumor-bearing mice, the fluorescence signal in the tumors rapidly increased compared to the normal region due to the enzymatic-triggered dissociation of the EPN in vivo. These results suggest that the EPN can provide both tumor diagnosis and therapy simultaneously, and has great potential for biological studies and clinical treatments of various cancers.

Keywords: Photosensitizer, Nanoparticle, Drug delivery, Cancer therapy

[P2.30]

6-Deoxyglucose as a DNA base mimic: duplex stability, structure and replication by DNA polymerases

R. Lucas[1], E. Vengut-Climent*[1], P. Peñalver[1], I. Gómez-Pinto[2], M. Arévalo-Ruiz[1], A. Aviñó[2], R. Eritja[2], C. González[2], J.C. Morales[1]

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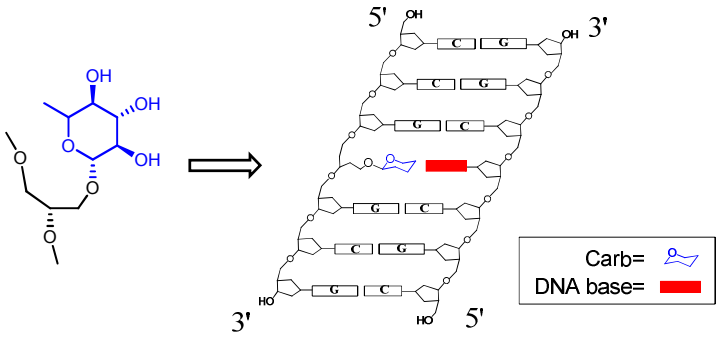
Introduction: Alternative DNA bases have been developed for a better understanding of DNA structure and function, for applications such as diagnostics or biosensors and for expanding the genetic alphabet.[1] All approaches reported for DNA base re-design (alternative hydrogen bonded bases, nonpolar DNA bases and metal mediated DNA base pairs) are based on aromatic scaffolds.

Recently, we have used a bioconjugate model to show how natural and hydrophobic carbohydrates stack on top of a DNA double helix mimicking the stacking observed for aromatic DNA bases.[2] Sugar stacking is also observed on top of the guanine tetrad of a G-quadruplex DNA structure.[3]

Methods: We have designed and synthesized a 6-deoxyglucose (6dGlc) derivative, a non-planar, non-aromatic structure, to incorporate the monosaccharide inside a DNA duplex. Then, we have studied DNA thermal stability, structural characteristics by NMR and enzymatic replication capabilities.

Results: DNA duplex containing 6dGlc decreases stability by 4-8 °C in comparison with a thymine base containing the same anchoring to DNA. In fact, 6dGlc shows selectivity for purine bases and structural studies using NMR and molecular dynamics confirm that a 6dGlc-guanine pair can be accommodated inside a DNA double helix. Finally, we found that *Bst 2.0* DNA polymerase inserts selectively T in front of glucose and is able to catalyse full-length DNA containing a glucose-T base pair.

Conclusions: We have shown how monosaccharides such as 6-deoxyglucose (6dGlc), a non-planar, non-aromatic structure can behave as a DNA base mimic.



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A.; Eritja, R.; González, C.; Morales, J. C. *Chem. Commun.* **2012**, *48*, 2991.

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J. C. *Chem. Eur. J.* **2013**, *19*, 1920.

Keywords: DNA mimic, Carbohydrate, DNA structure, DNA replication

[P2.31]

Photosensitizer conjugated polymeric micelles of triblock copolymers for enhanced cellular internalization for photodynamic therapy

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Recently, photodynamic therapy (PDT), used photosensitizer, has been increasing attention due to its convenience therapeutic method. PDT was used to cure various cancers including skin cancer, colon cancer and lung cancer. However, photosensitizer (PS) has some disadvantages for clinical applications such as low solubility in aqueous media and tumor-specific targeting efficiency. Therefore, we suggest novel biocompatible photosensitizer conjugated polymeric micelles (PCM) for increased solubility in aqueous media and enhanced internalization into cells of photosensitizers. In the ^{1}H- NMR spectra, PMC were successfully synthesized. Average 150nm of spherical micelles were prepared by dialysis method. The SOG efficiency and fluorescence activity of PMC in aqueous media dramatically increased compared to free PS. Moreover, confocal imaging and fluorescence-activated cell sorting (FACS) analysis confirmed its enhanced internalization rate in mouse colon tumor (CT-26) cells. In animal study, the PCM was accumulated at tumor site via EPR effect. After accumulated in tumor, the fluorescence signal was gradually enhanced. And PCM exhibited enhanced tumor growth inhibition efficiency. On the basis of these results, this PCM overcomes many of the problems associated with PSs, such as poor solubility, cellular internalization and tumor targeting efficiency.

Keywords: micelle, photosensitizer, photodynamic therapy, cancer therapy

[P2.32]

Thermo-sensitive nanoparticle based on natural polymer for anti-cancer drug delivery

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Stimuli-responsive biomaterials are of great interest because of their properties and applications. In this study, we demonstrate thermo-sensitive nanoparticle (TSN) prepared with thermo-sensitive oligomer grafted natural polymer, as an anticancer drug delivery carrier. The phase transition temperature of TSN in aqueous solution showed around 35 °C. To confirm the potential of this carrier, we conducted an in vitro release study with DOX (a model drug) loaded TSN as a function of temperatures. The total amount of released drugs from the DOX-loaded TSN was increased with increasing temperature for 50 h. In the 50% inhibitory concentration (IC_{50}) analysis, the IC_{50} values of drug released from the DOX-loaded TSNs were approximately 6.3 and 10.2 μg/mL at 37 and 40 °C, respectively. These results suggest that the TSN can be a promising nanocarrier for cancer treatments.

Keywords: cancer therapy, drug delivery system, thermo-sensitive, nanoparticle

[P2.33]

Synthesis of new naphthoxazine-fused heterocycles via the modified Mannich reaction

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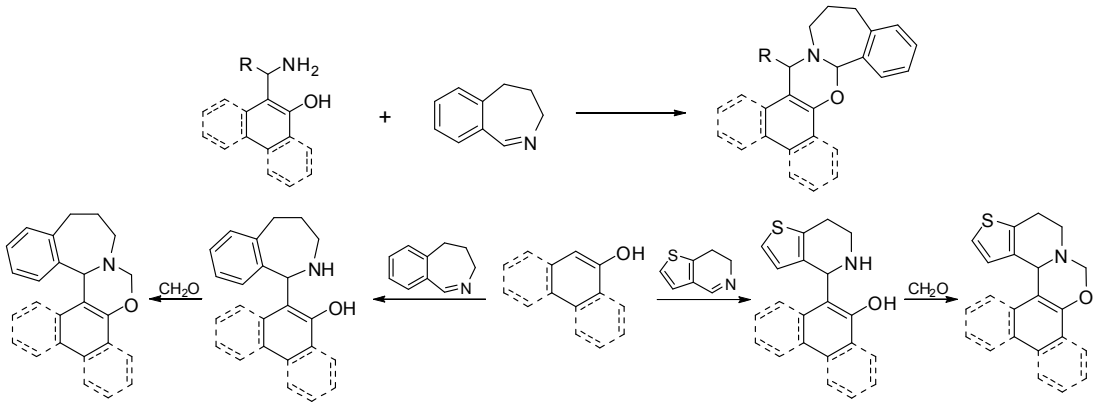
University of Szeged, Hungary

The Mannich reaction is an important C–C bond formation reaction that is widely used in the syntheses of secondary and tertiary amine derivatives and as a key step in the syntheses of many bioactive molecules and complex natural products.[1] We recently reported unexpected transformations between □-aminobenzylnaphthols and 3,4-dihydroisoquinolines to furnish naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinolines under microwave (MW) irradiation.[2-4] It was the major aim of this work to extend this recent reaction starting from 4,5-dihydro-3*H*-benz[*c*]azepine.



By the reaction of 4,5-dihydro-3*H*-benzo[*c*]azepine and □-aminobenzylnaphthols, substituted naphth[1,2-*e*][1,3]oxazino[3,2-*a*]benz[*c*]azepine derivatives were synthesized. The synthesis of the analogue naphth[1,2-*e*][1,3]oxazino[3,4-*a*]benz[*c*]azepines were achieved by the reaction of naphthol analogues with 4,5-dihydro-3*H*-benz[*c*]azepine followed by the ring closure with formaldehyde. This latter reaction was extended by using 6,7-dihydrothieno[3,2-*c*]pyridine as cyclic imine.

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Keywords: aminonaphthol, naphthoxazine, benz[c]azepine, Mannich

[P2.34]

pH-responsive paramagnetic micelle for cancer diagnosis

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Department of Biotechnology, Republic of Korea

The most extensively and clinically used MRI contrast agents are paramagnetic gadolinium (Gd^{3+}) chelates, which enhance the signal intensity by reducing the longitudinal relaxation time (T1) of water protons close to the Gd^{3+} ion. Despite the biomedical potential of MRI, the use of clinically available Gd^{3+}-based contrast agents is compromised by their intrinsic low efficiency, which results in a need for high doses. To overcome the limitations of small molecule MRI contrast agents, various nanoparticle systems have been explored as platforms for the conjugation of small molecule contrast agents. Although this approach has led to enhanced MR relaxivity, many of these systems do not achieve rapid diagnosis within a few minutes, which is attributed to their time-dependent accumulation and the heterogeneous nature of tumors.

Herein, a cancer diagnosis MRI contrast agents has been developed using pH-sensitive polymeric micelles. The cancer diagnosis MRI contrast agents with pH sensitivity were self-assembled based on well-defined amphiphilic block copolymers, consisting of methoxy poly(ethylene glycol)-b-poly(L-histidine) (PEG-p(L-His)) and methoxy poly(ethylene glycol)-b-poly(L-lactic acid)-diethylenetriaminopentaacetic acid dianhydride-gadolinium chelate (PEG-p(L-LA)-DTPA-Gd). The cancer diagnosis MRI contrast agents have a spherical shape with a uniform size of ~40 nm at physiological pH (pH 7.4). However, in acidic tumoral environment (pH 6.5), the cancer diagnosis MRI contrast agents were destabilized due to the protonation of the imidazole groups of p(L-His) blocks, causing them to break apart into positively charged water-soluble polymers. As a result, the cancer diagnosis MRI contrast agents exhibit highly effective T1 MR contrast enhancement in the tumor region, which enabled the detection of small tumors of ~3 mm^3 in vivo at 1.5 T within a few minutes.

Keywords: MRI contrast agents, pH-responsive polymeric micelle, cancer diagnosis

[P2.35]

Catalyst-free coupling of partially unsaturated β-carboline with indole and naphthol derivatives

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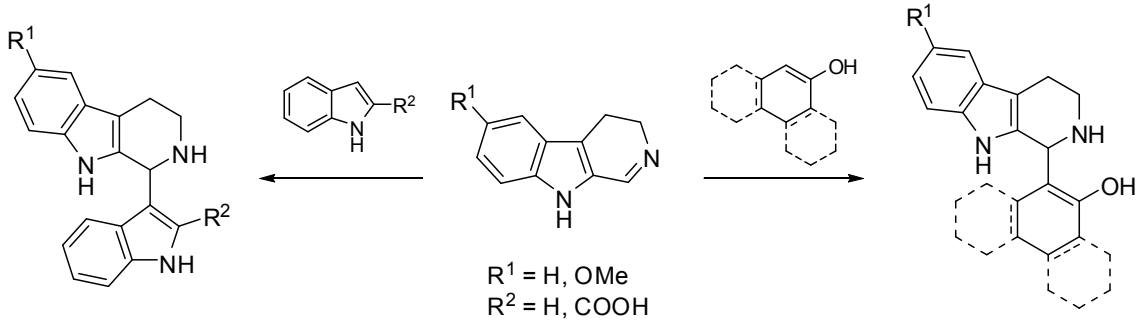
University of Szeged, Hungary

In our earlier investigations by the direct aza-Friedel-Crafts reaction of indole or indole-2-carboxyilic acid with dihydroisoquinolines new 3-substituted indole derivatives have been prepared by catalyst-free conditions under microwave irradiation.[1]



R^1 = H, OMe
R^2 = H, COOH

□-Carboline derivatives are widely distributed in nature, and many of them display important biological activities. Moreover, a vast number of □-carboline compounds have found applications as pharmaceuticals.[2] In present work we developed a new approach for the preparation of 1-substituted □-carbolines, starting from electron-rich aromatic compounds such as indole, indole-2-carboxylic acid, 2-naphthol or its analogues and partially unsaturated □-carboline derivatives as cyclic imine. All the reactions were optimized and were accelerated under microwave conditions.

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Acknowledgement: TÁMOP-4.2.2.A-11/1/KONV-2012-0052.

Keywords: beta-carboline, indole, aza-Friedel-Crafts, Mannich

[P2.36]

Asymmetric oxidation of substituted cyclopentane-1,2-diketones

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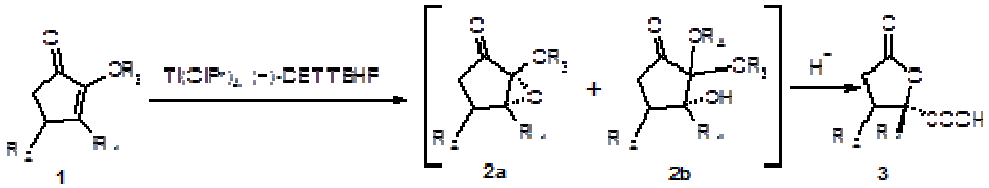
University of Technology, Estonia

Asymmetric oxidation of ketones is a convenient tool to introduce oxygen next to the carbonyl group, first proposed by Baeyer and Villiger in more than 100 years ago.[1] On the other hand, epoxidation of allylic double bond is another powerful oxidation tool, discovered by Sharpless more recently.[2] We have combined these two reactions - asymmetric epoxidation of enolate double bond, followed by the Baeyer-Villiger reaction - in one cascade for a wide variety of 1,2-diketone substrates **1**, resulting in the formation of substituted □-lactone carboxylic acids **3** with high yields and excellent enantioselectivities. Both, a stoichiometric and a catalytic mode of the reaction can be applied. The mechanistic and synthetic aspects of the reaction will be discussed.



For the substrates with R_2 = OH, depending on the combination of protecting groups at R_2 and at enol OH, different competing pathways exist: a cascade oxidation of 1,2-diketone and/or epoxidation of allylic alcohol. The products and enantio- and diastereoselectivity of the reactions with differently substituted substrates (R_1= alkyl; R_2 = H, OH or O-silyl group; R_3= H or silyl group), as well as ratios of the reaction products **2a** and **2b** from enantiomeric and racemic substrates **1** (R_2 = OH; R_3 = silyl group) will be discussed.

Application of the asymmetric oxidation approach in the synthesis of different chiral compounds (tetrahydrofuran derivatives, nucleoside analogues, homocitric acid, lycoperdic acid etc) will also be discussed.

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[2] Katsuki, T., Sharpless, K. B. *J. Am. Chem. Soc*., **1980**, *102*, 5974.

Keywords: asymmetric oxidation, lactone acid, 1,2-diketones

[P2.37]

Efficient synthesis of MeBmt, the unusual amino-acid of cyclosporin A

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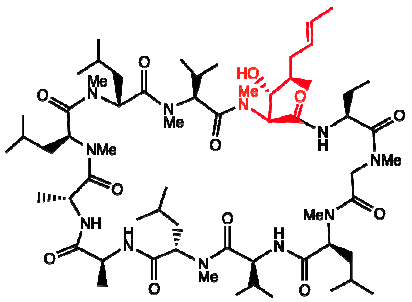
University of Liverpool, UK

The cyclic undecapeptide cyclosporin A **1**[1] has attracted considerable medicinal attention as both an immunosuppressant[2] and an antiviral agent.[3] A significant structural feature of **1** is the unusual amino-acid (4R)-4-[((E)-2-butenyl]-4-methyl-L-threonine (MeBmt, **2**), which poses a major synthetic challenge.[4] An activated form of the hexenoic acid **3a** or the corresponding aldehyde **3b** offer potential intermediates *en route* to **2**.



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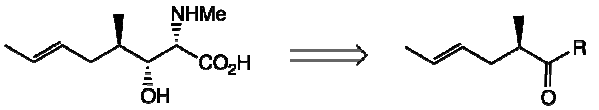
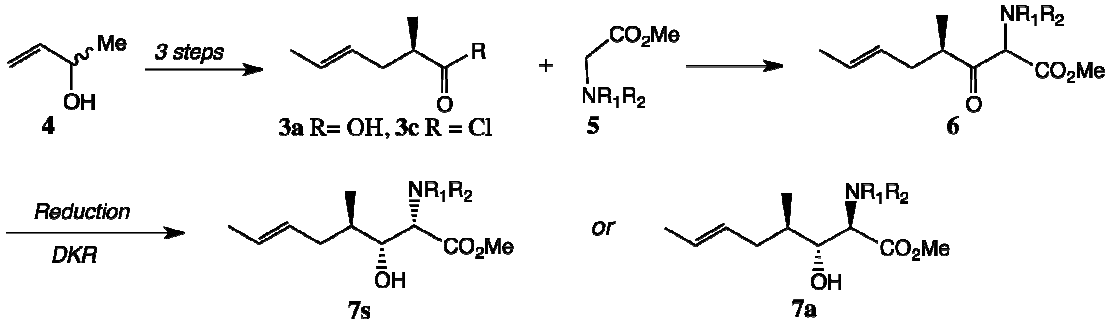


2 **3a**, R = OH; **3b**, R = H

Carboxylic acid **3a** is available in an efficient sequence starting from (±)-2-methyl-3-butenol **4**, involving an enzyme resolution followed by acylation and Claisen ester enolate rearrangement, as we shall demonstrate. We shall present a highly convergent synthesis of **2** from **3a**, involving firstly a $TiCl_4$-catalysed crossed Claisen condensation of the type described by Tanabe *et al.*[5] between the acid chloride **3c** derived from **3a** and an appropriate glycine or sarcosine derivative of general structure **5**.



Reduction of the resulting ketoesters, of general structure **6**, has proved to be a very good route to □-amino, □-hydroxy amino-acid derivatives **7s/7a**. Under dynamic kinetic resolution conditions employing a Ru catalyst, either the *syn*- or *anti*-diastereoisomer may be the preferred product,[6] with the absolute stereochemistry controlled by the chiral ligand [(*R,R*)- or (*S,S*)-Ts-DPEN]. The chirality of the side chain of acid **3a** is maintained under these conditions; effectively the DKR step is catalyst controlled. We have found significant differences in the stereochemical course of the reduction of substrates **6**, depending on the presence or absence of *N*-methylation and the electronic character of the protecting group, amide or carbamate. Overall, the sequence offers a highly convergent synthesis of MeBmt **2**.

References 1. *Eur. J. Appl. Microbiol.* 1976, **3**, 125. 2. *Helv. Chim. Acta* 1976, **59**, 1075. 3. *Hepatology* 2006, **43**, 761. 4. *Biosci. Boitech. Biochem.* 1995, **59**, 2228-2230. 5. *J. Am. Chem. Soc.* 2005, **127**, 2854-2855. 6. *Chem. Eur. J.* 2012, **18**, 7219-7223.

Keywords: Cyclosporin, Amino-acid, Immunosuppressant, Stereoselectivity

[P2.38]

Photochemical internalization using stimuli-responsive photodynamic nano-micelle

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Photochemical internalization (PCI), a progressive approach to extended photodynamic therapy (PDT), is promising technique for a number of nanocarrier in improving drug delivery efficacy. The mechanism involves using photosensitizer which localizes on endosomal/lysosomal membrane, to breakdown endosomal/lysosomal membranes and then release the endocytosed drugs into the cytoplasm by reactive oxygen-induced process. However, PCI causes phototoxicyty due to poor target selectivity. This leads to side effects as normal cell and vascular damage for clinical application. Therefore, it is necessary to demonstrate advanced drug delivery carrier system with stimuli-responsive system to control photo-activity of photosensitizer (PS).

Herein, we demonstrate that enzyme-sensitive photodynamic nano-micelles (PDNMs) are capable of encapsulation of the anticancer drugs and PS-mediated effective cancer therapy. PDNMs were self-assembled from PS or Quencher (Qc) conjugated to amphiphilic copolymers. PDNMs have about 100 nm with a spherical shape. The quenching efficiency of the PDNMs was dependent on the ratio of PS/Qc. However, in the presence of the enzyme, enzyme sensitive linkers of PDNMs are cleaved which leads to collapse of PDNMs, trigger drug release and restore photo-activity. In comparison with anticancer drug treatment alone, the combined treatment of anticancer drug loaded PDNMs with PCI synergistically induced the death of normal and drug-resistant cancer cells in vitro. These results suggest that this strategy can be utilized new platform for enhanced cancer therapeutic agent and effective cytosolic delivery of chemical and biological therapeutics.

Keywords: Photochemical internalization, cytosolic drug delivery, stimuli-responsive polymer, cancer therapy

[P2.39]

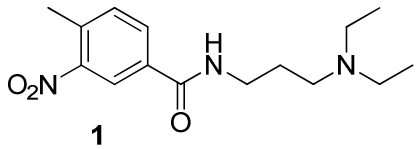
Synthesis of potential reactivators of nerve agent inhibited acetylcholinesterase

C. Lindgren*[1], J.M. Hillgren[1], C.D. Andersson[1], F. Ekström[2], A. Linusson[1]

[1]Umeå University, Sweden, [2]Swedish Defence Research Agency, Sweden

Acetylcholinesterase (AChE), an enzyme important for the termination of synaptic transmission of the neurotransmitter acetylcholine, can be inactivated by organophosphorous compounds (OPs) through phosphonylation of the catalytic serine residue. OPs have been used in chemical warfare, for instance the sarin terrorists attack in the Tokyo subway in 1995 or more recently in the civil war in Syria 2013. Pyridinium aldoximes are used as antidotes for nerve agents, attacking the phosphorus atom on the phosphonylated serine residue leading to reactivation. However, the efficiency of reactivation is affected by the structure of both the antidote and the nerve agent, for instance HI-6 can reactivate AChE inhibited by sarin but not tabun.[1]

A statistical molecular design has been based on a hit from a high throughput screen. The hit compound was divided into synthons, resulting in three sets of building blocks. A D-optimal design was applied to the resulting combinations for the selection of a subset used in SAR modelling, with the purpose to design and synthesize inhibitors targeting AChE.[2] One of the resulting compounds, **1**, has been the starting point for synthesis of potential reactivators of nerve gas inhibited AChE. The aim of this project has been to synthesize analogues to **1** where different nucleophiles have been introduced in the place of the tertiary amine and the length of the carbon chain has been varied. The compounds have been tested as binders and reactivators of AChE inhibited by tabun and sarin with promising results, and X-ray crystal structures have been solved to further study the binding modes of the substances.



1

[1] F. Worek et al.; *Biochemical Pharmacology*; 68 (**2004**) 2237-2248.

[2] C. D. Andersson et al.; Manuscript in preparation.

Keywords: AChE, Oximes, Nerve agents

[P2.40]

Sucrose derivatives as promising complexing agents for chiral cations

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Polish Academy of Sciences, Poland

Supramolecular chemistry deals with the study of noncovalent host – guest interactions. Especially interesting are interactions between chiral partners, which are responsible for e.g. enantioselective recognition. Synthesis of macrocyclic receptors designed to this goal is based on common enantiomerically pure starting materials such as: amino acids[1], binaphtyl[2], or sugars[3]. Examples of such receptors with these chiral building blocks incorporated in the macrocyclic structure are presented in **Figure 1**.

