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Program

and

Book of Abstracts

Vienna Doctoral School of Chemistry

Panel C

Retreat 2021

05.11.2021-07.11.2021

DoSChem
Panel C

Program

	Friday, 5.11.		Saturday, 6.11		Sunday, 7.11.
9:00	Arrival/Bus Transfer	9:00	Session 3 09:00 Davide Zanetti 09:20 Julia Kronberger 09:40 Bogdan Brutiu 10:00 Mario Waser	9:00	Session 4/Closing 09:00 Konstantin Raabe 09:20 Ian Oesterle 09:40 Daniela Reichinger 10:00 Christoph Kreutz
		10:30	Poster + Coffee		
				11:30	Departure/Bus Transfer
12:00	Lunch	12:00	Lunch/Free Time		
13:30	Session 1 13:30 Opening 13:40 Hideaki Ogawa 14:10 Kateryna Che				
		14:00	Visit of Stift Admont		
14:30	Coffee Break + Posters				
16:00	Session 2 16:00 Lara Polak 16:20 Nathalie Wörz 16:40 Chr. Wittmann	16:00	Coffee/Posters		
17:00	Welcome Drink/Free Time	17:00	Free time		
18:00	Dinner	18:00	Dinner		

Booklet of Abstracts

NMR of RNA- From methodological advances to the elucidation of functional RNA dynamic

Christoph Kreutz

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Abstract

I will introduce our recent additions to advance the stable isotope (SI) labelling procedures for nucleic acids and how we use these tailor-made SI labelled RNAs and DNAs in NMR spectroscopic applications.

As a recent example the ^{19}F-^{13}C-aromatic labelling of RNA nucleobases to unlock the TROSY effect in RNA will be presented.

Further, synthetic routes will be presented, which give access to chemical building blocks of naturally occurring RNA modifiers, such as, 6-methyl adenosine (m^6A). These modified building blocks were further labelled with nuclear magnetic resonance (NMR) active ^{13}C or ^{15}N stable isotopes.

Thereby, detailed NMR investigations on the effects of the modifiers on structural and dynamic features of RNA were possible. In detail, the effect of the m^6A modification on the annealing properties of RNA will be presented.

Chiral Ammonium Salt Ion Pairing Organocatalysis

Mario Waser

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Over the last years our group had a major interest in the use of chiral quaternary ammonium salt catalysts for asymmetric transformations. We hereby focus on the development of novel chiral catalysts as well as on the introduction of new synthesis methods using chiral ammonium salt catalysts.
In this talk I will give an overview about our efforts on the design and development of a versatile class of chiral bifunctional ammonium salts and our ongoing work focusing on the use of chiral ammonium salt catalysts to access novel chiral β-amino acids.

T1

Conformational selection of vasopressin upon V1a receptor binding

Kateryna Che, Gregory L. Olsen, Markus Muttenthaler, Dennis Kurzbach

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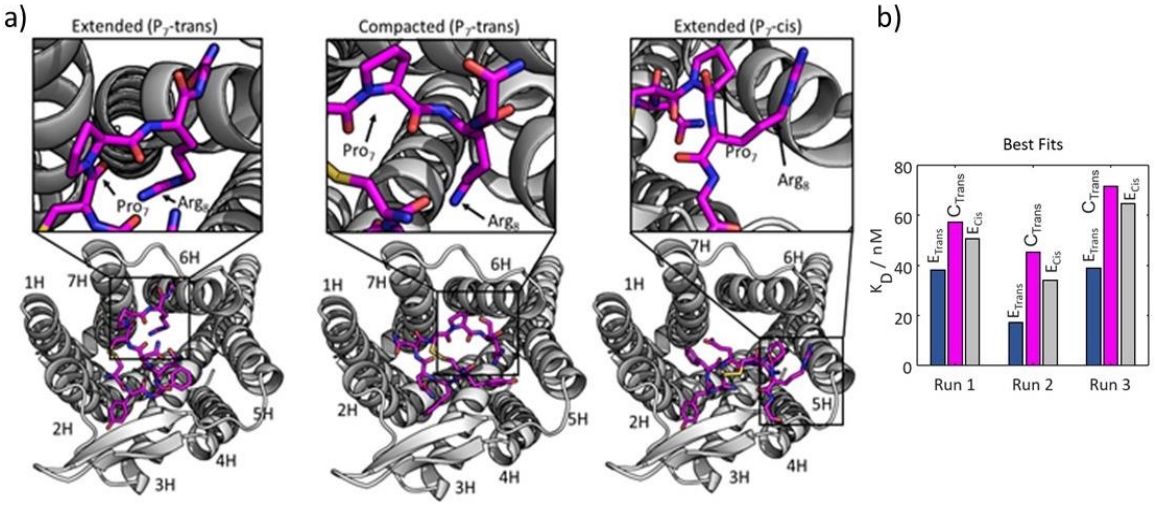