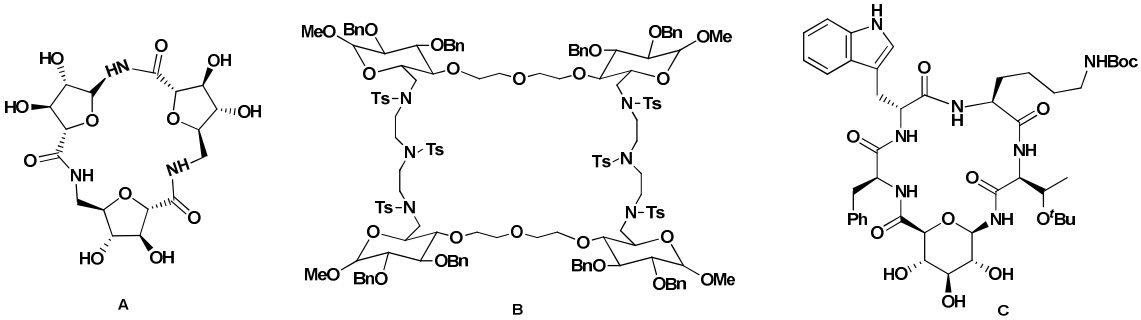
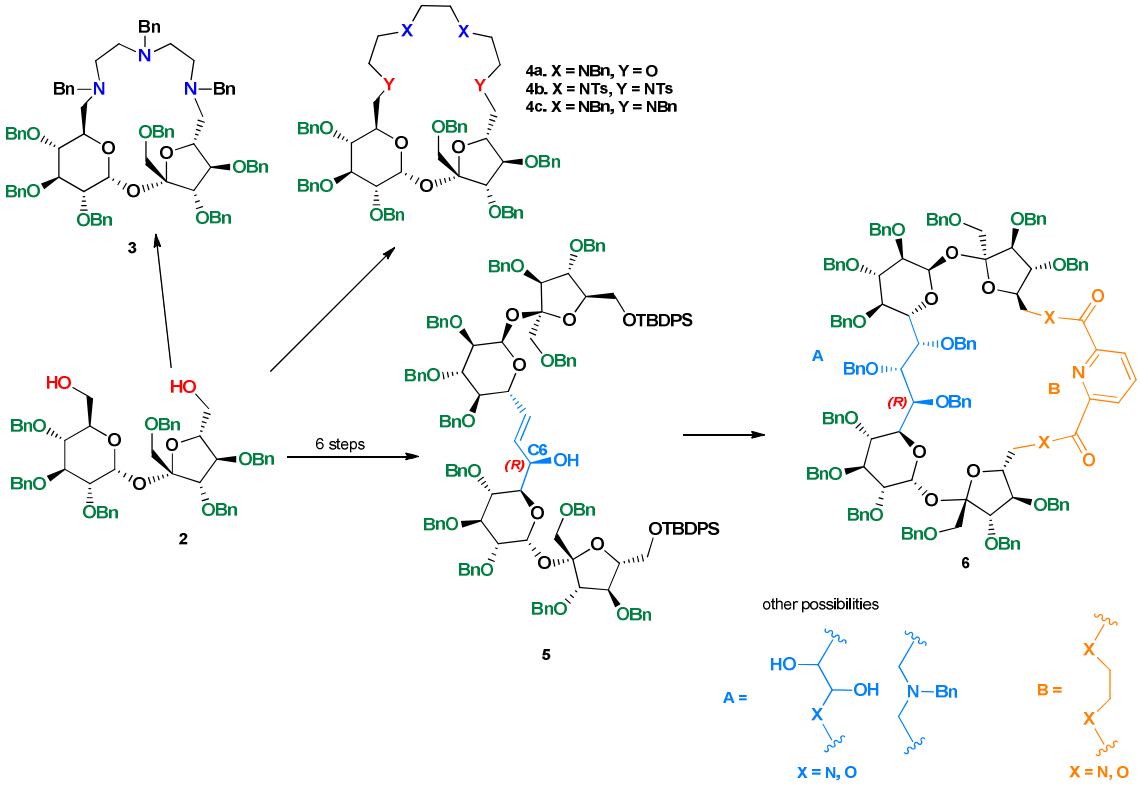


Figure 1: Different types of enantiomerically pure macrocyclic structures

Our group is engaged in the application of carbohydrates as building blocks in the preparation of the receptors able for enantioselective recognition of chiral guests. Although there are many examples in the literature of use of simple sugars to construct such receptors, only limited examples of receptors employing di-saccharide units are known. We have reported that sucrose can be a convenient platform for such macrocyclic receptors able to differentiate chiral cations. Starting from hexa-*O*-benzylsucrose, easily available in our laboratory,[4,5] we were able to prepare a number of derivatives of type **3** and **4**. Compound **4** exhibited high enantioselectivity toward (S)-α-phenylethylammonium cation.[6]

In this communication we will present another approach allowing to prepared macrocyclic derivatives containing two sucrose units in the molecule. The synthesis is initiated from protected sucrose **2** which is converted into α,β-unsaturated ketone in 6 steps. Reduction of the carbonyl group in this enone with $Zn(BH_4)_2$ provided alcohol **5** with high selectivity. The R-configuration at the newly created stereogenic center was verified by advanced NMR and CD experiments. Further steps will involve protection of the free OH as benzyl ether and oxidation of the double bond with OsO_4/NMO (this reaction should be highly diastereoselective acc. to the Kishi rule) Proper manipulation with the protecting groups followed by subsequent reaction with 2,6-pyridinedicarbonyl dichloride should open a route to a new class of macrocyclic compounds of type **6** (**Scheme 1**).



Scheme 1: Examples of macrocyclic compounds containing sucrose subunit.

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[6] Bartosz Lewandowski and Slawomir Jarosz, *Chem. Commun.*, **2008**, 6399–6401

Keywords: Sucrose, macrocyclic receptors, chiral cations

[P2.41]

Synthetic route development of potent 5-lipoxygenase activating protein (FLAP) inhibitors

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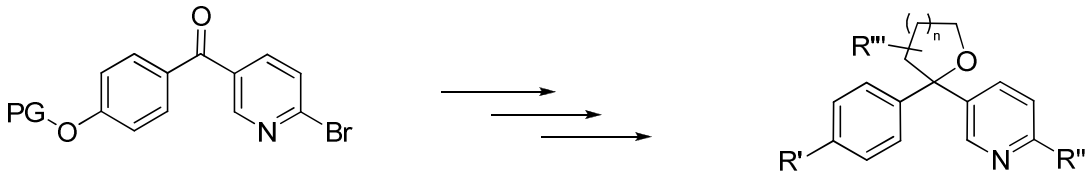
The candidate drug AZD6642 is a potent small molecule inhibitor of the 5-lipoxygenase activating protein (FLAP) in the 5-LO pathway. FLAP inhibitors reduce the production of bioactive leukotrienes, that are associated with inflammatory and vasoactive actions, and may therefore be valuable in the treatment of a variety of inflammatory diseases, e.g. atherosclerosis. AZD6642 was developed through a fast-follower approach with the objective to optimise a number of key parameters, e.g. potency and metabolic stability.

A variety of synthetic routes to this family of FLAP inhibitors will be covered, with main focus on core modifications and optimisation of side-chains. These routes include innovative syntheses that allow formation of different ring-sizes via ring-closing metathesis, substitutions in the central ring as well as preparation of modified tetrahydrofuranes via S_N1 and S_N2 reactions. Some biological data related to these inhibitors will also be revealed.



Keywords: FLAP, ring-closure, substitutions, metathesis

[P2.42]

Carbohydrate-based polymers with highly differentiated microstructures for drug delivery

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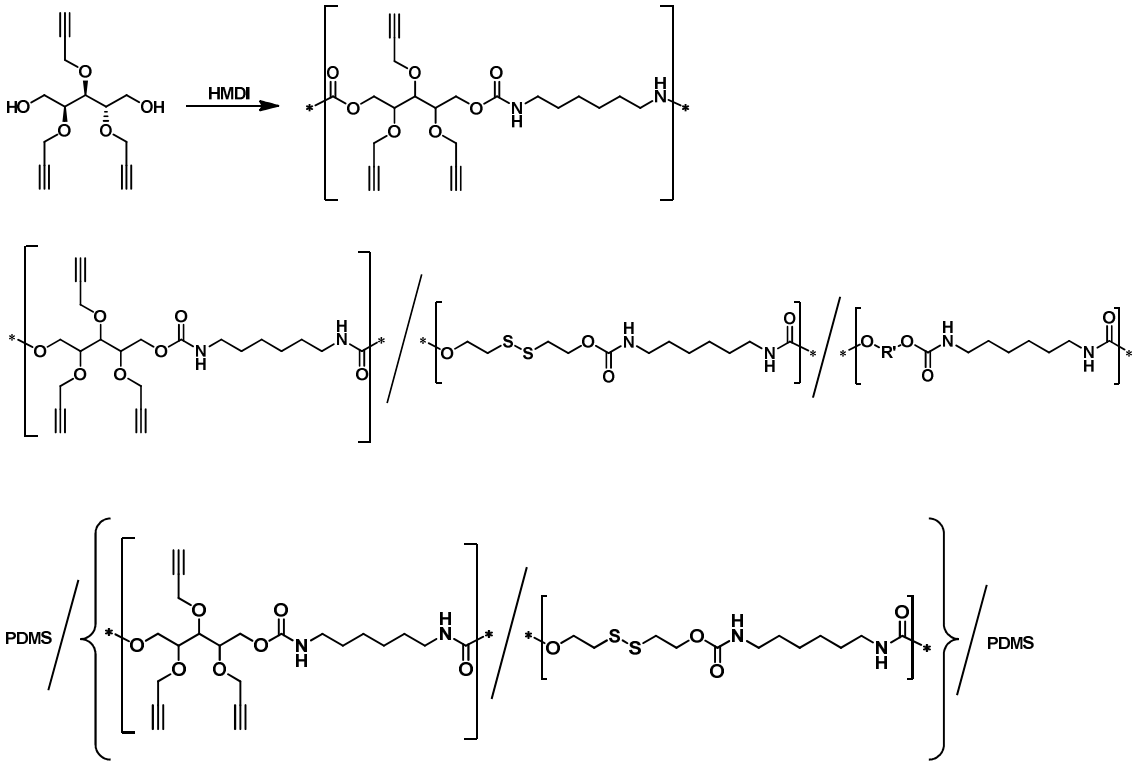
A topic of great interest in polymer science focuses on the synthesis of new biodegradable polymers to use them in biomedical applications; in particular, as drug or gen delivery systems (DDS or GDS). On the other hand, stimuli-responsive macromolecules are polymers that respond with marked changes in their properties to small variations in their environment [1]. Some of these smart materials belong to the group of reduction-sensitive polymers according to they react to glutathione [2]. Thus, the design of reduction sensitive polymers has resulted in opportunities for novel biomedical applications as these materials can be selectively degraded under reductive environments.

The aim of this work is the preparation of new homopolyurethanes and *random*- / *block*- or *comb*-copolymers, derived from L-arabinitol, able to self-assemble into supramolecular amphiphilic structures. To obtain these kinds of structures, we combined the preparation of highly differenciated microstructures in the polymer *via* click chemistry (the azide-alkyne Huisgen cycloaddition reaction [3]) and the incorporation of disulfide segments to transform them into biodegradable polymers [2].

We firstly investigated the synthesis of a batch of alkynyl-based polyurethanes susceptible of being derivatized by the azide-alkyne coupling reaction mentioned above. The incorporation of aliphatic units into the polymer backbone, poly(dimethylsiloxane) (PDMS) blocks or disulfide-diethanol units were carried out in order to modulate de lipophilic nature of the final material as well as its degradability.



The synthesized polymers react later -*via* click chemistry- with chemically diverse azides leading to the formation of graft-copolymers which may self-assemble into nanostructures. Several reaction conditions were studied (solvents, ligands, temperature, and Cu (I) and (II) salts).

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Keywords: Polyurethanes, Drug delivery, Sugar-based polymers, Biodegradable Polymers

[P2.43]

Isolation of phytochemicals from Launaea spinosa and their hepatoprotective effect on HepG2 cells damaged with t-BHP

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Phytochemical investigation of the flowering aerial parts of *Launaea spinosa* (Asteraceae) led to isolation of a new phenolic compound identified as diferulyl methyl tartrate ester (**6**), in addition to five known metabolites; Esculetin (**1**), Esculetin-7-O-glucoside (Cichoriin) (**2**), Fertaric acid (**3**), acacetin-7-O-glucoside (**4**), and acacetin-7-O-glucuronic acid (**5**). The structures of the isolated compounds were determined by comprehensive analyses of their 1D and 2D NMR and comparison with previously known analogs. To evaluate the hepatoprotective activity of isolated compounds against oxidative stress, we measured the cell viability in HepG2 cells damaged with *t*-BHP, a strong oxidative stress inducer. Treatment with *t*-BHP (200 μM) significantly decreased HepG2 cell viability to 11.5% of the control cells. Pre-treatment with compounds **1**, **4**, and **5** (10, 20 μM), or quercetin (10 μM) significantly protected HepG2 cell death induced by *t*-BHP in a dose-dependent manner. The hepatoprotective activity of compounds **1**, **4**, and **5** on HepG2 was further investigated through determination of aspartate aminotransferase (AST), alanine transaminase (ALT), superoxide dismutase (SOD) activities and malondialdehyde (MDA).

Keywords: Launaea spinosa, Hepatoprotective, acacetin-7-O-glucoside, acacetin-7-O-glucuronic acid

[P2.44]

Synthesis of biodegradable polymers containing disulfide bonds and preliminary studies as colon-specific drug delivery systems

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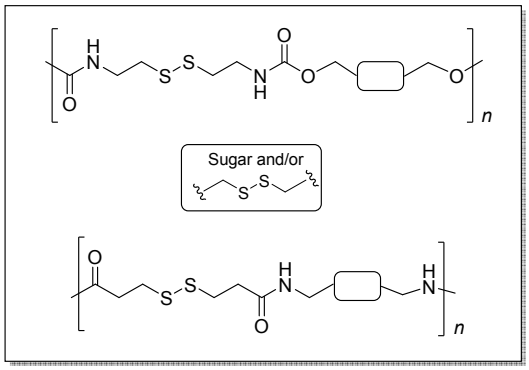
Microflora-activated systems appear to be the most promising approach for colon-specific drug delivery (CDDS) because of the increased amount of bacterial population and associated enzyme activity in the colon. Biodegradable polysaccharides, which pass intact from the upper gastro intestinal tract, have been used in the initial approaches for CDDS achieving limited success. On the other hand, major metabolic processes occurring in the colon are hydrolysis and reduction by hydrolytic and reducing enzymes, respectively.

Synthetic carbohydrate-based polymers have shown to be biodegradable and biocompatible materials.[1,2] Furthermore, the presence of disulfide bonds along the polymer chains will ensure the biodegradation of the polymers under reductive conditions. Thus, a series of polymers containing both carbohydrate moieties and disulfide bonds have prepared to be evaluated as CDDS.



Polyurethanes are prepared by the polycondensation reaction of bis(beta-isocianatoethyl) disulfide and 2,2'-ditihiodiethanol or alditols. Polyamides are prepared from the active esters of 3,3'-dithiodipropionic acid and cystamine or sugar-based diamines.

Preliminary studies as CDDS of the above mentioned polymers are under course. All disulfide bonds are readily reduced in the presence of glutathione.

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Keywords: biodegradable polymers, carbohydrate-based polymers, colon-specific drug delivery, disulfide bonds

[P2.45]

Intra-cell chemical and structural analysis using deep-subwavelength mid-IR absorption imaging

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In the first instance, we have developed a new “Digistain” mid-IR Imaging technique to augment conventional H+E histopathology protocols. It uses the absorption of certain mid-IR light wavelengths (3μm to 15μm) that excite well-known chemical bond vibrations, to map out, quantitatively, the 2D spatial distributions of chemical compounds in a tissue biopsy specimen. It does this with unprecedented spatial resolution, in a few seconds.

We have already used it to image tissue slices from cancer patients. We have shown that it reveals chemical changes in the tissue that are markers for cancer, and which potentially offer a means of diagnosis that is both more accurate and predictive than standard histopathology techniques currently available. A prototype machine is undergoing clinical trials.

Secondly, at a rather more technically advanced level, we are developing a new probe based chemical analysis method, so-called s-SNOM, to work with a recently available new range of tuneable diode lasers that span this wavelength range. S-SNOM (scattering Scanning Near-Field Optical-Microscopy) brings an extremely sharp (~10 nm radius) AFM tip close to a specimen, and the way it scatters the mid-IR light allows the chemical composition of a tiny region (~20 nm across) under the tip to be inferred.

By subsequently rastering the tip across, say a single cell, an ultra-high-resolution picture of its chemical composition can be built up in a way that has never been possible before.

The new ability that this brings to study the chemical structure of a single cell, is expected to have very wide applications across the biosciences, allowing “ single cell studies” of heterogeneity, plasticity etc, in a wide range of clinically important topics, including cancers, immunological studies, drug resistance and toxicity studies.

Although the technology is in its infancy, we genuinely believe that it is a game-changer, and the talk will feature a range of examples taken mostly from cancer and immunology studies.

Keywords: Chemical Imaging, Drug discovery, Chemical analysis

[P2.46]

Progress towards a total synthesis of (–)-exiguolide

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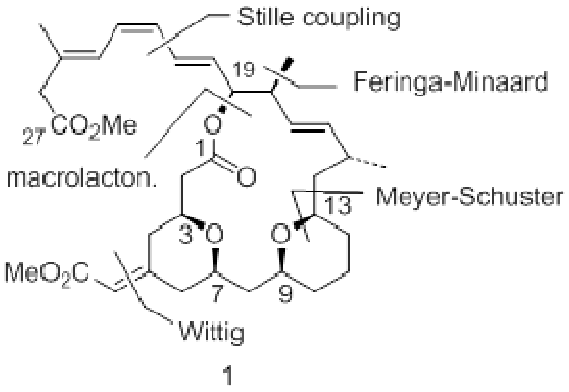
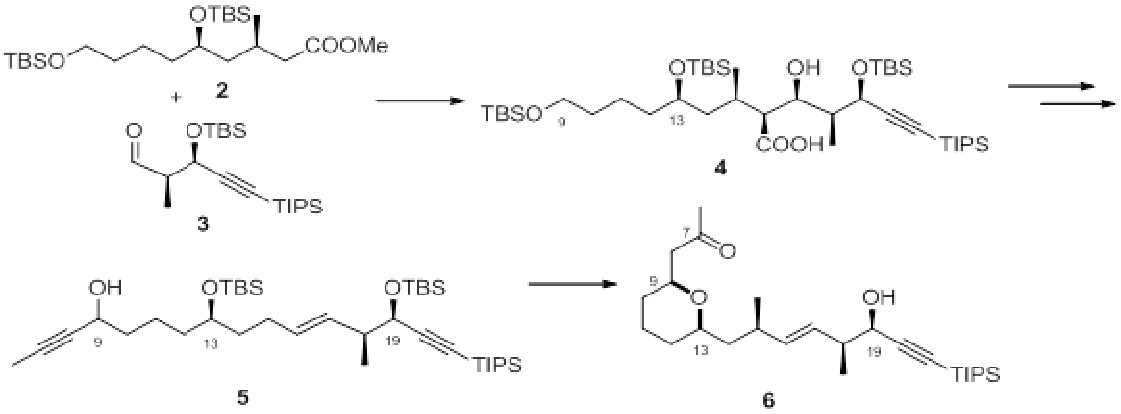
Exiguolide (**1**) is a natural product, that was isolated 2006 from the marine sponge *Geodia exigua* by the Ikegami group[1]. This molecule shows antiproliferative ability against NCI-H460 human lung large cell carcinoma and A549 human lung adenocarcinoma cell lines[2].

Current work focuses on the synthesis of (–)-exiguolide by using the gold-catalysed Meyer-Schuster-rearrangement for introducing the first of two tetrahydropyran rings of exiguolide (cf. fragment (**6**)) **(**Scheme 1)



Scheme 1: Retrosynthetic scheme for (–)-exiguolide

In this current work fragment (**6**) was synthesized by Meyer-Schuster-Rearrengement of propygylic alcohol (**5**) followed by intramolekular Oxo-Michael-addition[3]. Fragment (**5**) itself was prepared from hydroxy ester (**4**). Aldehyde (**3**) is known and was made by an Evans-aldol reaction. Ester (**2**) would be obtained in nine steps from pentanediol. The required stereocenters were introduced by Feringa-Minaard reaction and Brown-allylation in excellent stereoisomeric ratios (Scheme 2).



Scheme 2: actual synthesis

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Keywords: exiguolide, gold catalysis, Meyer-Schuster rearrangement, stereocenter

[P2.47]

Click reactions with azides derived from 5-methyluridine

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Azide-alkyne cycloaddition reactions, also known as “click reactions”, are very useful in range of biological applications such as fluorescent labelling of biomolecules. Two groups of click reactions are known. First of them, copper catalysed click reactions, are very useful for triazoles preparation. But due to the copper ions toxicity towards biological systems it´s impossible to use them in biological applications. On the other hand, non-catalyzed (copper free) click reactions can be used for this purposes because of copper catalyst absence. But only very reactive alkynes, especially based on cyclooctyne, react according to this principle and their amount is still limited.

Our attention was paid to reactivity study of azides derived from 5-methyluridine towards catalysed and copper free click reactions. Range of structurally new triazoles was prepared by catalysed click reactions with four model acetylenes (Figure 1.). All these triazoles will be tested on biological activity.

Copper free click reactions were tested with dibenzoazocine derivative (Figure 1.). All products were formed quantitatively and very fast. In this case we also studied fluorescent properties of prepared conjugates. Unfortunately, both absorption and emission proceeded at very low wave lengths.

Use of different linkers and fluorescent probes can allow preparation of dibenzoazocine library which can serve for fluorescent labelling of biomolecules *via* click chemistry.

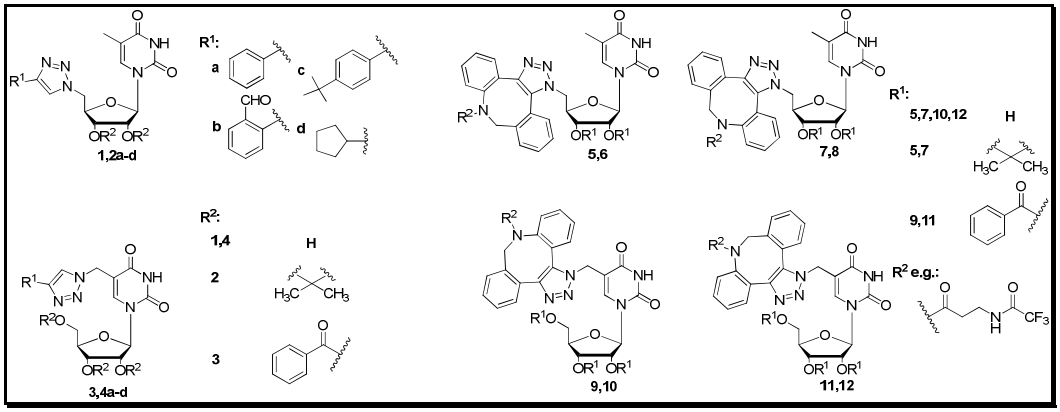

Figure 1.: Triazoles prepared by catalyzed and copper free click reactions

Acknowledgement: Research of this project was supported by these projects CZ.1.07/2.2.00/28.0184 and CZ.1.05/2.1.00/01.0030.

Keywords: click reactions, 5-methylurudine, dibenzoazocine, fluorescent properties

[P2.48]

Direct arylation of purine on solid phase and its use for chemical libraries synthesis

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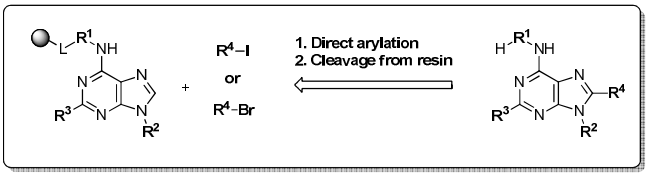
Direct arylation is an efficient and suitable method for formation of a regioselective C-C bond in one step. In this research we described an expeditious and efficient methodology for solid-phase synthesis of 2,6,8-tri or 2,6,8,9-tetrasubstituted purine derivatives using direct C^8-H arylation following two nucleophilic substitutions and optionally *N*-alkylation to access derivatives with three or four diverse positions. In combination with solid-phase synthesis it can be used as a powerful tool for high-throughput synthesis of chemical libraries.



The versatility of the method was documented by the preparation, isolation and full characterization of fourteen 2,6,8,9-tetrasubstituted purines. An optimized reaction sequence provided target compounds in very good purity. The conditions were evaluated for aryl iodides as reactants, but aryl bromides were also found to be applicable as reactants though reaction times were prolonged. The method was applied, also, for the synthesis of 2,6,8-trisubstituted compounds. The method is suitable for high-throughput synthesis of chemical libraries from commercially-available synthons to afford, rapidly, a set of compounds for biological screening. In our case, the all prepared compounds were subjected to MTT cytotoxicity test and in general, significant anticancer activity has been detected. The method thus represents an additional tool for systematic biological study of purine derivatives using combinatorial chemistry.

This research was supported by projects CZ.1.07/2.3.00/20.0009 and CZ.1.07/2.2.00/28.0184 coming from European Social Fund and Internal grants of Palacky University (No. PřF_2013_027). The infrastructural part of this project (Institute of Molecular and Translational Medicine) was supported from Operational Program Research and Development for Innovations (project CZ.1.05/2.1.00/01.0030).

Vaňková, B., Krchňák, V., Soural, M.,Hlaváč, J. *ACS Comb. Sci.* **2011,** *12,* 496-500.

Keywords: purines, direct arylation, coupling reaction, solid-phase synthesis

[P2.49]

Synthesis, structural characterization and antitumor activity of new copper(II) complex with N-substituted sulphonamide ligand

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Cancer is a worldwide major cause of death, chemotherapy being the treatment of choice for most types of cancers, despite the amount of limitations, due to its lack of specificity and its side effects.

It has been proven that copper complexes have anticancer effect , but the mechanism and pharmacokinetics are not fully elucidated yet. In this study we evaluate the anticancer effect of a new Cu(II) complex $[Cu(L)_2(py)_2(H_2O)]$ with a N-sulfonamide ligand, N-(5-(4-methylphenyl)-[1,3,4]–thiadiazole–2-yl)-toluenesulfonamide (HL) new synthetised.

The X-ray crystal structure of the ligand and of the complex have been determined. In the complex, the Cu(II) ion is five-coordinated, forming a CuN_4O chromophore. The ligand acts as monodentate, coordinating the metal ion through a single $N_{thiadiazole}$ atom. The molecules from the reaction medium (pyridine and water) are also involved in the coordination of the Cu(II) ion. The complex has a slightly distorted square pyramidal geometry. The complex was characterized by FT-IR, electronic, EPR spectroscopic and magnetic methods.

The copper complex was also evaluated using a transplantable tumor model on laboratory mice, Ehrlich Ascites Carcinoma inoculated intraperitoneally in female Swiss mice. The investigation was focused on antiproliferative parameters and also the assessment of side effect of tumor growth on general health status. The results showed an inhibition up to 80% of body weight gain and also the prevention of accumulation of the ascitic fluid up to ten fold. The tumor cell concentration was also affected, unfortunately the viability of the cells wasn`t influenced but the hematological parameters and peritoneal citology presented significant changes.

Keywords: copper(II) complex, sulphonamide, antitumor activity, crystal structure

[P2.50]

Hyperbranched low band-gap semiconducting copolymers for application in high-tech electronics

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Polymer materials have rapidly found wide applications as construction materials, chiefly owing to those properties including their resistance to corrosion, low specific gravity, aesthetic appearance, etc. that make them superior to metals or inorganic matrices [1].

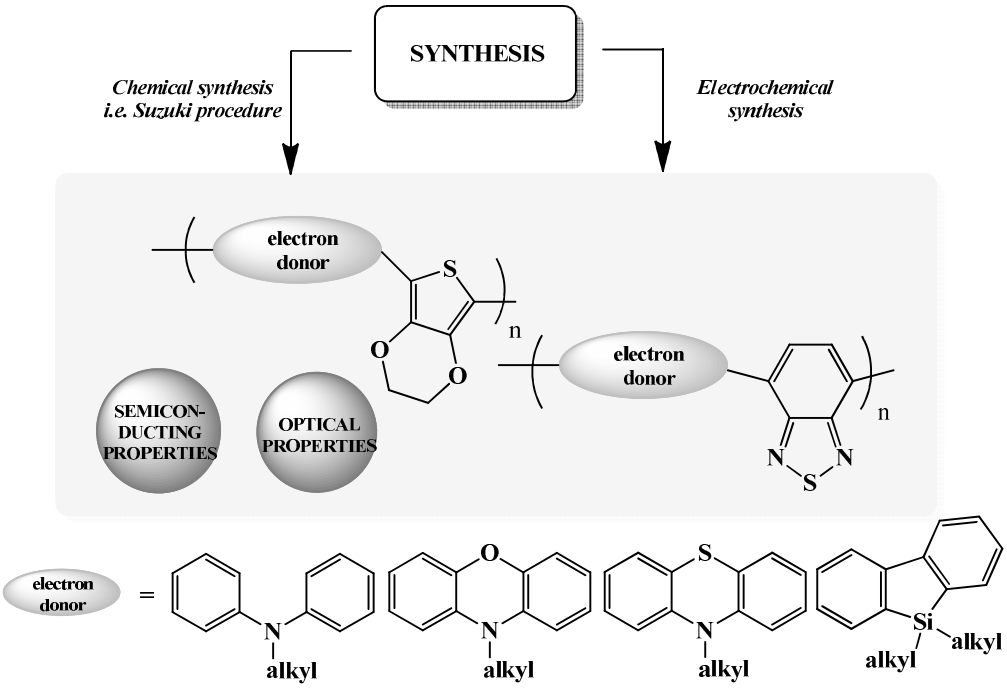
In addition hyperbranched polymers/copolymers have often good solubility, lower melt viscosity, and extremely high density of functional groups at the surface compared with the linear analogues. Hyperbranched polymers should therefore also increase the solubility of carbon-nanotubes [2].

Therefore, the strong interaction between organic and i.e. inorganic components creates unique photophysical, electrochemical and photochemical properties, which make these conjugated polymers potential materials for applications in electroluminescence, solar energy conversion, sensors, nonlinear optics and photo-refraction materials [3].

In this way, materials with properties typical of insulators, semiconductors, and even conductors, can be obtained. Therefore, our approach mainly targets in the formation of new electron accepting materials and their combination with classical electron-donor functionalities producing polymer electron donor − acceptors directly applicable to plastic solar cells as the polymeric layer or other elements of high-tech electronics and sensor devices.

The following materials are obtained by investigated in details methods: the cross-coupling of aryl halides with aryl boronic acids (*the Suzuki coupling*); the palladium-catalyzed reaction between an aryl and (or) alkyl halide and a vinyl functionality (*the Heck reaction*); and the palladium-catalyzed cross-coupling reaction of organostannyl reagents with a variety of organic electrophiles (*the Stille reaction*) or in process of electropolymerization [4].

Due to previous experience [5], we designed and synthesized a series of branched copolymer-derivatives bearing i.e. bisthiophene, ethylenedioxythiophene, benzothiodiazole as a functional unit core (Scheme).



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Keywords: C-C coupling reactions, copolymers, semiconducting materials, electronics

[P2.51]

A photochemical logic gate for cellular imaging

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Janelia Farm Research Campus, Howard Hughes Medical Institute, USA

Photolabile (caged) compounds are important tools to mark and manipulate cells. The utility of caging groups is wholly dependent on the precise, spatiotemporal delivery of light within a complex biological environment. Here, we refine and extend the utility of chemical cages by introducing an additional requirement for uncaging. Caging groups that require a second input to trigger photochemistry can serve as photochemical logic gates, where the introduction of logic allows for more sophisticated control of molecular activity in a complex biological setting. By incorporating a reversible ion-recognition unit into a photolabile cage, we have developed a molecular "AND" logic gate that requires coincident illumination and binding of a specific ion to induce photochemical reaction. Due to the importance of Ca^{2+} flux in biology, a calcium-sensitive photocage was targeted for proof-of-concept experiments. Through a modular, convergent synthesis featuring an atypical Mitsunobu reaction as the key step, a Ca^{2+}-dependent cage was synthesized that incorporated a photolabile *o*-nitrobenzyl group into the calcium ion chelator 1,2-bis(*o*-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid (BAPTA). After attachment of this new cage to a membrane-permeant coumarin and other fluorophores, the Ca^{2+}-dependent cage was found to exhibit a 600-fold enhancement in photochemical quantum yield in the presence of Ca^{2+}. Modulation of the K_d of the cage was achieved through changes in the substitution pattern of the BAPTA moiety, with the optimal analog displaying a Ca^{2+} K_d = 8 □M. The Ca^{2+}-dependent cage/coumarin construct was evaluated in a cellular context by incubation with cultured hippocampal neurons. A 40-fold increase in accumulated fluorescence was seen upon illumination of cells pretreated with ionomycin when compared to illumination of control cells. This calcium-dependent probe—the first example of an ion-dependent cage that functions in living cells—thereby constitutes a proof-of-principle "snapshot reporter" that exhibits a permanent fluorescence change correlated with transient analyte concentration during an illumination-defined epoch.

Keywords: Caged compounds, Calcium, Photochemistry, Logic gate

[P2.52]

Flexible, phase-transfer catalyzed approaches to 4-substituted prolines

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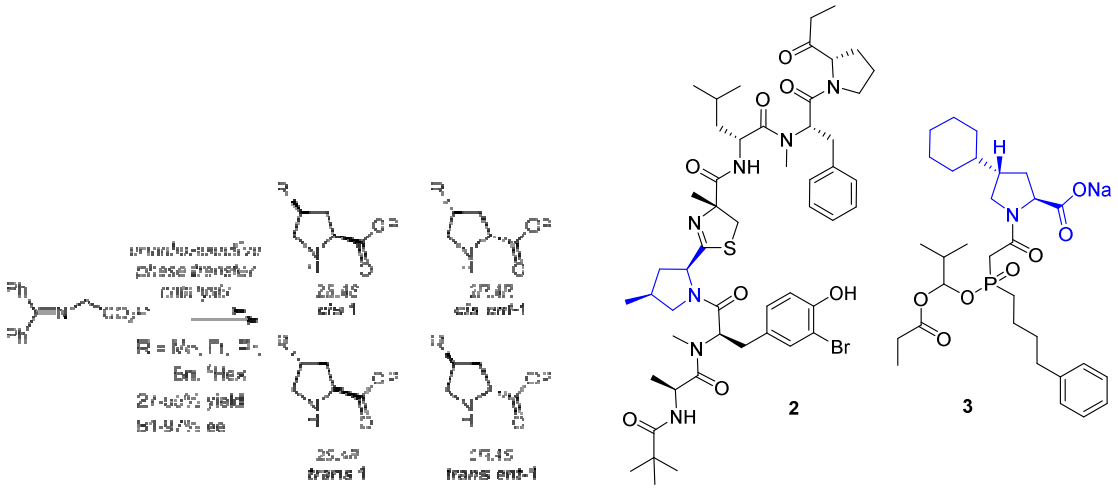
Proline is unique among the proteogenic amino acids as it forms a conformationally-restrained amide bond and can induce α-helices, β-sheets and numerous other changes in protein secondary structure. These conformational motifs are the basis of a number of biological interactions. Though less ubiquitous, inclusion of 4- substituted prolines **1** can have a dramatic effect on protein structure and therefore bioactivity.[1] Found in halovirs A-E (antiviral), clindamycin (antibiotic), spumigins (cytotoxic) and leucinostatins (antibiotic and antitumour), 4-substituted prolines are essential to their mode of action. Initially, our interest in **1** came about by investigation of the potent, cytotoxic peptide bisebromoamide **2** and the known ACE inhibitor fosinopril **3**, which both contain specific 4-substituted diastereomers.[2] However, existing synthetic routes are either lengthy, reliant on expensive chiral pool starting materials, poorly stereoselective or are restricted to accessing only one stereoisomer. We therefore developed a general route which would enable the stereoselective synthesis of diastereomers of 4-substituted prolines from commercially available achiral starting materials. Phase transfer catalysis allows direct access to both enantiomeric series, while *cis/trans* stereoisomerism is readily controlled through hydrogenation conditions.[3]



Asymmetric phase transfer catalysed Michael addition of a glycine Schiff base to α,β-unsaturated aldehydes and subsequent elaboration of the adducts, allows the rapid synthesis of a range of 4-substituted proline derivatives in only 5 steps with 27-55% overall yield and excellent enantiopurity.[4] Both *cis,* as in bisebromoamide **2**, and *trans*, as in fosinopril **3**, diastereomers can be synthesized in high d.r. and yield. The range of substituents (R) that can be employed, makes the method an ideal choice for the synthesis of 4-substituted prolines for incorporation into peptides, small molecule drug candidates and natural products.

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Keywords: 4-substituted proline, Unnatural amino acids, Michael addition, Phase transfer catalysis

[P2.53]

Catalysis with block-copolymer micelles: A combinatorial study

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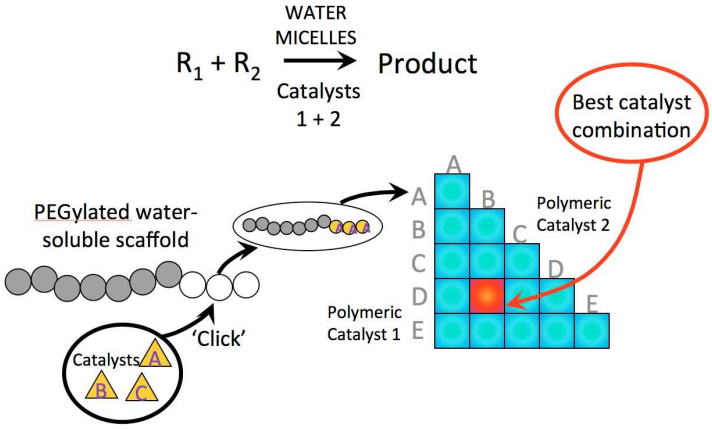
[1]King Abdullah University of Science and Technology, Saudi Arabia, [2]Lomonosov Moscow State University, Russia



A key step in a number of key bond-forming reactions, such as Mannich, Michael, Friedel-Crafts, and conjugate additions is the activation of an electrophilic reagent by Lewis acids or H-bond donors. Nature's enzymes perform these reactions in water effortlessly, by positioning the reactants and catalytic moieties within hydrophobic binding pockets.[1] Water is rarely the solvent of choice for chemist-designed reactions: it is not suitable for hydrophobic substrates or catalysts, and is highly competitive as a hydrogen bond acceptor and a Lewis base. Here, we shall describe our current progress towards enzyme-inspired catalysts. We prepared a number of "clickable" amphiphilic block-copolymer scaffolds, which we proceeded to functionalize with a number of potentially catalytic or co-catalytic functional groups.[2] When the polymers were

screened in systematically varied pairs, a number of effective catalytic systems were identified. This approach to catalyst discovery is general, and can be extended to other chemistries, polymer scaffolds and catalytic moieties.

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[P2.54]

Stereocontrolled synthesis of diastereomers of 3-aminocyclohexane-1,2,4 tricarboxylic acids

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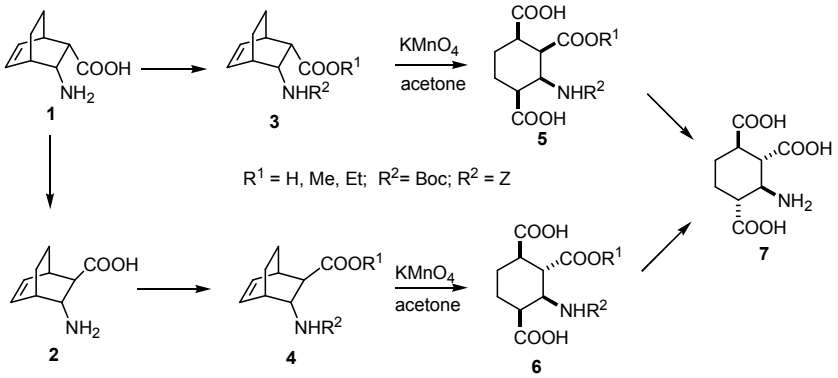
In consequence of their biological effects, conformationally constrained alicyclic □-amino acids have generated great interest among synthetic and medicinal chemists in the past decade. These compounds are found in natural products, they are also considered important precursors for pharmacologically interesting □-lactams and other bioactive compounds. These compounds may be applied as building blocks in peptide synthesis, the incorporation of novel □-peptides.[1]

As part of our program to synthesize structurally diverse □-amino acids our aim was to prepare alicyclic 3-aminocyclohexane-1,2,4-tricarboxylic acid diastereomers. We recently reported the development of a simple methology for efficient and stereoselective syntheses of the title amino acids starting from 2,3-*diendo*- and 2-*exo*-3-*endo*-3-aminobicyclo[2.2.2]oct-5-ene-2-carboxylic acids **1** and **2**.[2,3]



The ring opening of bicyclic derivatives can be achived by sterically controlled oxidative cleavage[4] of the carbon-carbon double bond of *N*-protected-2,3-*diendo*- and 2-*exo*-3-*endo*-bicyclo[2.2.2]octane □-amino acids and esters **3** and **4**. Compounds **3** and **4**, in acetone, were treated an aqueous solution of $KMnO_4$ at 0 °C to give tricarboxylic acid derivatives **5** and **6** after chromatographic separation and crystallization. The sodium methoxide mediated isomerization of **5** and **6** (R^1=Me) yielded the termodinamically most stable stereoisomer amino tricarboxylic acid **7**.

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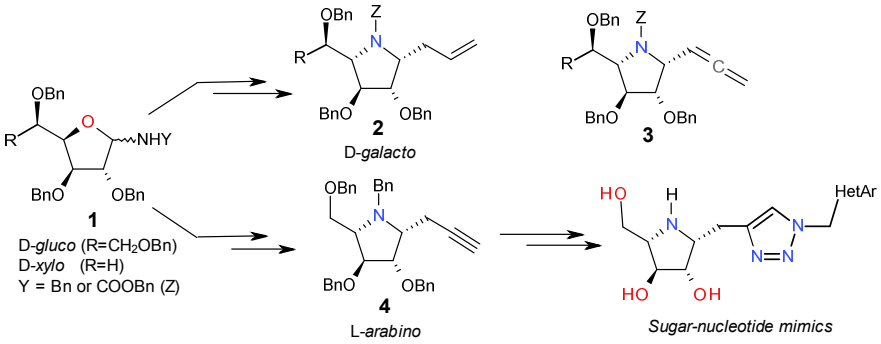
Keywords: beta-amino acid, stereoselective, oxidative cleavage, isomerization

[P2.55]

Novel glycoside mimics from glycosylamines: synthesis by way of 1-C-(2-propynyl) iminosugar derivatives

C. Nicolas*[2], C. Cocaud[1], F. Engo-Ilenga[1], O. Martin[1]
[1]*University of Orleans, France,* [2]*CNRS Orleans, France*

Sugar analogs with nitrogen in the ring, or iminosugars, are gaining increasing importance as therapeutic agents for a diversity of diseases: the *N*-butyl and the *N*-(2-hydroxyethyl) derivatives of DNJ (1-deoxynojirimycin) are already commercial drugs. In this context, our group has been actively inves-tigating new iminosugar derivatives designed to exhibit higher efficiency and selectivity towards specific enzymes, and has focused on the synthesis of **iminoglycosides mimics**. Of particular interest are derivatives in which the 'aglycone' is linked to the anomeric carbon by a C-C-bond (imino-*C*-glycosides). Such compounds have been shown to demonstrate exquisite selectivity and potent activity as glycosidase inhibitors for example towards GCase, the enzyme involved in Gaucher disease.[1] We have recently developed a concise synthetic approach to furanosides mimics such as **2** based on the chain extension of furanosylamines (e.g. **1**) as imine surrogates by the addition of an organometallic species:[2] such intermediates have been used for the synthesis of a diversity of galactofuranoside mimics. In parallel we have searched for conditions to introduce a substituent carrying a triple bond in order to further extend the type of glycoside analogs accessible, in particular sugar nucleotide mimics. While conditions based on the use of silylated reagents gave systematically 1-*C*-allenyl derivatives such as **3**, we have been able to achieve the addition of a propargyl group without rearrangement, namely using organozinc reagents.



The resulting intermediates open access to a diversity of sugar nucleotide mimics which are potential inhibitors of glycosyltransferases. Details of these investigations and applications will be reported.

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Keywords: Iminosugars, Glycosidase inhibitors, Carbohydrate chemistry

[P2.56]

N-trifluoromethylthiophthalimide: a stable electrophilic SCF_3 reagent and its application in the catalytic asymmetric trifluoromethylsulfenylation

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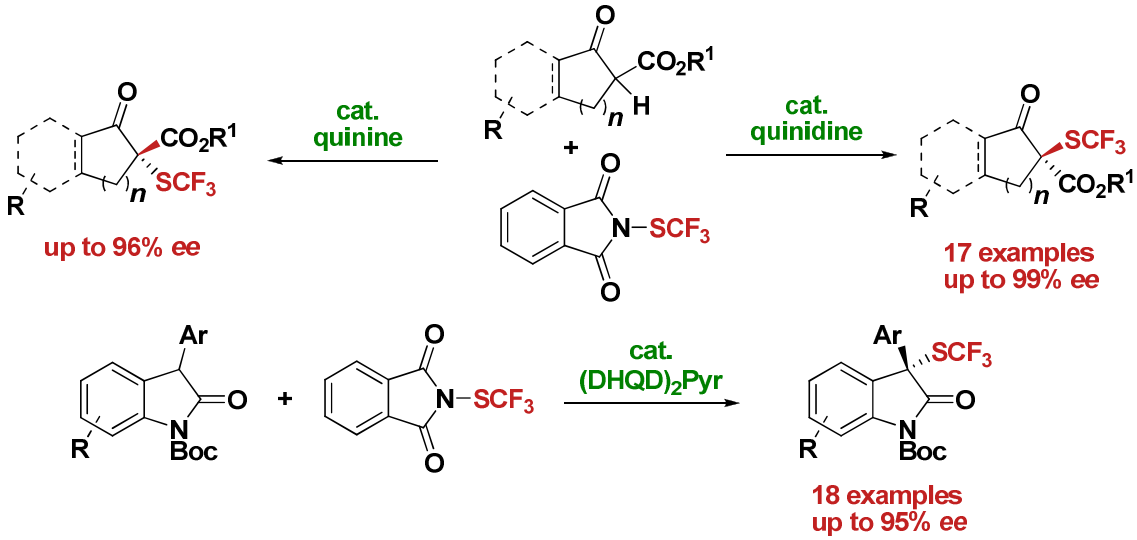
RWTH Aachen University, Germany

Over the years, much attention has been devoted to the development of efficient methods for the stereoselective introduction of fluorinated moieties into organic molecules because of their ability to significantly change the physical and chemical properties of the parent compounds.[1, 2] Among various established fluoroalkyl groups, the trifluoromethanesulfenyl group (SCF_3) is of current interest because of its remarkable properties, in particular its high stability and electronegativity, which can be useful in the rational modification of drug candidates. There has only been few reports on the use of electrophilic trifluoromethylsulfenylation reagents for the formation of C-SCF_3 bonds,[3, 4] with the formation of C(sp^3)-SCF_3 bonds scarcely investigated. We now report a highly enantioselective cinchona alkaloid catalyzed trifluoromethylsulfenylation of β-ketoesters[5] and 3-aryl oxindoles with N-trifluoromethylthiophthalimide as an electrophilic SCF_3 source.