Figure 1. VP-V_1aR complexes computed for: extended trans (left), compact trans (center) and extended cis (right). The transmembrane helix (TMH) numbering is indicated. Note how VP residue Arg^8 varied its position (between TMHs 4 to 6), while Tyr^2 and Phe^3 always bound to TMH 3 and 4. b) Representation of K_D for the complexes with the best scores in our docking experiments computed for the extended trans (left), compact trans (center) and extended cis (right) sub-ensembles for three independent MD runs.

Vasopressin (VP) is a small regulatory neuropeptide that plays multiple essential roles in the body. Special attention is received by VPs influence on the cardiovascular system.[1] VP and its ligand-receptor systems have thus been the subject of longstanding research and drug design.[2] However, despite these extensive efforts, important structural and dynamic details of its receptor interactions remain unclear.

We employed virtual screening strategies to reveal features of conformational selectivity upon VP-V1aR complex formation. We dissected the VP conformational space into three sub-ensembles, each containing distinct structural sets for VP's three-residue C-terminal tail. We observed that Proline trans-configured tail conformations bound to the receptor with three-fold enhanced affinities compared to compacted or cis-configured conformations.

This method enabled identification and characterization of a conformational selection-type complex formation mechanism that confers novel perspectives on targeting the VP-V1aR interaction at the level of peptide-receptor encounter, and input for ligand design strategies provide more potent and selective VP analogs.

1. Mondritzki, T. *et al.* Cardiac output improvement by pecavaptan: a novel dual-acting vasopressin V1a/V2 receptor antagonist in experimental heart failure. *European Journal of Heart Failure* 23, 743–750 (2021).
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T2

Influence of the Ligand Bite Angle on Rare-Earth Metal Hydroamination Catalysis

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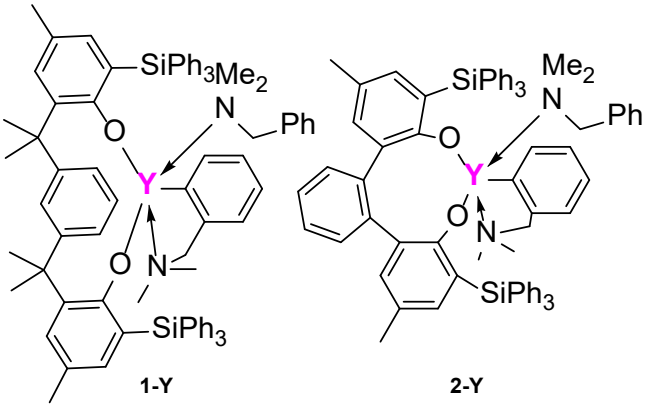
A long-standing challenge in synthetic organic chemistry is the efficient formation of carbon-nitrogen bonds, which are omnipresent in natural products, pharmaceuticals and functional materials [1]. One method to achieve this, is via the direct addition of N-H bonds to carbon-carbon unsaturated bonds, the so-called hydroamination reaction, which can occur in both inter- and intramolecular fashion.

To improve on already existing hydroamination catalysts [2,3], we examined the effect of the ligand bite-angle on the activity of Yttrium-based hydroamination catalysts. Two different ligands with similar electronic properties were obtained and their respective catalysts **1-Y** and **2-Y** were tested in intramolecular hydroamination reactions.



In preliminary catalytic experiments, **2-Y** seemed to be superior over **1-Y** as full conversion was obtained at shorter reaction times and with lower catalyst loadings, even for less activated substrates such as the *gem*-dimethylaminopentene.

Current studies focus on examining the effects of the steric demand of the SiR_3 groups on the catalytic activity with both ligand backbones. Moreover, the precise structures of the yttrium complexes using both ligands as well as the aptitude of the catalysts in the more challenging intermolecular hydroamination reaction are still under investigation.