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Keywords: fluorine, cinchona alkaloid, organocatalysis, trifluoromethylsulfenylation

[P2.57]

A new synthetic catalytic approach to Cromakalim analogues: reprofiling for neurodegenerative disease treatment

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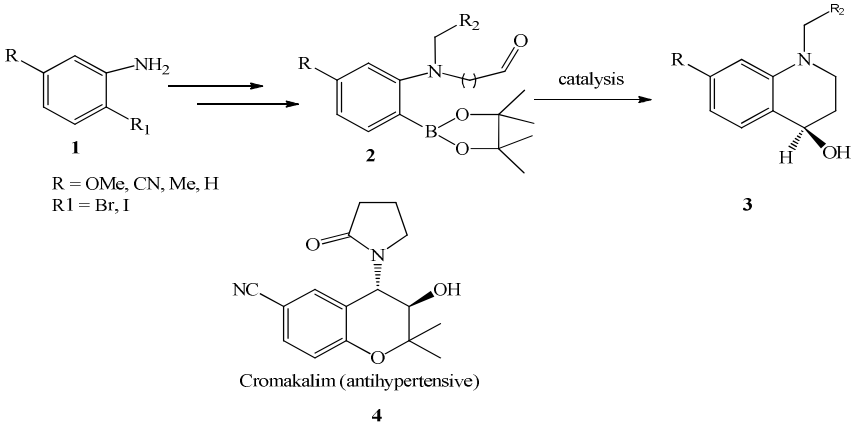
Universidade de Évora, Portugal

Over the years scientists has been focusing their attention on diseases affecting the central nervous system, in order to allow a better quality of life for humans. Two prominent current CNS diseases are, Parkinson's and Alzheimer 's diseases.

We are currently looking at reprofiling cromakalim[1] (an antihypertensive drug) for targeting Alzheimer's and Parkinson's diseases, and thus have identified the target structural type **3**. For this goal we are employing a novel intramolecular palladium catalyzed arylation approach[2,3], using a family of arylboronic ester aminoaldehydes. Our latest results will be discussed in this communication.



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Acknowledgements: This work is supported by the project INMOLFARM - Molecular Innovation and Drug Discovery (ALENT-57-2011-20) financed from the FEDER-INALENTEJO program ALENT-07-0224-FEDER-001743, as well as the project PEst-OE/QUI/UI0619/2011.

Keywords: Cromakalim, Neurodegenerative, Synthetic Catalytic

[P2.58]

A new diagnostic device to prion diseases

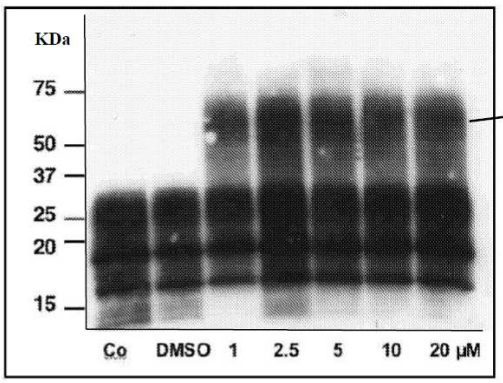
M. Robitzer[1], V. Perrier[2], T. Imberdis[2], A.D. Rodrigues*[1]
[1]ENSCM, France, [2]INSERM, France

Prion diseases or transmissible subacute spongiform encephalopathies (TSSEs) are fatal neurodegenerative conditions which affect humans and animals[1]. The accumulation of prion protein isoforms (PrP^{Sc}) in the brain tissues and the high resistance of those isoforms to proteinase K are the main reasons of brain degeneration followed by the death of the patients.

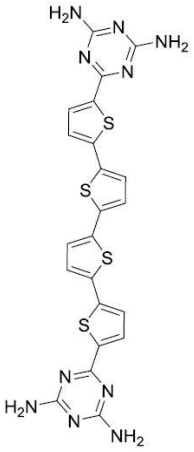
To provide earlier diagnosis of prion diseases enhancing in this way the survival chances of patients our research group has synthesized a highly active molecule 6,6'-([2,2':5',2'':5'',2'''-quaterthiophene]-5,5'''-diyl)bis(1,3,5-triazine-2,4-diamine)2, called MR100[2].

This new compound hosting a 1,3,5-triazine-2,4-diamino function is the first drug exhibiting an oligomer-induced activity specific to the pathologic isoform of prion protein. The unexpected dimerization of PrP^{Sc} after incubation with MR100 allows the differentiation between healthy and diseased individuals generating a very sensitive diagnostic device.

The synthetic approach and the detailed characterization of MR100 will be presented as well as its biological activities as new chemical interacting with prion proteins.



Western blot PrP^{Sc} detection: Co = control sample without MR100 treatment and DMSO = solvent to all essays



MR100

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Keywords: Prion disease, Diagnostic device, Prion protein, Drug design

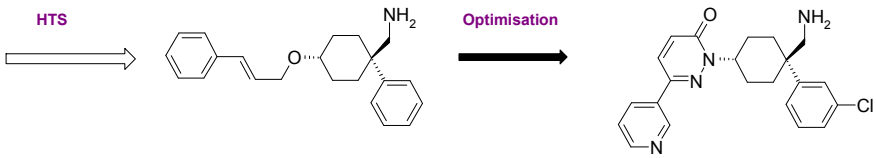
[P2.59]

Following different paths to DPP-IV inhibitor candidates

D.E. Clark, J.M. Sutton*

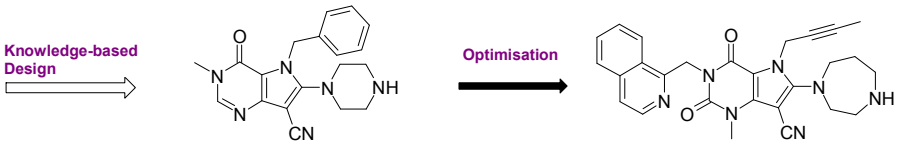
Argenta, UK

This presentation will describe a two-year collaboration between Novartis and Argenta, whose aim was to discover novel inhibitors of dipeptidyl peptidase IV (DPP-IV) for the treatment of type 2 diabetes. Structurally distinct pre-clinical candidates were delivered from two different hit generation strategies: HTS [1] and knowledge-based design [2]. This presentation will summarise the paths taken in both cases and some of the lessons learned along the way.



1A, DPP IV IC_{50} 11.9 µM

2A, DPP-4 IC_{50} = 0.004 µM



1B, DPP-4 IC_{50} = 2.1 µM

2B, DPP-4 IC_{50} = 0.005 µM

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Keywords: DPP-IV, Structure-based drug design, Medicinal chemistry, Diabetes

[P2.60]

Innovative sequential catalytic imine arylation/Suzuki-Miyaura coupling with arylboron reagents: A powerful route to bioactive compounds

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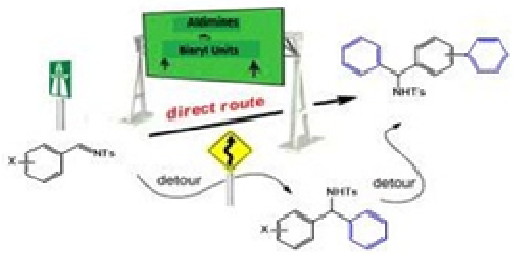
University of Évora, Portugal

During the past 40 years, several methods have profoundly changed the procedures for the synthesis of biologically active molecules, important key intermediates for API synthesis and organic functional materials. Transition metal catalysts have played a crucial role leading to the successful creation of new C-C bonds in a controlled and selective manner. The synthesis of biarylarylmethylamine units is a worthy endeavour considering that many biologically active compounds contain this motif, e.g. Valsartan (Diovan®), an important angiotensin receptor blocker indicated for treatment of high blood pressure, congestive heart failure or post-myocardial infarction (Figure 1). Since we have significant experience in transition-metal catalysed arylation reactions with boronic acids and derivatives[1], and as an extension of this work we have developed an innovative, high yielding one-pot sequential palladium catalysed imine arylation/Suzuki-Miyaura coupling reaction converting suitably activated *N*-protected aldimine substrates to biarylarylmethylamines (Scheme 1).[2] The successful application of this catalytic transformation in the homogeneous phase led to its application in the heterogeneous phase.[2] We are currently adapting this methodology for the synthesis of molecules for use in the treatment of neurodegenerative diseases, like Alzheimer's and Parkinson's diseases. These studies will be described in this communication.



Scheme 1.

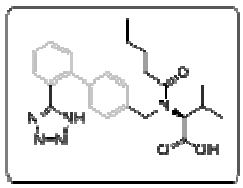


Figure 1. Valsartan

Acknowledgements: We are grateful for the award of a PhD Grant to C.S.M. (SFRH/ BD/45132/2008) from the FCT and for INMOLFARM-ALENT-57-2011-20 project for funding. We acknowledge Lab-RMN at FCT-UNL for the acquisition of the NMR spectra.

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Keywords: Imine Arylation, Suzuki-Miyaura Coupling, Heterogeneous Catalysis, Arylboron Reagents

[P2.61]

Efficient solid-phase synthesis of some benzo[e]imidazo[1,2-b][1,2,4]thiadiazin-2-one 5,5-dioxides with diversity in two positions

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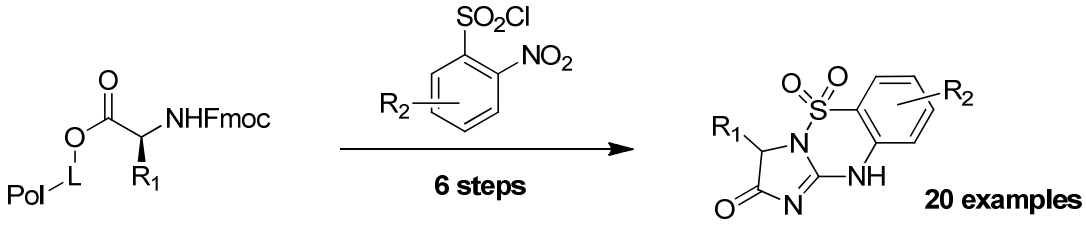
Palacky University, Czech Republic

Anagrelide (Agrylid/Xagrid),[1,2] is a drug used for the treatment of essential thrombocytosis,[3,4] overproduction of blood platelets and chronic meyloid leukemia. In this work we report the solid phase synthesis of the anagrelide sulfonylanalogues, 4,4-dioxo-1,4-dihydro-4□6-thia-1,3a,9-triaza-cyclopenta [b]naphthalene-2-ones. Initial biological testing of the target Anagrelide analogues has been performed.



This synthesis was achieved using Fmoc-□-amino acids and 2-nitrobenzenesulfonylchlorides (2-NosCls) as the key building blocks. Fmoc-□-amino acids were immobilized on Wang resin and transformed to the corresponding 2-nitrobenzenesulfonamides in two steps. After reduction of the nitro group, Fmoc-thioureas were synthesized followed by cyclization of the 1,2,4-benzothiadiazine-1,1-dioxide scaffold with diisopropylcarbodiimide (DIC). Cleavage of the Fmoc protective group followed by spontaneous cyclative cleavage gave the target products in very good yields.

Acknowledgement The authors are grateful to projects CZ.1.07/2.3.00/20.0009 and CZ.1.07/2.3.00/30.0060 coming from European Social Fund and from Palacky University (internal grants No. PrF_2012_023 and PrF_2013_027). The infrastructural part of this project (Institute of Molecular and Translational Medicine) was supported from the Operational Program Research and Development for Innovations (project CZ.1.05/2.1.00/01.0030).

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Keywords: solid-phase synthesis, benzo[e]imidazo[1,2-b][1,2,4]thiadiazin-2-one 5,5-dioxides, Anagrelide

[P2.62]

Synthesis of new epicocconone analogues: Application in fluorescence and proteomics

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Epicocconone is a natural product isolated from the fungus *Epicoccum Nigrum* by Karuso[1] *et al.* It is an azaphilone able to react with primary amine to form a fluorescent enaminic product (Fig 1). It allows labelling and release of a peptide which is very useful to stain proteins on 2D electrophoresis gels[2].

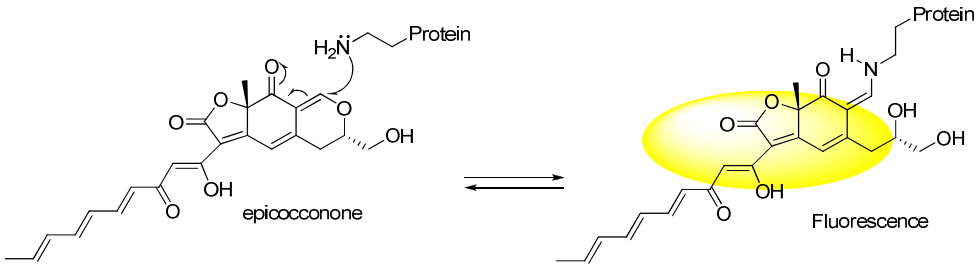

Fig 1. *Mechanism of protein labeling*

Within our group, the work is focused on the synthesis of analogues of the natural compound *via* two key reactions: an oxidative dearomatisation to build the azaphilone core[3] and a condensation with different dioxinones to introduce different substituents of the acylfuranone moiety[4] (Fig 2).

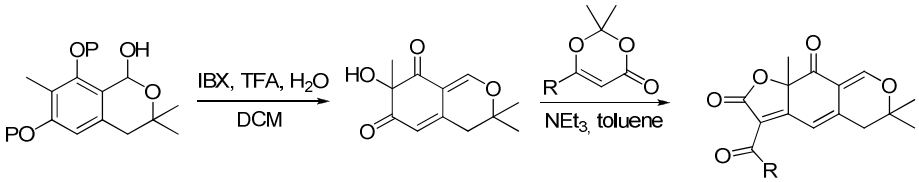

Fig 2. *Keys steps for the analogues synthesis*

The goal of the project will be to synthesize new analogues and understand the effects of the structural modifications on the fluorescence.

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Syzgantseva, O. A. ; Tognetti, V. ; Joubert, L. ; Boulangé, A.; Peixoto, P. A.; Leleu, S. ; Franck, X. ; *J. Phys. Chem. A*. **2012**, *116* (33), 8634–8643

Keywords: fluorescence, epicocconone, oxydative dearomatisation

[P2.63]

Design, synthesis and biological evaluation of new triarylpyrazole derivatives as nonsteroidal antiestrogens

N.S. Habib[1], M.A. Khalil[1], K.A. Ismail[1], H.A. Abd El Razik[1], M.A. Ragab*[2], E.A. Afify[3]

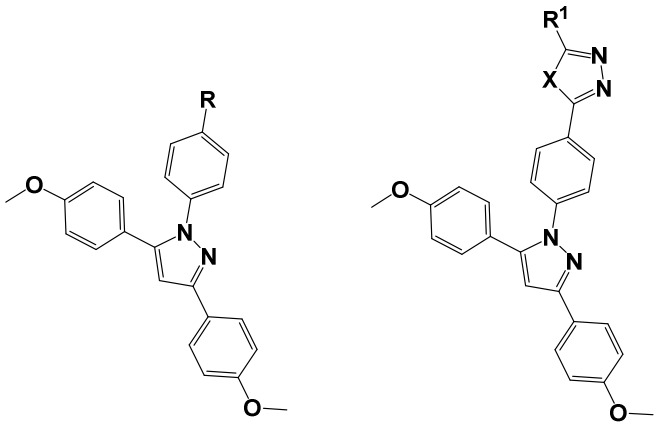
[1]Alexandria University, Egypt, [2]Damanhour University, Egypt, [3]King Abdulaziz University, Saudi Arabia

Breast cancer is one of the most commonly diagnosed cancers comprising 23% of all the female cancers and the second leading cause of cancer deaths in women worldwide today. Several studies have established that estrogens are predominantly involved in the initiation and proliferation of breast cancer and much effort are now being advoted to block estrogen formation and actions.

It has been documented that different nonsteroidal antiestrogens that exhibit potent antitumor effects represent a major advance in the management of breast cancer. Although Tamoxifen and Toremifen have been successfully used in treatment of hormone dependent breast cancer they have shown to increase the risk of endometrial cancer.

Therefore, considerable effort by many research groups has been devoted to the search for more effective novel non-steroidal subtype selective antiestrogens with better safety profiles.

On the other hand, pyrazole-containing compounds have received considerable attention owing to their diverse chemotherapeutic potentials including versatile antineoplastic activities. In addition, it has been reported that certain pyrazoles exhibit ERα selective agonism. Structure modification of this ERα selective scaffold was considered relevant to prepare ERα selective antiestrogens. In view of the aforementioned facts, and as a continuation of a research program concerned with the synthesis and characterization of new compounds endowed with antiestrogenic activities, it is reported herein, design and synthesize of novel triarylpyrazole derivatives, substituted basically with novel basic side chain and polar groups (series A). Moreover, bioisosteric replacement was considered of interest thus it was designed to incorporate chemotherapeutically-active heterocyclic rings (thiadiazoles, oxadiazoles and triazoles) within the structure (series B), hoping to impart some synergism to the target compounds and improve the activity. Some compounds were evaluated for their uterotrophic and antiuterotrophic activities, besides selected compounds were screened for their anticancer activities. Some of the newly synthesized compounds showed promising results.



A **B**

Keywords: Non-steroidal, Anti-estrogen, triarylpyrazole, breast cancer

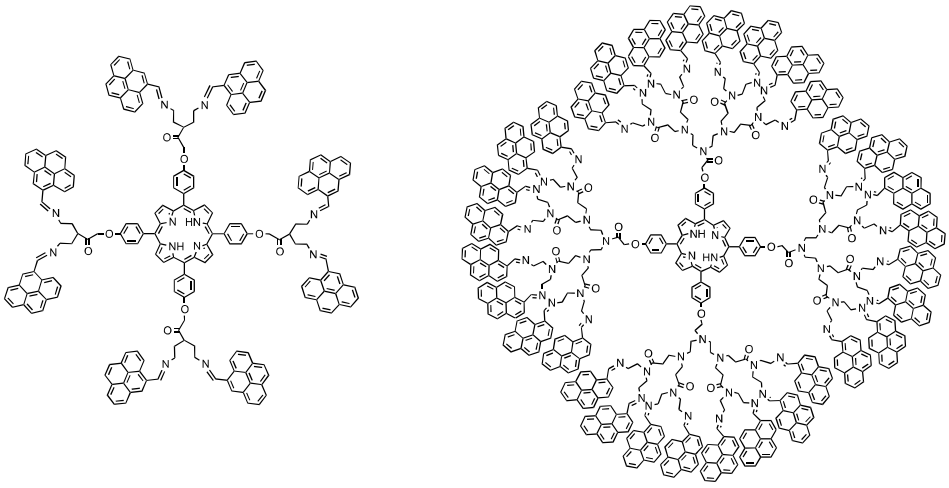
[P2.64]

Synthesis of high fluorescent multi-pyrene/porphyrin-dendrimer

M. Martínez-García*[1], M.E. Martínez-Klimov[1], E. Martinez-Klimova[2] et al

[1]UNAM, Mexico, [2]Imperial College, UK

Research on the photosystems I and II in plants and cyanobacteria has been intense for the last 20 years. The rates for singlet energy transfers (on a 2–40 ps time scale) and excitation energy (exciton) migration (0.3–0.6 ps) are very fast in these natural systems. For these living organisms, the special pair, composed of a cofacial bis(chlorophyll) or bis(bacteriochlorophyll), is placed at the centre of a large antenna network of chlorophyll units. In attempts to mimic both energy and electron transfers in these antenna proteins containing the reaction centre, researchers have often opted for employing dendrimer architectures. Particularly dendrimer-containing porphyrins. Porphyrin dendrimers with different kinds of functional groups in their terminal groups or core, and numerous applications for these molecules have been found in different fields such as catalysis, biomedicine, energy or charge-transfer systems, sensors, charge transfer of light-emitting layer in organic light emitting diodes (OLEDs), *etc.* In addition to the above advantages, dendrimers manifest a highly ordered structure and produce thin films with various functional groups on the top surface of the substrate, making possible the creation of unique materials in which surface characteristics are controlled at a molecular level. In the present work, we report the synthesis of dendrimers with molecules of pyrene on the periphery and a tetraphenylporphyrin core.



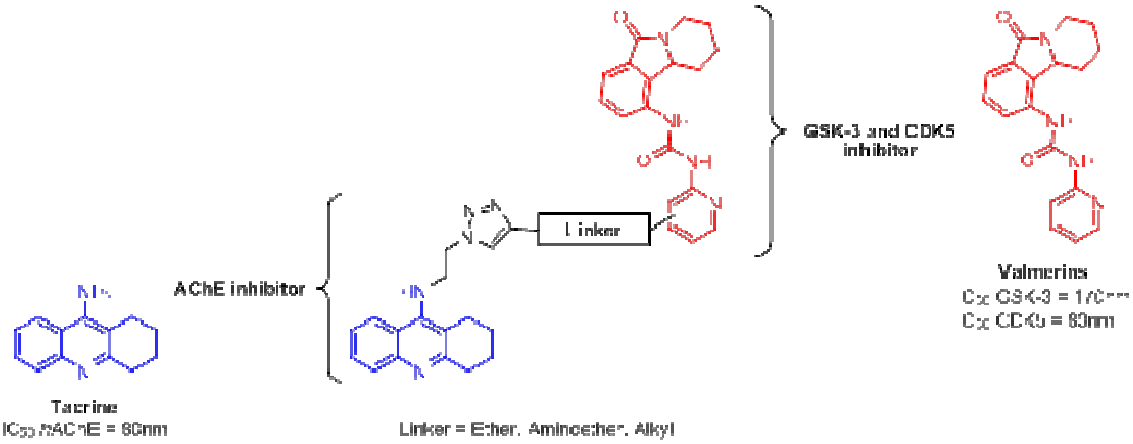
Keywords: Pyrene, Phorpyrin, Dendrimers, Energy transfer

[P2.65]

Synthesis of multi-target directed ligands against Alzheimer's disease: Acetylcholinesterase inhibitor associated to kinases inhibitor

K. Oukoloff*[1], L. Jean[1], P.Y. Renard[1], J.P. Colletier[2], N. Coquelle[2], S. Routier[3]
[1]University of Rouen, France, [2]IBS, France, [3]University of Orléans, France

Alzheimer's disease (AD) is a neurological disorder whose one of the consequences is the massive loss of a neurotransmitter called acetylcholine[1]. A way to re-establish the cholinergic transmission is to inhibit acetylcholinesterase (AChE), an enzyme that hydrolyses acetylcholine. During the past decades, several AChE inhibitors have been commercialised (Tacrine, Donepezil, etc...). Tacrine exhibit nanomolar binding affinity for the enzyme. Since AD involves multiple pathogenic factors whose mechanisms aren't completely known, actual drugs can only slow the progression of the disease and a single target approach should be reconsidered[2]. Recently, other targets such as glycogen synthase kinase 3 and cycle dependent kinase 5 have been discovered in AD mechanism. Indeed, GSK-3 and CDK5 plays a role in Tau protein. Lately, *Routier et al*.[3] have developed a new series of GSK-3 and CDK5 inhibitors which name is Valmerins that exhibit nanomolar binding affinity for these kinases.



From this perspective, we are preparing multi-target compounds based on the structure of an AChE inhibitor and bearing a GSK-3/CDK5 inhibitor as new potent drugs for AD.

[1]Bowen *et al*. *J. Neurochem.* **1983**, *40*, 503–509.

[2]León *et al*. *Med. Res. Rev.* **2011**, *33*, 139-189.

[3]Routier *et al*. *J. Med. Chem.* **2012**, *55*, 9589–9606.

Keywords: Alzheimer's disease, Acetylcholinesterase, Kinases, Multi-Target Directed Ligands

[P2.66]

A new fluorogenic reporter system to illuminating the DNA replication process based on thiol release 7-hydroxycoumarin

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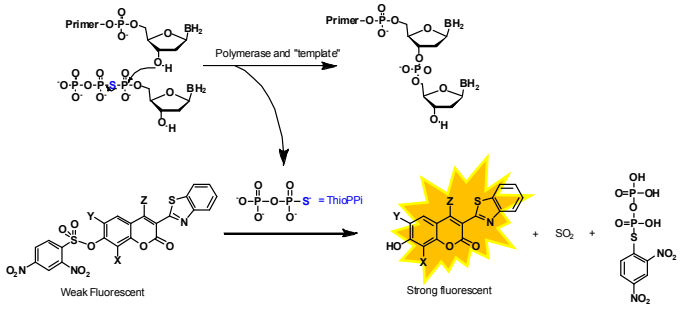
[1]UMR 6014, France, [2]UMR 6302, France

Research in nucleic acids has contributed to major advances in the past decade in multiple fields of science and technology. This project consists to develop a new fluorogenic system suitable for illuminating the DNA replication process. The goal is to explore a novel class of nucleotide (synthesis and replication ability) which only differ from the natural nucleotides by the replacement of the bridge oxygen between phosphorus P_α and P_β by a sulfur atom. This modification will allow to increase the nucleophilic character and to follow the release of the thiopyrophosphate[1] (ThioPPi) anion upon enzymatic event and through covalent-bond chemistry.

We have decided to use a non usual fluorogenic reaction (S_NAr or Michael addition) between a thiol-reactive pro-fluorophore and the ThioPPi anion to generate a specific fluorescent signal related to the replication process[2]. We have synthesized novel water-soluble phenol-based fluorophores derived from 7-hydroxycoumarin, each having a distinct emission maximum within the visible spectrum, in order to discriminate the four thionucleotides. Then, conversion into thiol-sensitive fluorogenic probes through the chemical modification of their hydroxyl group was achieved. Depending on the type of thiol-reactive quenching moiety used (2,4-dinitrobenzenesulfonyl ester[3], 2,4-dinitrophenyl ether[4], …) and the water-solubilizing group(s) pre-introduced into the coumarin core, dramatic differences in the thiol-induced fluorescence activation of these pro-fluorophores under physiological conditions were observed and have enabled to select the well compromise between water solubilizing group and thiol trigger unit[5].



Scheme 1: *DNA replication from thionucleotide under thiol-reactive pro-fluorophore reaction*

Phan R. *et al*. **Org. Lett**. 2000, 2, 2287-2289.

Chen X. *et al*. **Chem. Soc. Rev**. 2010, 39, 2120–2135.

Chen X. *et al.* **Chem. Soc. Rev**. 2010, 39, 2120-2135.

Lin W. *et al.* **Chem. Commun**. 2010, 46, 1503-1505.

Roubinet B. *et al.* **Dyes. Pigm**. 2014, submitted.

Keywords: fluorescence, nucleic acid, thiol-trigger unit, water solubilizing group

[P2.67]

Metal-catalysed regioselective functionalisation of enamides

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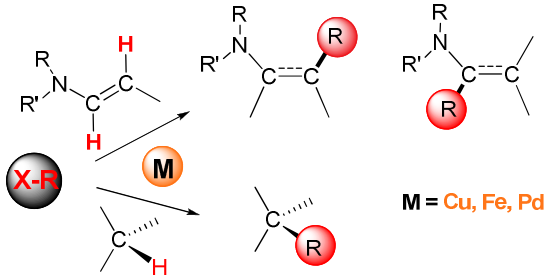
The development of efficient methodologies to generate biologically relevant molecules constitutes an essential area to create libraries of molecules by varying functional groups, building blocks, stereochemistry and molecular framework in order to obtain molecular diversity.[1] Diversity-Oriented Synthesis" (DOS) is perhaps the most promising strategy to improve the number of compounds in order to find a lead for medicinal chemistry programs: large molecular diversity can be generated in only few steps starting from simple materials. To this end, particular attention is paid to identifying improved methods for heterocyclic synthesis and their subsequent functionalisation. This feature is largely determined by two aspects: i.e. reaction economy and selectivity (chemo-, regio- and stereoselectivity) that call for the development of more efficient and also ecofriendly procedures.



The design of new synthetic routes to functionalised enamines has been of long-standing interest to the chemical communities as these motifs are contained in several bioactive natural. In connection with our ongoing project, we focused our attention on the development of efficient methodologies to introduce *via* an intermolecular pathway various functional groups onto the alpha and/or beta position of enamide. Consequently, direct C-H bond transformations, which allow the use of less expensive and more readily available starting materials without prior functionalisation, has been investigated and thus represent an atom-economic and step-simplified strategy. Herein, we wish to report our results in this area using either copper or iron catalytic system.

References

(a) Gigant, N. ; Gillaizeau, I. *Org. Lett.* **2012**, 14, 3304-3307. (b) Gigant, N. ; Gillaizeau, I. *Org. Lett.* **2012**, 14, 4622-4625. (c) Gigant, N. ; Dequirez, G. ; Retailleau, P. ; Gillaizeau, I. ; Dauban, P. *Chem. Eur. J.* **2012**, 18, 90-94. (d) Gigant, N. ; Chausset-Boissarie, L. ; Gillaizeau, I. *Org. Lett*. **2013**, 15, 816-819. (e) Gigant, N. ; Chausset-Boissarie, L. ; Belhomme, M.-C. ; Poisson, T. ; Pannecouke, X. ; Gillaizeau, I. *Org. Lett*. **2013**, 15, 278-281.

Keywords: enamides, metal-catalysed, copper, iron

[P2.68]

Development of bimodal probes for pet/optical imaging involving xanthenes dyes

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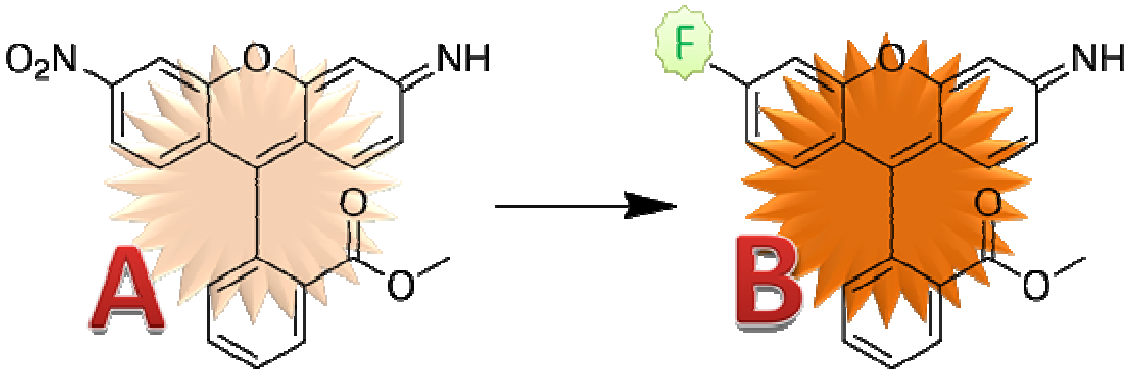
[1]Universite de Rouen, France, [2]Universite de Bourgogne, France, [3]Advanced Accelerator Applications, France

In recent years, there is a growing interest about the molecular imaging to develop new hybrid probes combining advantages of both detection method (resolution for optical imaging and detection sensibility for TEP in our case). Thus, some fluorescing molecules have been recently radiolabeled with Fluorine-18 and/or Carbon-11[1], however those strategies are difficult to generalize and cannot be used in biological application as they cannot be conjugated with interesting target such as cancer relative protein.[2]

In order to fill this technological gap, we propose to develop a new method of radiolabeling, that can be applied to a wide series of fluorophores with a spectral range of 500-950nm (from green to near-infrared). Those probes will have water-soluble group and a function that can be linked with an active biomolecule. It's important to develop fast and easy reaction of radiolabelling. This is why the nucleophilic behaviour of the fluorine anion [18F$^-$] (Sn2 and SnAr reaction) is a wise choice for labelling efficiency fluorophores.



[^{18}F$^-$]

The objectives of this project was set to provide new fluorination methods. In order to develop new bi-modal probes for PET and optical imaging. This methodology was thought to have a low or non-fluorescent probe just before the last step of fluorination. This way give us two advantages, firstly, the possibility to follow the fluorination by a spectrofluorimeter. Secondly, with the spectral properties of the fluorinated molecule that is supposed to be much higher than the precursor will confirm us the successful fluorination reaction.

[1] (a) Heinrich. & al. Appl. Radiat. Isot, 2010, 68, 96, (b) Ting. & al. Bioconjugate Chem., 2010, 21, 1811, (c) Li. & al. Chem. Commun., 2011, 47, 9324, (d) Hendricks. & al, Angew. Chem., Int. Ed., 2012, 51, 4603.

[2] Zhang & al. Cai, Theranostics, 2011, 1, 135.

Keywords: Fluorescence, Xanthene, Radiofluorination, Bimodal probes

[P2.69]

Preparation of medical films, based on substances, isolated from the plants of Limonium gmelinii genus

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Al-Farabi Kazakh National University, Kazakhstan

Substance “Limonidin” extracted from plants of *Limonium* Mill genus in the form of a dry extract, contains a significant amount of flavonoid aglycones quercetin and myricetin, and their glycosides, various forms of flavan-3-ols (mono-, di- or oligomeric), and amino acids, including essential, polyene acids, a wide range of trace elements, vitamins, which, due to their synergistic effect lead to its high therapeutic effect. From different species of *Limonium* Mill genus, six previously not described in literature new compounds were isolated and identified as: 3-O-β-D-glucopiranoside of campesterine, 3,5,7,3',4',6'-hexahydroxyflavon, 3-O-α-L-(2''-galloil)-arabinopiranoside of myricetin, 3,5,7,3',4',6'-hexahydroxyflavan and (-)-epigallocatechine-(4β→8)-(-)-3,5,7,3',4',6'-hexahydroxyflavan and (+)-gallocatechine-(4α→8)-[(-)-epigallocatechine]$_5$-(4β→8)-(-)-epigallocatechinegallat. Preclinical studies of substance «Limonidin», isolated from the roots of *Limonium gmelinii* roots, showed its high antioxidant, hepatoprotective, antimicrobial, antimutagenic and antiviral properties. It is an active modifier of metabolic malfunctions of tumor and tumor-carrying organisms, increases potential possibility for reinforcement of anabolic processes. A new form – polymer “Limonidin” film was developed by its immobilization on a polymer composite substrate. The influence of the concentration of drugs on the dynamics of their release from the gels was studied. Polymer films “Limonidin” have prolonged effect, and, after appropriate clinical trials, might be recommended for use in practical medicine for long-term elimination of the pain syndrome.

Studies were funded under the Technology Commercialization Project, supported by the World Bank and the Government of the Republic of Kazakhstan.

Keywords: polymer films, prolonged effect

[P2.70]

Getting a new herbal remedy in the form of a gel

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Al-Farabi Kazakh National University, Kazakhstan

Full provision of domestic production of medicines in Kazakhstan is one of the main priorities of socio-economic policy of the Government of Kazakhstan, as well as of the current state program of import substitution and increase of locally produced medicines to 40-50 % by 2014. On the basis of the genus *Limonium gmelinii*, having recoverable reserves in Kazakhstan and entered into the State Pharmacopoeia of the Republic of Kazakhstan, and harmonized with the European Pharmacopoeia, a substance was obtained, permitted for use in medicine as a highly effective anti-inflammatory, antiviral, and hepatoprotective drug, which improves the immune status of the body. This substance is an active principle, using which a new remedy in the form of a gel was developed. As auxiliaries for the obtained phytopreparation, carbomol, propylene glycol, sodium benzoate, and some other permitted for medicinal use ingredients, were studied. Produced phytopreparation was studied by all quality requirements provided for this dosage form in accordance with the regulations of the State Pharmacopoeia of the Republic of Kazakhstan. These indicators include the following: description, genuineness, uniformity, particle size, pH, weight of the package contents, microbiological purity, quantification of the active ingredient. A program for long-term stability studies produced a medicament for its storage in the claimed packaging at a given temperature and relative humidity.

Studies were funded under the Technology Commercialization Project, supported by the World Bank and the Government of the Republic of Kazakhstan.

Keywords: new herbal remedy, improves the immune status

[P2.71]

A novel method and a novel catalytic system for selective acid catalysed organic addition and substitution reactions

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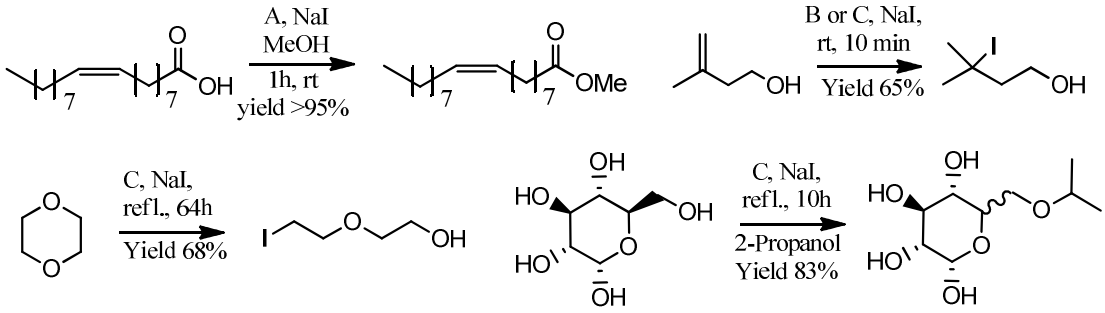
University of Eastern Finland, Finland

Here we describe a novel green chemistry invention[1] which enables to prepare selectively various acid catalyzed organic reactions without any special reaction conditions or complex separation steps and to synthesize compounds, which are difficult or impossible to prepare by other known methods. Typical examples of these reactions are: esterification reaction at room temperature with quantitative yields, opening of cyclic ethers (e.g. Crown ethers) to haloalkanols, selective substitution of primary HO-group to iodine in the presence of other types of HO-groups and addition of iodine to multiple bonds.

The present invention is based on the ability of solid materials (e.g. water insoluble aminobisphosphonic acids[2]) to donate protons (H^+) to starting materials combined to simultaneous use of a nucleophile (e.g. NaI), which acts either as a catalyst, like in esterification reaction, or as a reagent, e.g. in addition of iodine to multiple bonds in organic addition and substitution reactions. In most cases reaction products are easily isolated, since solids are removed by filtration and after solvent evaporation the products are ready for the next synthetic steps. Some typical examples with reaction conditions and yields are shown below.



Scheme 1. Some reaction examples related to invention descriped here (A = solid resin containing PO_3H_2 groups, B = $H_2N(CH_2)_{10}C(OH)[P(O)(OH)_2]_2$, C = solid resin containing SO_3H groups).

References:

1. Turhanen, P. and Vepsäläinen, J. Patent application FI20136328.

2. Turhanen, P., Peräniemi, S. and Vepsäläinen, J. Patent WO2012131170 (A1).

Keywords: Novel synthetic method, Reactions on solid support, Selective acid catalyzed reactions, Green chemistry method

[P2.72]

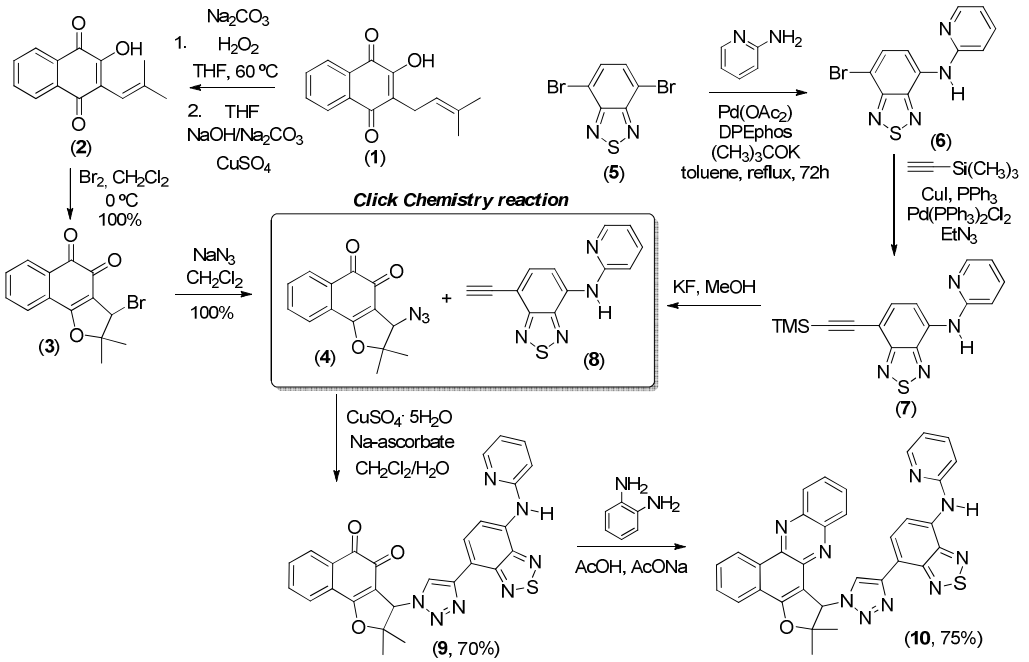
Design, synthesis and application of fluorescent 2,1,3-benzothiadiazole-triazole-linked biologically active lapachone derivatives

E.H.G. da Cruz[1], P.H.P.R. Carvalho[3], J.R. Corrêa[3], D.A.C. Silva[1], E.B.T. Diogo[1], B.C. Guido[3], B.C. Cavalcanti[2], C. Pessoa[2], B.A.D. Neto[3], E.N. da Silva Júnior*[1]

[1]Federal University of Minas Gerais, Brazil, [2]Federal University of Ceará, Brazil, [3]University of Brasilia, Brazil

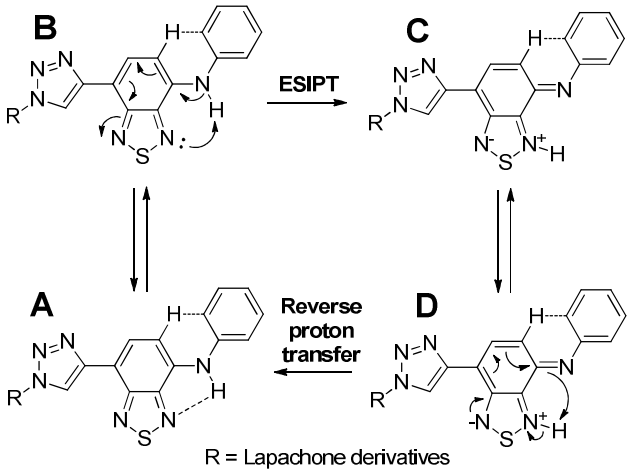
2,1,3-Benzothiadiazole (BTD) is an important nuclei used in the chemistry of photoluminescent compounds.[1] Lapachones were reported with potent antitumor activity.[2] Due our interest in biological application of BTD derivatives and based on our expertise in developing new antitumor lapachones, we accomplished the synthesis, photophysical, antitumor evaluation, and cell imaging experiments of two new BTDs-triazole-linked fluorescent structures. Theoretical calculations were also accomplished.

Click reaction between **4** and **8** afforded the designed fluorescent BTD-triazole-linked lapachone derivatives **9** and **10** (Scheme 1).



Scheme 1. Route to obtain compounds **9** and **10**.

Compounds **9** and **10** were planned to perform an efficient ICT stabilizing process in the excited state (Scheme 2) and were evaluated against twenty cancer cell lines and three normal cells. Substance **9** was considered highly active and more potent than doxorubicin against six cancer cell lines. Compound **10** was inactive against all cancer cells, but considered as an interesting molecule for bioimaging proposes and possibly indicating the preferential cellular region of action of **9** (Figure 1). In summary, the presented molecular architecture of these two novel systems opened up a new avenue for the development of novel rationally designed fluorescent probes with enhanced antitumor activity.



Scheme 2. Proposed ESIPT mechanism.

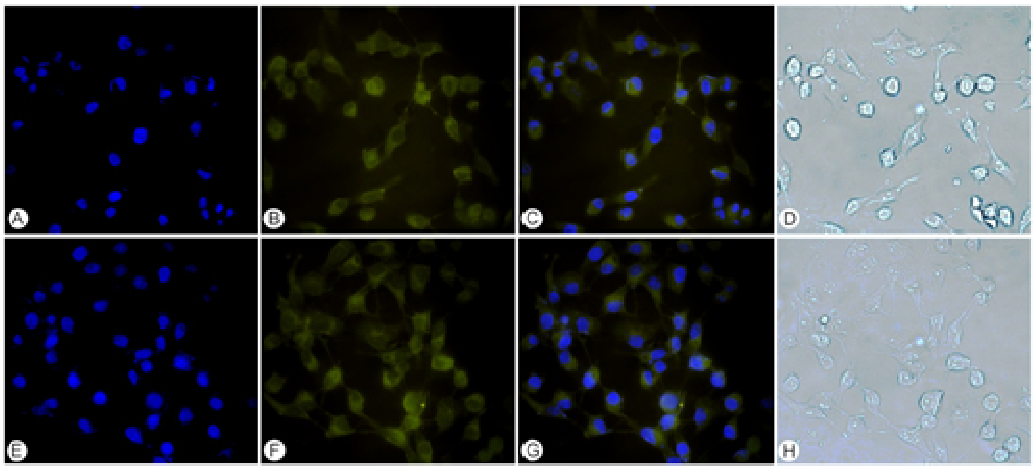


Figure 1. MDA-MB-231 staining with **10** plus DAPI and phase contrast images. (A) and (E), nucleus staining with DAPI (blue). (B) and (F) show a fluorescence pattern associated with perinuclear region plus a slight homogenous stain through the cell cytoplasm (green) obtained with **10**. (C) and (G) are the overlapping of the DAPI and **10** staining patterns, while (D) and (H) shows the phase contrast image of MDA-MB-231 cells normal morphology.