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T3

Targeting bacterial effector proteins with activity-based probes

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The ongoing antibiotic resistance crisis is a major threat for public health and characterized by rising mortality rates caused by multi-resistant bacteria [1]. Consequently, there is an urgent need for new therapeutic methods [2]. Along with the development of novel antibiotic classes, alternative strategies, such as virulence inhibition, are of particular importance [3]. Attenuated virulence helps the host immune system to clear the infection and is achieved by treatment with anti-virulence drugs. Many bacteria utilize so-called effector proteins to invade the host and start the infection process. Thus, inhibitors of bacterial effector proteins are promising anti-virulence drug candidates and therefore are of potentially high interest for the development of new antimicrobial drugs. [4-6]
In this study, effector proteins that interfere with human ubiquitin (Ub) and ubiquitin-like (Ubl) signaling were selected. These effector proteins all feature a nucleophilic active site cysteine and have either a deubiquitinase (DUB), E3 ligase, or glutamine deamidase activity [7]. The selected effector proteins were heterologously overexpressed in *Escherichia coli* and a small library of activity-based probes (ABPs) was tested for labeling selectivity and specificity. Within the last two years, we successfully developed several small molecule probes that enable labeling of some of the selected effector proteins in live cells. These labeled effector proteins include virulence factors from the human pathogens *Chlamydia trachomatis*, *Escherichia coli* (EHEC), *Burkholderia pseudomallei*, *Shigella flexneri*, and *Salmonella typhimurium*. Further, we developed a screening method for cell permeable inhibitors of the labeled enzymes as potential anti-virulence drugs. This method is based on the principle of competitive ABPP. Next, we plan to optimize the conditions of the competitive ABPP and start screening for highly selective cell permeable inhibitors, starting by the investigation of metabolites of commensal or probiotic bacteria.

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T4

Novel latonduine derived proligands and their copper(II) complexes show cytotoxicity in the nanomolar range in human colon adenocarcinoma cells and *in vitro* cancer selectivity

Felix Bacher,*[a] Christopher Wittmann,*[a] Márta Nové,[b] Gabriella Spengler,[b] Małgorzata A. Marć,[c] Eva A. Enyedy,[c] Denisa Darvasiova,[d] Peter Rapta,[d] and Vladimir B. Arion*[a]

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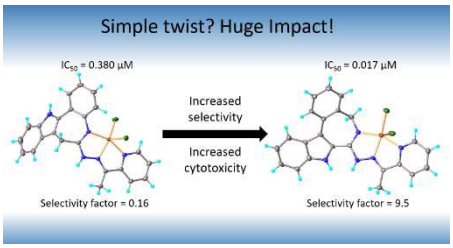

Our group of Prof. Dr. Vladimir Arion has studied the scaffold of Paullones thoroughly.[1] However, lacking feasible pharmacological profile turned the focus to the stereoisomer of Latonduine derivatives, which were recently published.[2] Even though increased cytotoxicity was observed, a lack in bioavailability was present.

By carefully tuning the skeleton to create a binding motif for copper(II) the pharmacological profile of the drugs were sought to be enhanced, as it was the case for Paullones.[1] These modifications lead not only to enhanced cytotoxicity but also to a sharply improved selectivity pattern towards malign cell lines.

The drugs were fully characterized be standard spectroscopic methods and X-ray diffraction. A comparison with the respective Paullone derived proligands and copper(II) complexes revealed the superiority of Latonduine derived molecules.

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T5

Photoredox intramolecular coupling catalysed by PXX

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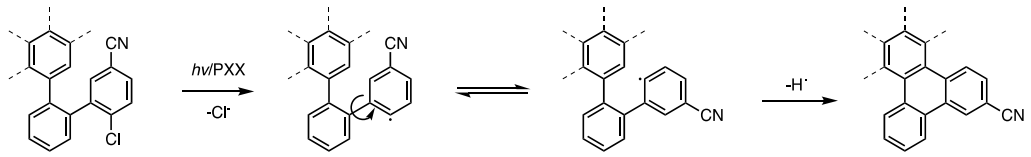
The revival of radical chemistry in organic synthesis over the past decade has also initiated resurgence in the interest in photochemistry.
In the field of photoredox catalysis, Ru(II)- and Ir(III)-based complexes are still the work-horses in terms of photocatalysts. However, the high cost of transition metals, especially iridium, resulting from their low abundance as well as high environmental impact of mining them encourages researchers to look also at fully organic derivatives.[1,2]
Exploiting the unique and interesting properties of peri-xanthenoxanthene (PXX) as fully organic powerful photoreductant (λ_{max} = 439 nm; $E^*_{1/2ox}$ = -2V vs SCE), we hereafter presenting a new method to obtain electron poor poly aromatic hydrocarbons (PAHs), which are important materials although often difficult to achieve synthetically, starting from aryl chlorides. The method developed, raised up from positive results on PXX catalysed intermolecular couplings, exploits a proximity to the electron neutral or electron rich ring to the poor one with chlorine atom, leading to the final cyclisation and extension of the system.[3,4]



We thus envisaged the possibility to offer to the community a new, versatile and cheap way to get new extended systems. Through the incorporation of the shown above system, is indeed possible to get extended PAH increasingly important for optoelectronic applications requiring a tuneable semiconducting material.