References:

(1) Neto, B. A. D. et al. *Eur. J. Org. Chem.* **2013**, 228. (2) Castro S. L. et al. *Eur. J. Med. Chem.* **2013**, *69*, 678.

Keywords: Lapachol, Quinone, Click chemistry, Benzothiadiazole

[P2.73]

1,2,3-Triazole-, arylamino- and thio-substituted 1,4-naphthoquinones: Evaluation against cancer cell lines and Trypanosoma cruzi

G.G. Dias[1], I.M.M. de Melo[1], W.O. Valença[2], C.A. Camara[2], M.G. da Silva[2], R.N. de Oliveira[2], B.C. Cavalcanti[3], C. Pessoa[3], S.L. de Castro[4], E.N. da Silva Júnior*[1]

[1]Federal University of Minas Gerais, Brazil, [2]Federal Rural University of Pernambuco, Brazil, [3]Federal University of Ceará, Brazil, [4]Oswaldo Cruz Institute, Brazil

1,2,3-Triazole-, arylamino- and thio-substituted naphthoquinones (24, 8, and 2 representatives, respectively) were synthesized in moderate yields (Figure 1 and Schemes 1-3) and evaluated against several human cancer cell lines (blood, ovarian, breast, central nervous system, colon, and prostate cancers and melanoma), showing, for some of them, IC_{50} values below 2 μM. The cytotoxic potential of the tested naphthoquinones was also assayed on non-tumor cells such as human peripheral blood mononucluear cells (PBMC) and two murine fibroblast lines (L929 and V79 cells). Alpha-lapachone- and nor-alpha-lapachone-based 1,2,3-triazoles (Figure 1) and arylamino-substituted naphthoquinones (Scheme 2) showed potent cytotoxicity against different cancer cell lines, data not presented due scope of this abstract. The compounds may represent promising new lead derivatives for anticancer drug development. In term of trypanocidal activity, the compounds were considered promising with IC_{50}/24h values less than observed for benznidazole, the standard drug. The structures were confirmed by ^{1}H-, ^{13}C NMR and high-resolution mass spectrometry.

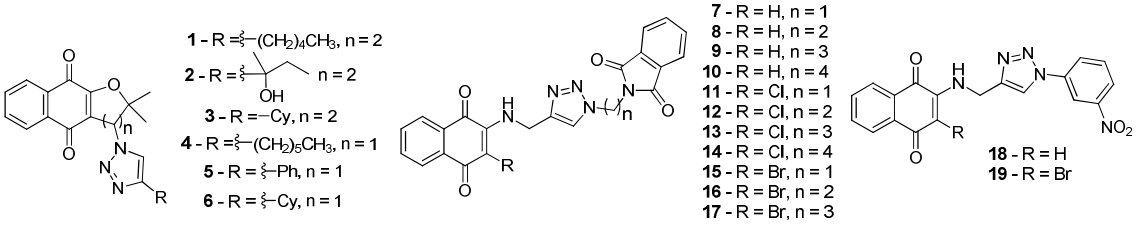
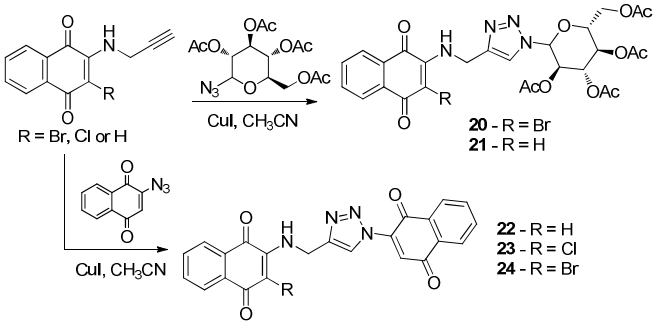
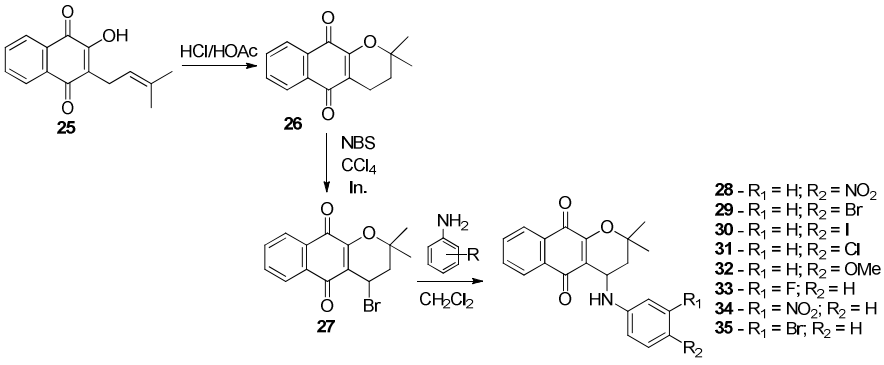


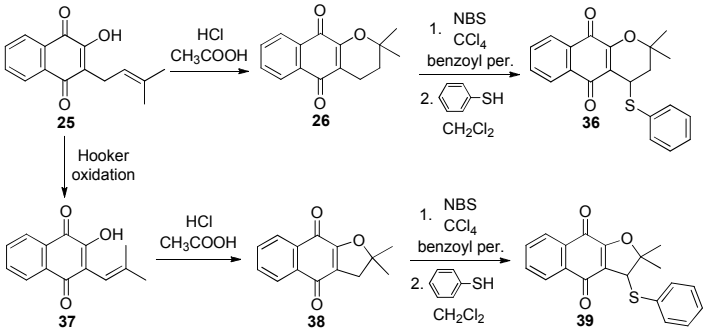
Figure 1. Nor-alpha-lapachone and alpha-lapachone-based 1,2,3-triazoles **1**-**6** and 1,4-Naphthoquinone-based 1,2,3-triazoles **7**-**19**.



Scheme 1. 1,4-Naphthoquinone-based 1,2,3-triazoles **20**-**24**.



Scheme 2. Arylamino-substituted α-lapachones **28**-**35**.



Scheme 3. Thio derivatives **36** and **39**.

Of the described substances, compounds **31** and **32** were considered highly active against several cancer cell lines (IC_{50} < 2 μM). Considering the selectivity index, compounds **36** and **39** have been identified as lead compounds for further investigation. As previously shown by Claus Jacob's group,[1,2] employing chalcogens is a productive approach. Our strategy to append arylamino groups to the 1,4-naphthoquinone structure was also successful, and several compounds with potent antitumor activity were presented that will be further investigated.

References:

(1) Shaaban, S. *et al*. *Eur. J. Med. Chem.* **2012**, *58*, 192. (2) Shaaban, S. *et al*. *Chem. Commun.* **2009**, 4702.

Keywords: 1,4-naphthoquinone, lapachol, Chagas' disease, Cancer

[P2.74]

Synthesis of new nucleotide sugar analogs modified within the diphosphate bridge

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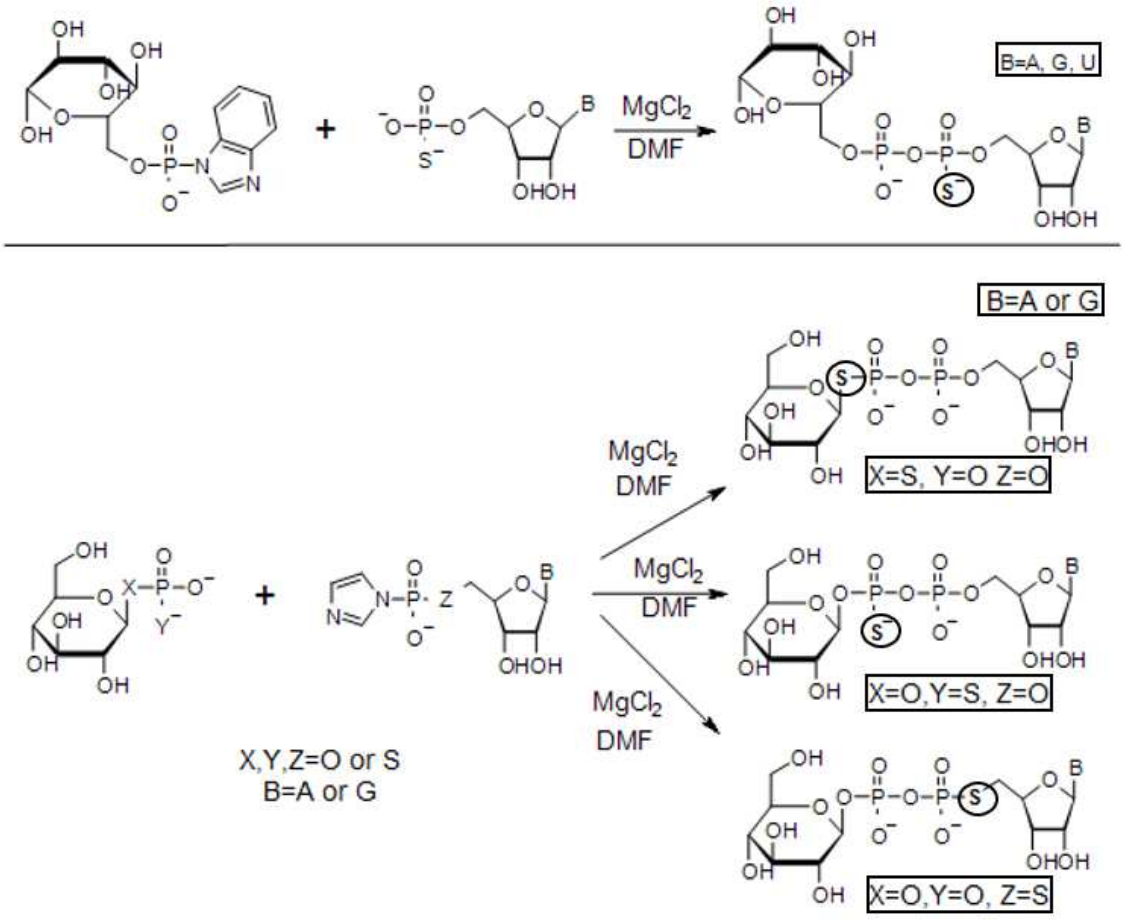
University of Warsaw, Poland

Being the substrates of most glycotransferases nucleotide sugars play an important role in sugar metabolism. Hence, nucleotide sugar analogs are highly desirable medicinal and chemical tools. First of all, they can serve as selective inhibitors of chosen glycotransferases. Moreover, they can be used as tools for obtaining modified oligosaccharides and glycoproteins, which can have a great impact both on medicine and sugar chemistry. Finally, nucleotide sugar analogs can be used to study the still unrevealed glycotransferase mechanisms. Previously, we have reported an efficient method for the synthesis of nucleotide sugars unmodified in the diphosphate chain.[1]

In this work, we report the synthesis of nucleotide sugar analogs containing a sulphur atom at various positions of the diphosphate bridge. The compounds were synthesized from an appropriate phosphobenzimidazolide or phoshopoimidazolide of a sugar moiety and an appropriate nucleotide *via* divalent cation coupling. The role of divalent cation is to coordinate the reacting molecules, increase their solubility and to activate the (benz)imidazole moiety as a leaving group.

The method presented here allows to achieve new nucleotide sugar analogs with high efficiencies. The reactions are conducted under mild conditions within short times.



[1] Dabrowski-Tumanski, P., Kowalska, J. and Jemielity, J. (2013), *Efficient and Rapid Synthesis of Nucleoside Diphosphate Sugars from Nucleoside Phosphorimidazolides*. Eur. J. Org. Chem., 2013: 2147–2154.

Keywords: nucleotide sugars, analogs, carbohydrate drugs, tiophosphate

[P2.75]

A facile microwave-assisted synthesis of some fused pyrimidine derivatives

S.A. Alissa*

PNU University, Saudi Arabia

The highly accelerated synthesis of thienopyrimidinones, theinopyrimidines, thioxotheino pyrimidinones and a thienotriazolpyrimidinone derivatives under microwave irradiation is reported. Compared to conventional conditions, microwaves method offered several advantage likes short time, good yields, simple procedure, mild conditions and easy workup.

The structure of synthesized compounds have been characterized on the basis of their elemental analysis and spectral data, and screened for their antimicrobial activity.

Keywords: Thienopyrimidine, Thioxo thienopyrimidine, Microwave irradiation, Antimicrobial activity

[P2.76]

The regioselective three-component synthesis of pyrazolopyrimidines

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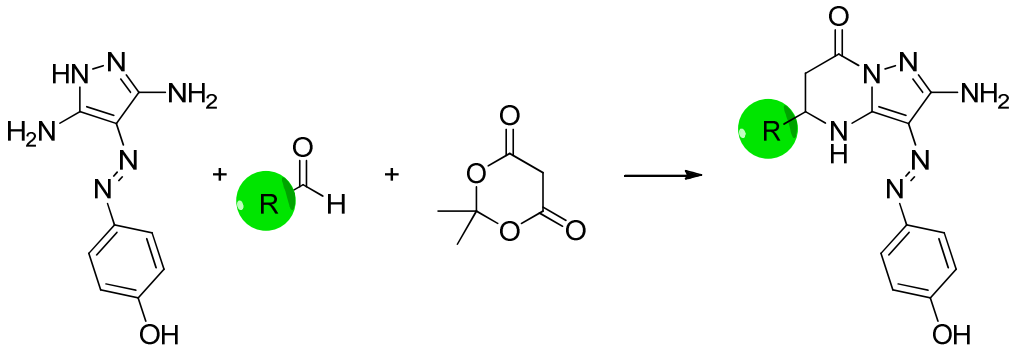
Palacky University, Czech Republic

Pyrazolopyrimidines are fused heterocyclic compounds which found a broad application in the medicinal chemistry. For instance, antibacterial activity, inhibition of cyclin-dependent kinases, and anticonvulsant activity of pyrazolopyrimidines have been reported.

In our group the regioselective multicomponent reaction leading to a series of pyrazolopyrimidines have been developed. All compounds were prepared in efficient and atom-economic manner from readily available starting materials. Pyrazolopyrimidines were obtained in high isolated yield. The regiochemical outcome of the reaction was determined using X-ray crystallography. In addition, the plausible mechanism of the multicomponent reaction was proposed.



Acknowledgement: Research of this project was supported by these projects CZ.1.07/2.2.00/28.0184, CZ.1.07/2.3.00/20.0009, PrF2012/027, PrF2013/036.

Keywords: multicomponent reaction, pyrazolopyrimidines, regioselectivity, Meldrum´s acid

[P2.77]

Synthesis, antiproliferative properties and QSAR studies of 2-Furylbenzimidazole derivatives

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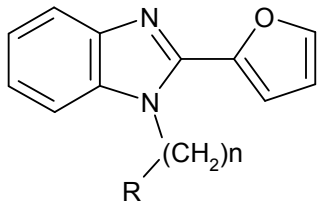
Progressive interest has been directed towards 2-furylbenzimidazole containing-compounds as anti-tumor active agents due to their antiangiogenic properties.[1,2] In the present study, a series of 2-furylbenzimidazole analogues have been synthesized possessing an aryl or heterocyclic residue, either directly attached to the benzimidazolyl *N*-1 or through a methylene function. Many of the synthesized compounds exhibited promising antiproliferative properties against HepG2 (liver) and MCF-7 (breast) tumor cell lines compared with cisplatin (reference standard) through in-vitro Sulfo-Rhodamine-B standard method bio-assay. Statistically significant QSAR models describing the bio-activity were obtained employing CODESSA-Pro software.



N = 0, 1; R = aryl, heterocyclic function

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Keywords: Benzimidazoles, Antiproliferative activity, MCF-7,HepG-2, QSAR

[P2.79]

Computational studies of the mechanisms of enzymatic activity and allosteric inhibition of dihydropteroate synthase, an antibacterial target

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St. Jude Children's Res. Hosp., USA

Introduction: Dihydropteroate synthase catalyzes a crucial step in the bacterial folate-synthesis pathway, the condensation of 6-hydroxymethyl-7,8-dihydropterin pyrophosphate (DHPP) with *p*-aminobenzoic acid (*p*ABA) to form 7,8-dihydropterote. Because this enzyme is essential for most bacteria but absent in higher animals it is an important target or antibiotics; for example, it is the target of the sulfonamide class of antibiotics.

Methods: We have made a series of computational studies using techniques ranging from quantum chemistry to molecular dynamics simulation to study both the catalytic mechanism of DHPS, and to understand the mechanism of a recently discovered compound that acts as an allosteric inhibitor.

Results and Discussion: Our quantum-chemical calculations predict an S_N1 mechanism of catalysis with the formation of a novel, positively-charged pterin species as an intermediate. This prediction has been confirmed by X-ray crystallographic structures of the protein trapped in the intermediate state and by the biochemical finding that the enzyme cleaves pyrophosphate from DHPP, albeit slowly, even in the absence of the second substrate. The calculations show how electrostatic features of the pterin-binding pocket stabilize the positively-charged intermediate, and the stabilization model is supported by site-directed mutagenesis studies. In addition, the calculations provide a detailed model of the transition state for the initial catalytic step, and should therefore by useful in the design of inhibitors that mimic the transition state. Our molecular dynamics (MD) studies focused on a novel allosteric inhibitor that binds in the dimer interface of DHPS which is not part of the active site. We performed MD simulations of the DHPS dimer with and without inhibitor and substrates, and an analysis of structural fluctuations showed correlations between the inhibitor binding site and the active site that suggest how inhibitor binding may damp active-site loop motions that are important for substrate release.

Keywords: DHPS, quantum chemistry, molecular dynamics, antibiotics

[P2.80]

A new synthesis of 2-trichloromethyl-1,3-diaza-1,3-butadienes from trichloroacetamidine and Vilsmeier-Haack reagents

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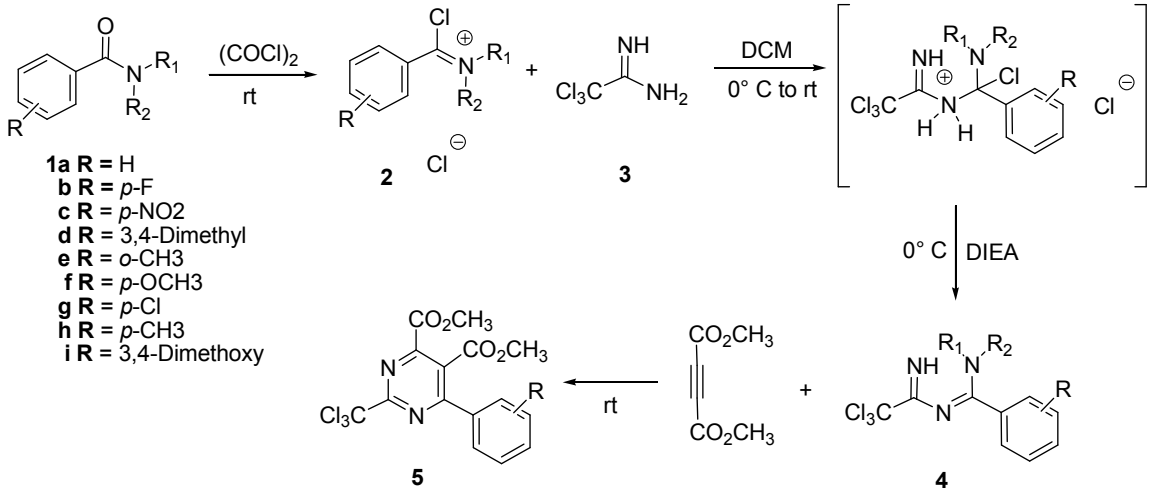
UAEMéx, Mexico

Actually, azadienes have become useful intermediates in organic synthesis. Especially, diazadienes have the ability to participate in [4 π + 2π] cycloaddition reactions; the 1,2- and 1,4-diaza-1,3-butadienes have been extensively studied in comparison with the 1,3-diaza-1,3-butadienes, that have been considered to be very unstable. Few reports on their synthesis and reactions have been published, and occasionally been postulated as reactive intermediates.[3,4] However, we reported that the trichloromethyl group confers them stability, and react efficiently with electron-deficient dienophiles. Actually, we have developed a new methodology to generate 2-trichloromethyl-1,3-diaza-1,3-butadienes **4** in good yield from trichloroacetamidine **3** and Vilsmeier-Haack reagents **2**. Essentially, this consisted of condensation of the Vilsmeier-Haack reagent derived from the corresponding *N,N*-dimethylbenzamide derivative **1a-e** or substituted *N*-benzoylmorpholide (**1f-i**) with trichloroacetamidine **3** to give the stable, crystalline diazadiene chlorides from which the corresponding basic diazadienes were liberated with di-*iso*propylethylamine in dichloromethane. Pure diazadiene **4** were identified by NMR spectra; additionally **4c** and **4g** were identified by X-Ray crystallography. These 4-aryl-1,3-diazadienes 4 undergo [4π + 2π] cylcoadditions with electron deficient acetylenes as dimethyl acetylenedicarboxylate to give adducts which are aromatised to pyrimidines 5 under mild conditions. Advantages and disadvantages of this metodology are discussed.



Keywords: !,3-Diazabutadienes, Vilsmeier-HaacK, Pyrimidines, Cycloaddition Reactions

[P2.81]

Delivery of peptides into cells by peptide-peptide hybrid method

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We describe a method for delivery of peptides into cell by using peptide-peptide hybrid. We synthesized the peptide and a cell-penetrating peptide (CPP) containing of heterodimeric leucine zippers (hdLzs). The peptides were previously developed by Bosshard *et al.* and the peptides are designed in such a way that they contain some basic amino acid units (Lys) or acidic amino acid units (Glu) in the sequences of the 29-mer leucine zipper peptide (these peptides are indicated as hdLz(K) and hdLz(E), respectively.). The 1/1 complex of the purpose peptide with the CPP was strongly formed by hydrophobic leucine interaction and electrostatic attraction of these hdLz(K) and hdLz(E). These peptides are synthesized by solid-phase peptide synthesis. An autophagy inductive peptide, beclin 1 and a peptide hormone, oxytocin successfully deliver into cells by this method. The beclin 1 that internalized into HeLa cell induced autophagy and the cell death was progressed.

Keywords: drug delivery system, cell-penetrating peptide, leucine zipper, beclin 1

[P2.82]

Access to the α-amino boronate motif via transition metal mediated intramolecular boroalkyl C-H amination

J.D. St. Denis*, C.F. Lee, Z. He, A.K. Yudin

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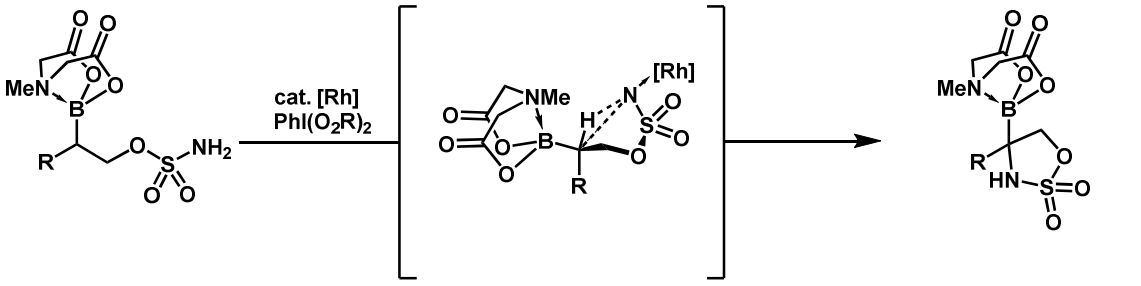

Advances in catalysis directed towards chemical synthesis can benefit from the rational design of new metal-based intermediates. Given the limited number of elementary steps in transition metal chemistry, innovative approaches are more likely to emerge from unusual combinations of functional groups that are close to the metal coordination sphere. Our recent explorations in the area of kinetically amphoteric molecules have led to α-boryl aldehydes, which in turn has opened doors for the development of several other amphoteric species. As part of this investigation, we reported the first example of C-B fragment migration driven by a Curtius rearrangement. Since then, we have been pursuing the application of densely functionalized boron-containing building blocks in catalysis. With the ultimate goal of exploiting novel metal-bound intermediates in organic synthesis we have developed a chemoselective synthesis of tertiary geminal borylamine derivatives via boroalkyl C-H amination to a rhodium-nitrene centre. In addition to reaction discovery, the influence of the boronate moiety on the mechanism and regioselectivity will also be described.

Keywords: Catalysis, Borylamines, Rhodium, C-H activation

[P2.83]

Incrementally increasing the flexibility of a peptide backbone: effect on macrocyclisation efficiency

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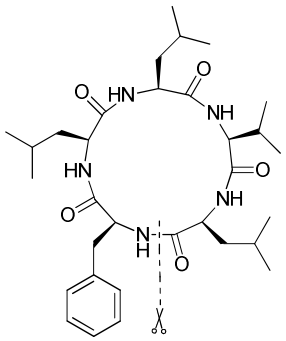
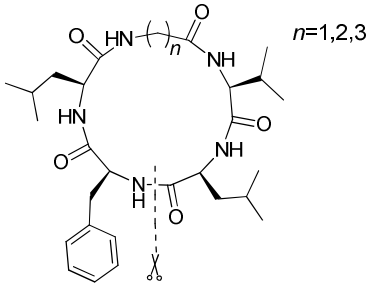
Cyclic peptides are good lead structures for drug discovery, but their synthesis is often very inefficient.[1] For example, the cyclic pentapeptide sansalvamide A (San A) shows promising activity against multiple cancer cell lines, but its synthesis via macrocyclisation is low-yielding.[2]

In this project, we have explored the concept of incremental ring expansion as a strategy for improving peptide cyclisation efficiency. One leucine residue of San A was replaced with glycine, *β*-alanine or GABA (see below), and this resulted in a series of analogues that were obtained in dramatically improved yields. This was attributed to the increased flexibility of the ring-expanded analogues, as determined by measuring the effective molarity (EM) of the corresponding linear precursors. Subsequently, cytotoxicity assays revealed that the ring-expanded analogues preserved useful activity against human colon cancer cells.

This concept of ring expansion will potentially facilitate the medicinal development of San A, but more broadly this work also represents a novel strategy for assisting the synthesis of analogues of other “difficult” cyclic peptides.



San A: difficult to cyclise



Analogues: easy to cyclise

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Keywords: Sansalvamide A, Anticancer, Effective Molarity, SPPS

[P2.84]

Hybrid design for nicotinic acetylcholine receptor (nAChR) ligands

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[1]University of Hawai'i at Hilo, USA, [2]University of Florida, USA, [3]Yale University, USA, [4]Idaho State University, USA

NAChRs are ligand-gated cation channels assembled as homo- or heteropentamers and permeable for Na^+, K^+ and Ca^{2+}. Various nAChR subtypes play an important role in complex cognitive processes like learning and memory.

Recently, we developed BPC, a high affinity partial agonist at beta2-containing nAChRs with antidepressant efficacy in a mouse model (JPET, 2013, 347:424-437). BPC is a hybrid derived from two different nAChR ligands and shows a promising on/off-target profile. Based on these results further hybrid compound libraries are synthesized to develop compounds with selective polypharmacological profiles for the treatment of various CNS diseases. These hybrid compounds can result from the overlap mode of e.g. two distinct pharmacological principles. For example, we generated heterodimer ligands with one part derived from natural products with antioxidant activity, from NSAIDs, using monoamine related targets, or compounds with known beta-amyloid interaction. The second part of the hybrid is derived from a nicotinic ligand. The compounds synthesized were evaluated for their nAChR affinities in different radioligand binding assays. [^{3}H]Epibatidine (α4β2*, α3β4* and muscle type nAChRs) and [^{3}H]methyllycaconitine or [^{3}H]alpha-bungarotoxin (α7* nAChRs) were used as radioligands and the receptor proteins were derived from rat brains, pig adrenals, and Torpedo californica electroplax. A broad spectrum of affinities (e.g. Ki values for α4β2*: < 10 nM to > 10,000 nM) were obtained providing important insights into structure-affinity relationships for the further development of designed multiple ligands.

Funding: This work was supported by P20RR016467.

[P2.85]

A new self-eliminating linker for tumour-targeted prodrug activation

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A major challenge in tumour-targeted prodrug therapy is the ability to control where and when the active drug is released.[1] The *p*-aminobenzyloxycarbonyl (PABC) linker[2] has been used extensively in site-specific activation of drugs and imaging probes (Figure 1a).[3] While this strategy has provided amine-based prodrugs (X=NH) which are relatively stable to physiological conditions, linkers in which the prodrug is masking a phenolic or alcoholic drug (X=O) are susceptible to enzymatic and chemical degradation. Due to the prevalence of bioactive drugs containing a phenolic or alcoholic substituent, *p*-aminobenzyl ether linkages have been designed as more stable alternatives to carbonate-based drugs.[4] However, these linkers exhibit relatively slow release rates and are restricted to reactive phenols (low pKa). We set out to develop a new linker which can deliver stable, tumour-targeted phenolic or alcoholic prodrugs.

Herein we report the synthesis, stability and release kinetics for an allyloxy-based prodrug/probe (Figure 1b) and compare this to a carbonate-based prodrug/probe released under the same triggered conditions. Stability studies demonstrated that the allyloxy-prodrug/probe is stable over 24 hours at physiological pH, compared to the carbonate-prodrug/probe which showed 20% degradation under the same conditions. Once triggered, the allyloxy-linker showed rapid release of phenolic drug/probe, comparable to the carbonate-linker release rate. We continue to develop this area of research by exploring new ways to improve the triggered release rate while maintaining stability of the linker.

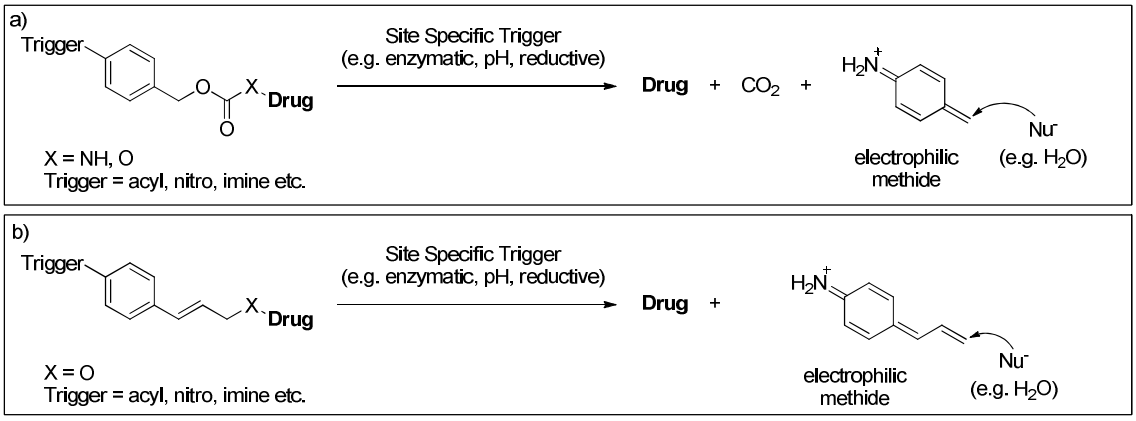

Figure 1.

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Toki, B.E.; Cerveny, C.G.; Wahl, A.F.; Senter, P.D. *J. Org. Chem.* **2002**, 67, 1866-1872.

Keywords: Prodrug Activation, Targeted Chemotherapy

[P2.86]

Palladium-catalyzed decarboxylative acylation of phenylacetamides with α-oxocarboxylic acids

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The development of new carbon-carbon bond-forming reactions continues to be an essential goal in organic chemistry. Traditional metal-catalyzed cross-coupling reactions between aryl metal reagents and aryl halides are well-established methods for the construction of C–C bonds and synthesis of complex molecules. Recently, transition-metal-catalyzed decarboxylative cross-coupling reactions using aryl carboxylic acids as aryl surrogates have received much attention since such transformations provide new opportunities to use readily available carboxylic acids as starting materials for organic synthesis.

Transition-metal-catalyzed oxidative acylation of sp^2 C–H bonds in aromatic compounds with various directing groups, e.g., pyridines, oximes, acetanilides, and indole, with aldehydes or alcohols were reported. However, decarboxylative C–H bond acylations using α-oxocarboxylic acids as acyl surrogates were relatively unexplored. Goossen first demonstrated a palladium-catalyzed decarboxylative crosscoupling reaction of aryl bromides with α-keto carboxylate salts as acyl anion equivalents to afford diaryl ketones. Ge described elegant studies on a palladium-catalyzed decarboxylative acylation of acetanilides and phenylpyridines with α-oxocarboxylic acids as acyl sources via C–H bond activation. Recently, Guo and Duan described a decarboxylative acylation of cyclic enamides with α-oxocarboxylic acids to provide β-acyl enamides.

Herein we described our recent result on a Pd-catalyzed decarboxylative *ortho*-acylation of *O*-methyl ketoximes and phenylacetamides with α-keto acids via C–H bond activation. This protocol provides an efficient access to a range of *ortho*-acyl phenylacetamides, which can be easily converted to 3-isochromanone derivatives.

Keywords: Palladium-Catalyzed, Decarboxylative Acylation, sp2 C–H bonds, C–H bond activation

[P2.87]

The synthesis and biochemical evaluation of a series of n-alkylsulfonate-benzyl triazole based compounds as inhibitors of aromatase

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The enzyme aromatase converts androgens (e.g. testosterone) and androgen-precursors (e.g. androstenedione) to the estrogens (namely estradiol and estrone respectively). Inhibition of aromatase is expected to result in estrogen ablation within breast cancer cells which would therefore be expected to lead to a decrease in the stimulation of estrogen-dependent breast cancer cells. We therefore report here: the synthesis of a range of n-alkanesulfonate derivatives of 4-hydroxybenzyl triazole (**1**); their biochemical evaluation and; the rationalisation of their inhibitory activity.

In the synthesis of the potential inhibitors, triazole was reacted with 4-hydroxybenzyl alcohol to give **1**. Derivatisation of **1** involved reaction with the appropriate n-alkanesulfonyl chloride. In general, the reactions proceeded in poor to good yield without any major problems; poor yield was due to the purification steps which proved to be troublesome requiring repeated column chromatography.

Biochemical evaluation of the compounds was undertaken using literature assay procedure using JEG-3 cells as the source of aromatase and ^{3}H-androstendione as substrate.

Consideration of the inhibitory activity of the triazole-based compounds against aromatase show the compounds, in general, to possess weaker potency in comparison to the two standard inhibitors namely, anastrozole (92.9% inhibition at [I]=500nM) and letrozole (94.3% inhibition under similar conditions). The most potent compound was found to be n-octyl derivative of **1** which was found to possess 91.6% inhibition under similar condition with an IC_{50} value of 20.0nM; as such, the compound was ~5 times weaker than anastrozole. Structure-activity relationship determination study of the compounds suggests that hydrophobicity appears to be a major factor in determining the overall potency within the alkyl sulfonate-based compounds with the longer alkyl chain containing compounds undergoing steric hindrance with the aromatase active site.

In conclusion, we have reported potent inhibitors of aromatase; the compounds are therefore good compounds to take forward for further development.

Keywords: AROMATASE, INHIBITORS, SYNTHESIS, EVALUATION

[P2.88]

Mode of action of a number of cytotoxic compounds possessing potent inhibitory activity against the cytochrome P-450 enzyme aromatase

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University of the West of Scotland, UK

We have utilised the scaffold highlighted within compounds such as anastrozole and letrozole (which are currently the first line treatment against estrogen dependent breast cancer) leading to the synthesis of compounds which have proved to be excellent aromatase inhibitors; however, our specific desire was the synthesis of enzyme inhibitors which would also possess high levels of cytotoxic activity. Here, we report the synthesis of the target compounds which we evaluated for aromatase inhibitory activity and cytotoxic activity.

Synthesis of the target compounds was achieved using standard literature method previously reported by us. In the determination of the mode of action of these compounds, cells (JEG-3, NCI-H295R) were suspended in DMEM and incubated (24h at 37ºC with 5% CO_2). Medium was removed and cell layer was washed with PBS. Phenol red free media containing inhibitor (the control lacked inhibitor) was added and the plates incubated. Cells were fixed using paraformaldehyde solution (4%) and permeabilised using methanol (at -20ºC for 5min). Cells were mounted in medium containing DAPI stain solution and visualised using a confocal fluorescence microscope.

A number of compounds (e.g. PS70 was found to possess IC_{50} value of 2.54nM) were found to be more potent than anastrozole (IC_{50}=3.99nM). Furthermore, a number of these compounds were found to possess excellent cytotoxicity activity (> 85%) at [I]=100μM; anastrozole was found to lack cytotoxic activity. Consideration of the mode of cell death (using DAPI staining assay) we discovered that the compounds possessed apoptotic activity since condensed nuclei and apoptotic bodies were observed as a result of incubating JEG-3 and NCI-H295R cells in the presence of compounds such as PS70 ([I]=100μM).

In conclusion, we have synthesised compounds which are both highly potent inhibitors of aromatase and possess cytotoxic activity and would therefore appear to be excellent compounds to take forward to preclinical trials.

Keywords: CYTOTOXICITY, EVALUATION, MODE OF ACTION

[P2.89]

Triazole-based derivatives of phenyl methyl azole as inhibitors of the enzyme aromatase (AR) and the variation in inhibitory activity between the isomers

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The conversion of androgens to the mitogenic estrogens is undertaken by the cytochrome P-450 enzyme aromatase (AR). AR inhibitors have been shown to be highly effective in the clinic as they reduce the estrogen production both within the tumour and the plasma, as such, anastrozole and letrozole are currently the first-line treatment against estrogen-dependent breast cancer. Both compounds are triazole-based and in our attempts to synthesise derivatives, we discovered that the synthesis (depending upon the route utilised) led to two different isomers. Here, we consider the biochemical evaluation of the synthesised and purified isomers.

Synthesis of the target compounds involved a reaction between the derivatives of phenyl methyl bromide starting material with 1,2,4-triazole (in the presence of anhydrous potassium carbonate) to give the isomers as a mixture. The two isomers (1,2,4-triazole and the 1,3,4-triazole) were therefore isolated by column chromatography. Biochemical evaluation involved the use of a literature-based a cell-based assay system using ^{3}H-androstenedione as substrate and JEG3 cells as the source of the AR.

The biochemical evaluation of the target compounds showed that them to be were weak inhibitors of AR, in particular, the 1,3,4-triazole-based compounds were found to be extremely weak inhibitors. The most potent compound within the series was found to be derivatives of 4-nitrophenylmethyl triazole, in particular, the 1,2,4-triazole derivative was found to possess 91.3% inhibition at [I]=500nM (IC_{50}=85.5nM) whilst the 1,3,4-triazole derivative was found to possess 47.9% inhibition under similar conditions. In contrast, anastrozole was found to possess an IC_{50} value of 4.61nM whilst aminoglutethimide was found to possess 46.4% inhibition (IC_{50}=479.13nM) under similar conditions.

In conclusion, the triazole derivatives of phenylmethylazole-based compounds have been found to be weak inhibitors in comparison to the gold standard inhibitors with the 1,2,4-triazole-based compounds being shown to be highly potent inhibitors in comparison to the 1,3,4-triazole derivatives.

Keywords: TRIAZOLE, INHIBITORS, ISOMERS, EVALUATION

[P2.90]

Anti-oxidant activity and inhibition of metalloenzymes

V. Vasireddy, J. Gandhi, C.P. Owen, S. Ahmed, S.H.N. Pang*
University of the West of Scotland, UK

Increase in matrix metalloproteinase (MMP) activity has been associated with the etiology of metastatic cancers and a variety of chemical functionalities able to undergo interaction with the Zn^{2+} at the active site have been considered. In our search for novel inhibitors of this family of enzymes, we have utilised an assay to determine antioxidant activity of compounds. More specifically, antioxidants that act as a reducing agent have been shown to reduce ferric tripyridyltriazine complex, resulting in a blue ferrous form which can be quantified. We therefore report the initial results into the discovery of a novel class of compounds as inhibitors of MMP family of enzymes and the correlation to the FRAP value as an indicator of anti-oxidant activity.

Synthesis of the target compounds was achieved using literature methodology reported by us. The inhibitory activity against the MMP family of enzymes was determined using literature methodology. The compound was allowed to incubate with the FRAP reagent. The results were compared with standard ascorbic acid in DMSO equivalent of FRAP value of 2.

The biochemical evaluation show the compounds to be weak inhibitors; the halogen-based compounds were weak inhibitors of all the MMP enzymes, however, compounds containing groups able to undergo hydrogen bonding were found to possess good level of inhibitory activity, e.g. 2-hydroxy-5-bromobenzaldehyde-N-cyclohexylthiosemicarbazone was found to possess ~2%, ~60%, ~15% and ~21% inhibitory activity against MMP1, MMP2, MMP3 and MMP13 respectively ([I]=100μM). Plot of percentage inhibition against FRAP value suggests a weak correlation between FRAP value and percentage inhibition.

In conclusion, the compounds have been shown to be weak inhibitors but specific inhibitors of the MMP family of enzymes, however, they have therefore proved to be excellent lead compounds in the design and synthesis of novel inhibitors of the MMP family of enzyme.

Keywords: ANTIOXIDANT

[P2.91]

Synthesis and evaluation of novel sulfamoylated derivatives of thiosemicarbazone-based compounds as inhibitors of estrone sulfatase (ES) and carbonic anhydrase II (CAII)

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Malignant neoplasms show an increased expression of carbonic anhydrase (CA) family of enzymes resulting in a hypoxic microenvironment develops together with increased acidity. A number of compounds have been used to target the CA family of enzymes, including acetazolamide (**1**) and estrone-3-*O*-sulfamate (EMATE); the latter compound has been shown to be a potent inhibitor of estrone sulfatase (ES) which catalyses the conversion of estrone sulfate to estrone and has been implicated in the development of breast cancer. We report the results of our initial study into the synthesis and evaluation of a novel range of sulfamoylated thiosemicarbazone-based compounds against ES and the CA family of enzymes, in particular, CA II.

In the synthesis of the potential dual-inhibitors, carbonyl containing starting material was heated to reflux with derivatives of thiosemicarbazide to give the target compounds followed by the conversion to the sulfamate-derivative. Biochemical evaluation against CA II involved a literature-based colourimetric assay whilst evaluation against ES involved ^{3}H-estrone sulfate.

The consideration of the inhibitory activity shows that the compounds are weak inhibitors of CA II in comparison to the standard compound **1** which was found to possess an IC_{50} value of 16.1nM. Within the range of compounds synthesised, **6** was found to be the most potent inhibitor against CA II with IC_{50} values of 13.8nM but was found to be a weak inhibitor (possessing an IC_{50} value of 947.74nM) of ES in comparison to EMATE (which was found to possess an IC_{50} value of 7.92nM). These compounds therefore represent a novel library of compounds as dual-inhibitors of both ES and the CA family of enzymes.

In conclusion, we have provided a novel series of inhibitors of CA II and therefore offer a new library of compounds in the treatment of a number of diseases including cancer.

Keywords: ESTRONE SULFATASE, DUAL INHIBITORS

[P2.92]

Synthesis and biochemical evaluation of N-hydroxybenzamide as potential inhibitors of the enzyme histone deacetylase (HDAC) types 1 and 2

J. Gandhi*, V.R. Vasireddy, C.P. Owen, S. Ahmed
University of the West of Scotland, UK

Histone deacetylase (HDAC) family of enzymes have been shown to have a direct impact on cell growth and proliferation and is therefore an important biochemical target in the treatment of cancers. In our search for inhibitors of this class of enzyme, we have investigated the hydroxamic acid derivatives of substituted benzoic acid in an effort to determine the inhibitory activity of these compounds; it should be noted that these compounds have not been previously reported in the literature, as a result we argued that the determination of the involvement of physicochemical factors within this series of compounds would aid our efforts to design and synthesis more specific and potent inhibitors of HDAC. We therefore report the synthesis and evaluation of a series of derivatives of *N*-hydroxybenzamide as potential inhibitors of HDAC type 1 and 2.

Synthesis of the target compounds involved the synthesis of the corresponding ethyl ester followed by reaction with potassium hydroxide and hydroxylamine solution in methanol. Crude product was recrystallized from aqueous ethanol. HDAC assay was carried out using standard literature procedure using HeLa cells nuclear extract as source of HDAC enzyme and chromogenic substrate.

The synthesis of the target compounds was achieved in moderate to excellent yield and without any major problems. The compounds were found to be weak inhibitors of HDAC types 1 and 2 in comparison, trichostatin which was found to possess ~99% ([I]=10μM). The most potent compound within the current range was found to be 4-iodo-*N*-hydroxybenzamide which was found to possess approximately ~97% inhibitory activity under similar conditions.

In summary, the compounds have proved to be weak inhibitors of HDAC types 1 and 2 but have proved to be good lead compounds in the design of novel inhibitors of this class of enzyme.

Keywords: Histone deacetylase, INHIBITORS, SYNTHESIS, EVALUATION

[P2.94]

P7170, an orally efficaceous, anti cancer clincal candidate targeting PI3K/mTOR and ALK1 kinases

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Piramal Life Sciences, India

Inappropriate PI3K/mTOR signalling is one of the most frequent occurrences in human cancer and is critical for tumor progression. The activation of PI3K/Akt pathway by various mechanisms is one of the most frequently observed defects in human malignancies. PI3K is therefore considered as a well validated target for cancer treatment, and hence the demand for inhibitors with drug like properties is needed. At Piramal, after having considered PI3K as a druggable target, our primary choice was to set up a small molecule based medicinal chemistry PI3K program. Our lead candidate P7170, with sufficient drug-like properties is currently in phase-I clinical trial for the treatment of cancer. In present talk the discovery of P7170 a PI3K/Akt/mTOR inhibitor with having unique potential of ALK-1 inhibition (for anti-angiogenic potential) will be discussed in detail.

Keywords: Anticancer, Kinase, PI3K, mTOR

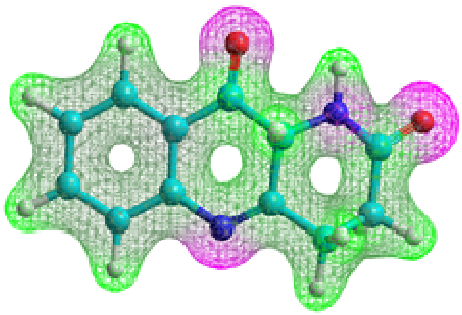
[P2.95]

DFT and QSAR investigations of antibacterial activities of quinazolinone derivatives

A.G. Al-Sehemi*, A. Irfan, S. Alrumman

King Khalid University, Saudi Arabia

The quinazolinone derivatives are good compounds which have been intensively used as biologically active compounds e.g., anticancer, antibacterial, anticonvulsant, anti-inflammatory, antiulcer, and analgesic etc. [1, 2]. We have studied the antibacterial activities of quinazolinone compounds against gram-positive (*Staphylococcus aureus*) and gram-negative bacteria (*Klebsiella pneumonia, Proteus bacilli* and *Shigella flexneri*). The studied compounds showed high antibacterial activities against studied strains with inhibition zones observation. The ground state geometries have been optimized by using density functional theory (DFT) at B3LYP/6-31G* level of theory. The absorption spectra have been calculated by using time dependent density functional theory (TDDFT). The ionization potential (IP), electron affinity (EA), energy gap (E_{gap}), electronegativity (χ), hardness (η), electrophilicity (ω), softness (S) and electrophilicity index (ωi) were computed and discussed. The physicochemical parameters have been studied by quantitative structure–activity relationship (QSAR). The computed properties of investigated compounds have been compared with the Chloramphenicol as well as available experimental data.



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Keywords: Antibacterial activity, Quantitative structure–activity relationship, Density Functional Theory

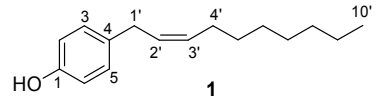
[P2.96]

Inhibitory activities of phenolics from the aerial parts of Piper bavinum against acetylcholinesterase and butyrylcholinesterase

J.H. Geum*[1], V.D. Hoang[2], D.C. To[1], J.S. Choi[1], B.S. Min[1]

[1]Catholic University of Daegu, Republic of Korea, [2]Vietnam Military Medical University, Viet Nam, [3]Pukyung National University, Republic of Korea

A new alkenylphenol, bavinol A (**1**), together with six known compounds (**2**–**7**) were isolated from the aerial parts of *Piper bavinum* (Piperaceae). The chemical structures of these compounds were determined by spectroscopic analyses including 2D NMR spectroscopy. The anti-Alzheimer effects of compounds **1**–**7** were evaluated from acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitory activity assays. Bavinol A (**1**), ampelopsin (**3**), and violanthin (**4**) exhibited AChE inhibitory activities with IC_{50} values ranging from 29.80 to 79.80 μM. Compound **1** also showed the most potent BChE inhibitory activity with an IC_{50} value of 19.25 μM.



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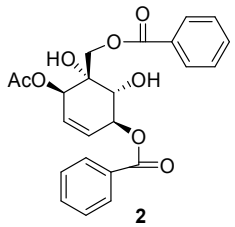

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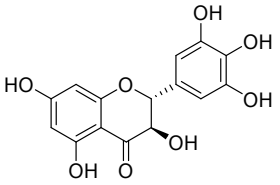

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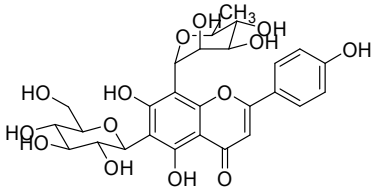

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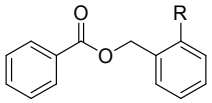
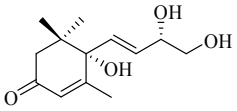


5 R = OCH_3
6 R = H



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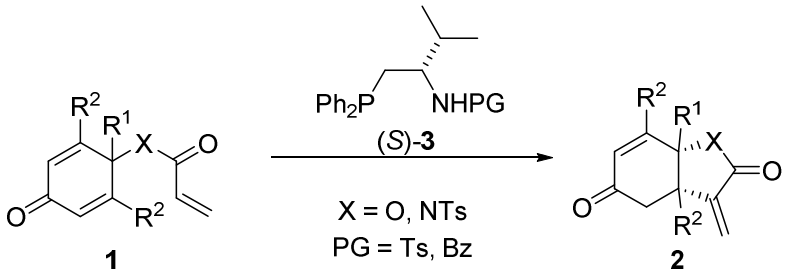
Keywords: Piper bavinum, piperaceae, AChE, Alzheimer's disease

[P2.97]

Enantioselective synthesis of α-methylidene-γ-butyrolactones and γ-butyrolactams: intramolecular Rauhut-Currier reaction promoted by bifunctional organocatalysts

S. Takizawa, T.M.N. Nguyen, K. Kishi, F.A. Arteaga*, M. Suzuki, H. Sasai
Osaka University, Japan

The Rauhut-Currier (RC) reaction is known to be a readily access to α-substituted enones *via* coupling of two different α,β-unsaturated carbonyl compounds, where one acts as a latent enolate. Although attractive systems based on achiral catalysis have been developed for the RC process, few examples of synthetically useful enantioselective RC transformations have been reported.[1,2] Highly selective construction of complex frameworks *via* the enantioselective RC reaction has been a challenge in asymmetric synthetic chemistry. Herein we report the bifunctional organocatalyzed intramolecular RC reaction of the prochiral dienones **1**. Aliphatic and aromatic substituted starting materials **1** were cyclized to give α-methylidene-γ-butyrolactones **2a**[3] or γ-butyrolactams **2b** in good yields and excellent enantioselectivities.



up to 98% ee

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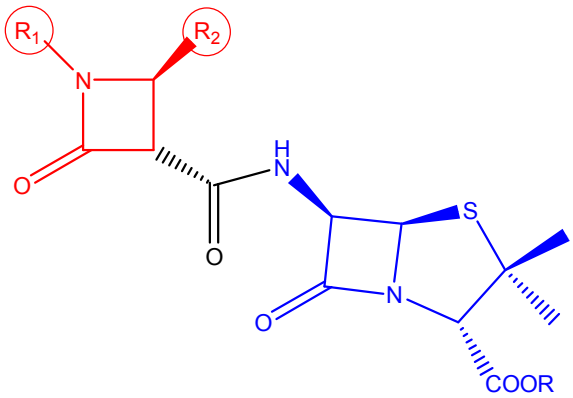
3. a) S. Takizawa, T. M. N. Nguyen, A. Grossmann, D. Enders, H. Sasai, *Angew. Chem. Int. Ed.* **2012**, *51*, 5423. b) S. Takizawa, T. M. N. Nguyen, A. Grossmann, M. Suzuki, D. Enders, H. Sasai, *Tetrahedron*, **2013**, *69*, 1202.

Keywords: Rauhut-Currier reaction, α-methylidene-γ-butyrolactone, γ-butyrolactam, Bifunctional organocatalysts

[P3.01]

Synthesis and biological screening of novel 2-azetidinone derivatives as antimicrobial agents

M. De Rosa*, A. Soriente, C. Saturnino
Università degli Studi di Salerno, Italy



-lactam antibiotics are a mainstay of antimicrobical therapy and play an important role treating infections with a broad spectrum of Gram-positive and Gram-negative bacteria. These molecules exhibit their bactericidal effects by inhibiting enzymes involved in the biosynthesis of bacterial cell wall decomposing the peptide-glycan network building blocks in the cell walls. In the last years the indiscriminate use of antibiotics has highlighted an alarming increase of drug-resistant bacteria and the most commonly acquired mechanism of antibiotic resistance is the ability of bacteria to express enzymes (-lactamases) inactivating these drugs.

The goal of the present work is to prepare a series of novel semi-synthetic -lactam compounds containing an azetidinone moiety joined to the amino-nitrogen of the 6-aminopenicillanic acid (6-APA).The synthetic route was designed because of the sensitivity of the 2-azetidinone towards ring-opening reaction by nucleophiles so to preserve the stability and the pharmacological activity of the 6-aminopenicillanic acid (6-APA). The general synthetic strategy involves the synthesis of structurally different -lactams derivatives by stereoselective Staudinger reaction [2+2]. The 2-azetidinones are sequently linked to the 6-APA affording the title compounds in high yield. SAR studies are performed introducing different functional groups on the azetidinone motif and all the synthesized compounds are screened as antibacterials against four human pathogenic bacteria (two Gram positive bacteria *Staphilococcus aureus* and *Streptococcus pneumonia* and two Gram negative bacteria *Klebisella pneumonia* and *Pseudomonas Aeruginosa)*.

Keywords: azetidone, antibitics, antimicrobical activity, 6-APA

[P3.02]

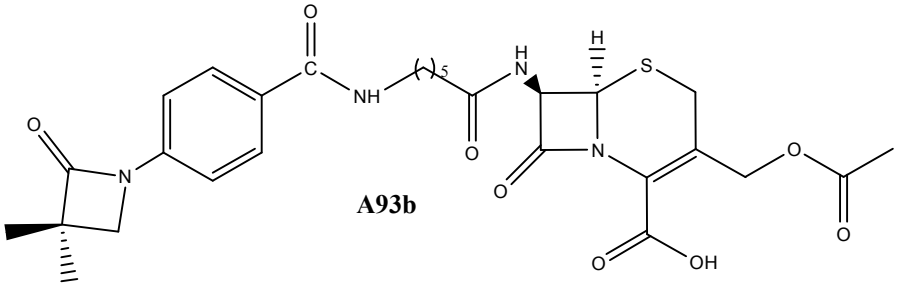
Antibacterial activity of new beta-lactam compounds

M. De Rosa*[1], C. Saturnino[1], A. Soriente[1], A. Caporale[1], N. Marra[1], M.S. Sinicropi[1,2], A. Caruso[1,2], M. Fiorillo[1,2], V. Dolce[1,2], A.R. Cappello[1] et al

[1]Università degli Studi di Salerno, Italy, [2]University of Calabria, Italy

-lactam compounds are evergreen molecoles. Since the discovery of Penicillin and with the emergence of drug-resitant bacteria, the design and the synthesis of new derivatives containing the 2-azetidinone ring motif have always drawn the researcher attention in order to discover new chemotherapeutic agents with improved stability and biological activity.

Here we describe the synthesis of new N- functionalized azetidin-2-one derivatives and evaluation for their antimicrobial activity. The best result was found with the compound titled A93b which, similarly to penicillins and cephalosporins, showed excellent activity againstGram +ve bacteria such as *Sthapilococcus aereus*, *Streptococcus pyogenes* and *Streptococcus pneumonia* (the MIC 50% values are 4, 4 and 2 µg/ml respectively). In particular the MIC values against *Sthapilococcus aereus* are the same of Ceftazidime, a great compound of cephalosporin's class.
Therefore, by the results obtained would seem that A93b mimics the behavior of penicillins. . Has been synthesized a new cephalosporine that is active against some resistant strains of bacteria. Further studies are in progress.



A93b

Keywords: b-lactams, antimicrobial activity, azetidinone derivatives, penicillins

[P3.03]

An iterative modelling and modular synthetic approach to tercyclic alpha-helix mimetics with measured aqueous solubility

A.G. Meyer*[1], P.J. Duggan[1], Z. Lim[1,2], K.L. Tuck[2]

[1]CSIRO Materials Science & Engineering, Australia, [2]Monash University, Australia

Protein-protein interactions (PPIs) play prolific and vital roles in biological systems pertinent to challenging disease states, and as such they make attractive targets for therapeutic intervention. A significant number of PPIs are mediated by *α*-helices, with the critical interactions most often at the *i*, *i*+3 (or *i*+4) and *i*+7 residues (**Figure 1a**). This key feature allows the α-helix motif to be exploited as a design template for drug discovery, enabling the targeting of PPIs that utilise this motif as an interface mediator. The concept of α-helix mimicry by a small molecule was successfully demonstrated in the seminal work of Hamilton who demonstrated that the 3,2□,3□□-substituted terphenyl scaffold could be used to mimic the key *i*, *i*+3 (or *i*+4) and *i*+7 residues. A range of variations to the terphenyl concept have subsequently been developed to address synthetic accessibility and aqueous solubility concerns associated with the original terphenyl scaffolds. We were interested in exploring *new* tercyclic scaffolds that would have *improved synthetic accessibility and aqueous solubility* over existing scaffolds. Employing an iterative molecular modelling approach to efficiently screen a range of putative tercyclic scaffolds, a structurally diverse set of new α-helix mimetics designed to have enhanced aqueous solubility was identified. The synthesis of these tercyclic α-helix mimetics was accomplished using a modular synthetic approach employing functionalised methoxyphenyl units, which were manipulated to allow the introduction of various nitrogen-based heterocycles (**Figure 1b**). Confirmation of these scaffolds ability to mimic the key *i*, *i*+3 and *i*+7 residues of a polyalanine α-helix will be presented (**Figure 1c**), and their measured aqueous solubility reported.

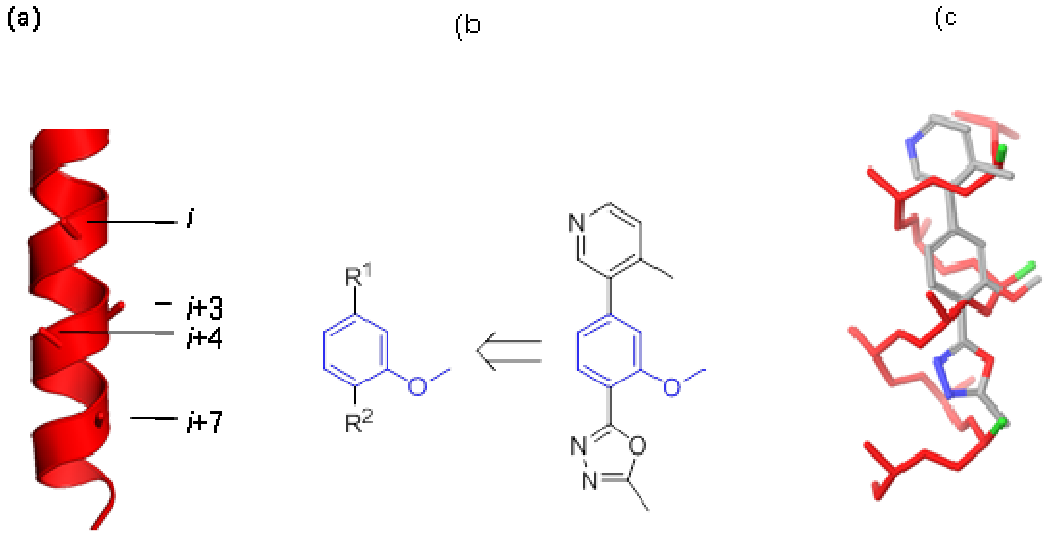


Figure 1: a) Ribbon structure of a polyalanine α-helix showing the *i*, *i*+3, *i*+4 and *i*+7 residues; b) manipulation of a functionalised methoxyphenyl unit to a tercyclic scaffold; c) a low energy tercyclic scaffold conformer (grey) overlayed with a polyalanine α-helix (red).

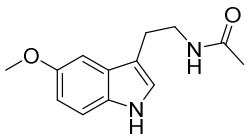
Keywords: alpha-helix, tercyclic, modelling, solubility

[P3.05]

New synthetic pathway to furo[3,2-b]pyridines with melatoninergic activity

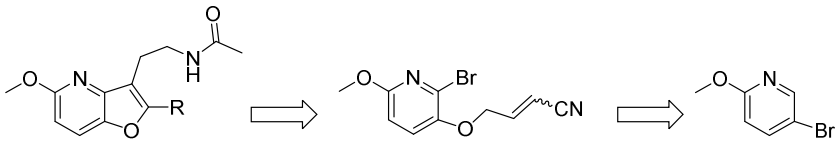
A. Couhert*[1], P. Delagrange[2], D-H. Caignard[2], F. Suzenet[1], G. Guillaumet[1]
[1]*Institut de Chimie Organique et Analytique, France,* [2]*Institut de Reche Servier, France*

Melatonin (or *N*-acetyl-5-methoxytryptamine) is a neurohormone secreted in the pineal gland. This regulator of the biological clock is thus involved in several physiological process and central nervous system disorders. Logically, the two high affinity associated receptors MT_1 and MT_2 become an innovative target for the development of new antidepressants.[1]



Scheme 1 : Melatonin

However, despite increasing interest in melatonin and its mode of action, only a few MT_1 or MT_2 selective ligands have been developed. In this context, we decided to synthesize a series of furopyridinic compounds[2] with various substitutents in position 2.[3] We propose an original strategy allowing easy modulation at C2 position at the end of the synthesis.



Scheme 2 : Developed synthetic pathway

First biological results will be presented and selectivity induced by C2-substitution will be discussed.

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Keywords: Melatonin, Furopyridin

[P3.06]

Synthesis of thiazolo[5,4-b]pyridine and [1,3]thiazolo[5,4-h][1,6]naphthyridin-8-one derivatives as potential m-TOR inhibitors

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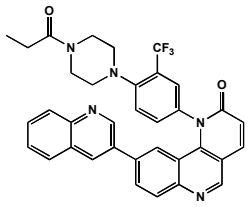
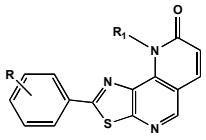
UNIPA, Italy

m-TOR (mammalian Target of Rapamycin) is a member of the PIKK family; this kinase can be considered an important biological target because it is involved in cell growth regulation, proliferation [1] and plays a central role in controlling a wide range of cellular functions, including transcription, mRNA turnover, actin cytoskeletal organization and autophagy. Moreover the PI3K/AKT/mTOR pathway is often deregulated in variety of cancers, including breast, lung, kidney, prostate, blood, liver, ovarian, thyroid, GI tract and lymphoma.[2]

For this reason there has been a growing awareness in the synthesis of new heterocyclic compounds capable of inhibiting mTOR. Torin 1 is a benzonaphthiridin-8-one derivative efficacious at a dose of 20 mg/kg in a U87MG xenograft model and demonstrating good pharmacodynamic inhibition of downstream effectors of mTOR in tumour and peripheral tissues. [3]



Torin 1



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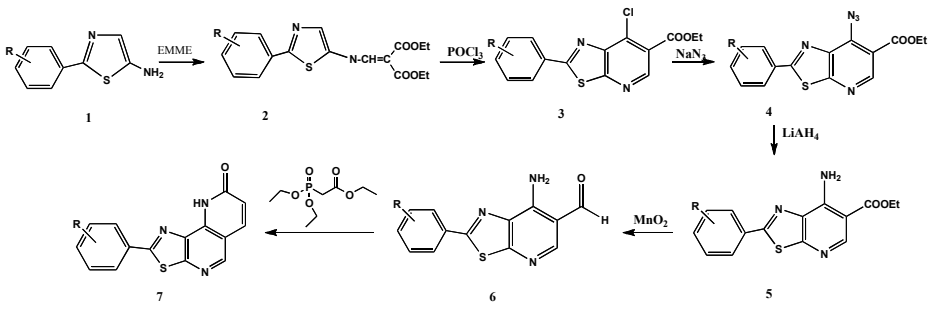
To further explore the potentiality of this class of compound, we have planned the synthesis of analogues in which the naphthiridin-2-one nucleus is condensed with a thiazole ring in order to evaluate its the influence on biological properties.



The synthetic pathway starts from the amines **1** properly prepared through cyclization of the corresponding thioamides. Reaction with diethyl ethoxymethylenemalonate and subsequent cyclization in presence of phosphorus oxychloride allowed the isolation of derivatives **3**. Nucleofilic substitution reaction with NaN_3 and reduction reaction with $LiAlH_4$ have led to thiazolo[5,4-b]pyridine intermediates **5**. Through oxidation reaction it was possible to obtain derivatives **6** which were reacted with triethylphosphonoacetate in order to obtain the desired final compounds **7**.

Derivatives **7** will be submitted to the National Cancer Institute of Bethesda in order to assess their possible antitumour activity; moreover considering that the literature is well documented with PI3K inhibitory activity of benzothiazole derivates [2,4] also some thiazolo[5,4-b]pyridine intermediates of type **3**,**4**,**5** and **6** have been submitted to NCI; results will be discussed.

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[4] WO2009133127A1, D. Swinnen et al., 055172 (2009)

Keywords: mTOR, benzonaphthiridin-8-one, Torin 1, thiazole ring

[P3.07]

Ferrocene - modified uracils: synthesis, structure and biological activity

J. Skiba*, K. Kowalski, I. Ott, L. Oehninger, J. Solecka, A. Rajnisz, B. Therrien
University Lodz, Poland

Although ferrocene itself is considered to be a non-toxic, biologically inert compound, many ferrocenyl derivatives exhibit significant anticancer, antibacterial, antiparasitic, antifungal and other biological activities. An effective strategy for obtaining biologically active ferrocenyl derivatives is based on the conjugation of the ferrocenyl moiety with biomolecules. In that respect, nucleobases, which are known to play a crucial role in biology and pharmacology, remain an attractive targets for ferrocenyl conjugation.Within our program directed to the search of new biologically active organometallic compounds, we focused our attention on the ferrocenyl-nucleobase conjugates [1,2]. In this poster we report the synthesis, electrochemistry, structure, anticancer and antibacterial activity studies of metallocene-nucleobase conjugates **1**, **2**, **3** (metallocene = ferrocene, ruthenocene; nucleobase = uracil, thymine, 5-fluorouracil) (Fig. 1).

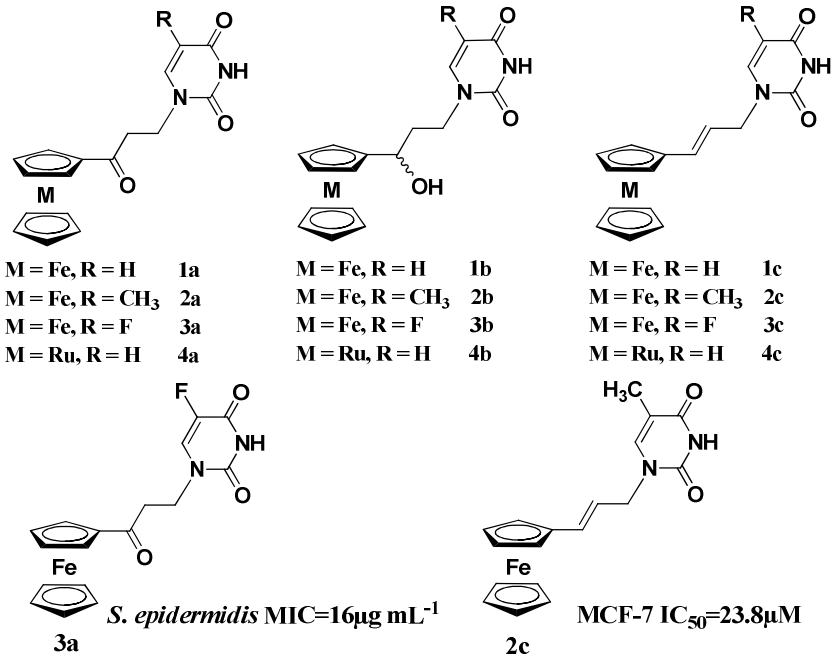

Fig. 1

Acknowledgments: J.S. thanks the National Science Centre in Cracow, Poland (Grant no. DEC-2012/05/N/ST5/01055) for financial support.

[1] K. Kowalski, A. Koceva-Chyła, A. Pieniążek, J. Bernasińska, J. Skiba, A.P. Rybarczyk, Z. Jóźwiak, *Journal of Organometallic Chemistry*, **2012**, *700*, 58. [2] K. Kowalski, J. Skiba, L. Oehninger, I. Ott, J. Solecka, A. Rajnisz, B. Therrien, *Organometallics*, **2013***, 32,* 5766–5773

Keywords: Nucleobases, Metallocene bioconjugates, Antibacterial activity, Anticancer activity