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T6

Radiolabeling of [^{89}Zr]Zr-Atezolizumab for its clinical evaluation in patient stratification for PD-L1 immune checkpoint inhibition therapy

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Atezolizumab is a monoclonal antibody designed to target and inhibit the ligand (PD-L1) of the programmed cell death receptor 1 (PD-1). The PD1/PD-L1 signaling pathway is part of the human immune response and represents one of the so-called immune checkpoints. Immune checkpoints have been targeted successfully in cancer therapy to prevent tumors of escaping their elimination by the immune system [1].

The highly specific antibody is already approved for the treatment of several tumor types under the trade name Tecentriq©. Nevertheless, the precise stratification of patients suitable for the therapy is still difficult. Therefore, positron emission tomography (PET) imaging using zirconium-89 radiolabeled Atezolizumab is currently under investigation as a non-invasive method for selecting patients for therapy with Tecentriq©. [2]

The meanwhile sixth clinical trial involving [^{89}Zr]Zr-Atezolizumab is going to be conducted at the Medical University of Vienna (NCT04564482). The primary aim of this work was the required production of three “Master Batches”, including their quality control according to the patient safety regulations.[3] An established protocol was successfully adapted and optimized, including the radiolabeling of Atezolizumab-N-SucDFO with zirconium-89 (RCP >99% and RCY >65%) and purification of the product. The radiotracer was evaluated by size-exclusion chromatography (SE-HPLC), instant thin layer chromatography (iTLC) and competitive binding assays using the isolated extracellular domain of PD-L1. Upon regulatory review of the sterility of the “Master Batches”, the radiotracer will be ready for clinical application at the facility.

Additionally, the mAb and its DFO conjugate have been characterized by mass spectrometry. Furthermore, the immunoreactivity of the radiolabeled antibody has been investigated with more advanced methods (Lindmo assays [4]). For further investigation of the binding properties of the radiotracer, internalization studies with MDA-MB-231 (human breast cancer) cells were conducted.

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T7

Stable and easily available sulfide surrogates allow a stereoselective activation of alcohols

Jérémy Merad,[‡ab] Ján Matyašovský,[‡a] Tobias Stopka,[‡a] Bogdan R. Brutiu,[§a] Alexandre Pinto,[§a] Martina Drescher[a] and Nuno Maulide[*]

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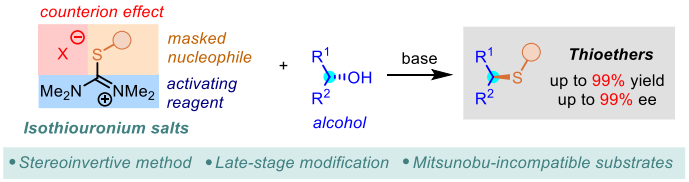
Sulfur is the 5th most abundant element (after C, H, O and N) in pharmaceuticals and agrochemicals. More than 20% of recently approved drugs contain at least one sulfur atom.1 Thioethers (or sulfides) are traditionally synthesized *via* a S_N2-type strategy starting from the corresponding alcohol and thiol. However, thiols are notoriously malodorant compounds, susceptible to oxidation and very few are commercially available.
In contrast, isothiouronium salts are odorless, stable and easily accessible compounds, which can function as an activator for the hydroxyl group. Kajigaeshi reported a general one-pot two-step strategy for preparation of thioethers from primary alcohols and isothiouronium salts.2
We report the use of isothiouronium salts as versatile deoxasulfenylating agents enabling a stereoselective, thiol-free protocol for synthesis of thioethers from alcohols.3 This method is applied to biologically relevant compounds.



‡ and § authors contributed equally

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T8

Photoactivatable probes to study long-term memory formation

K. Raabe*, M. Muttenthaler**

Memory formation is a crucial neurological process that is not only necessary for adaptive survival but also determines an individual's personality, wellbeing and mental health.[1] The mechanisms responsible for memories, however, are not fully understood. A growing body of evidence suggests increased synaptic strength based on experience-dependent activity patterns, termed long-term potentiation (LTP), as fundamental mechanism for long-term memory formation.[2]

Different stimuli can trigger a multitude of intracellular signaling cascades that lead to occurrence of LTP and ongoing research implicates the necessity of *de novo* or altered protein synthesis for memory to develop.[3,4] To understand the intracellular machinery, the structural elucidation and identification of memory-proteins is critical and could provide invaluable insights into LTP. Considering that memory formation occurs in a specific brain area at a specific time[5] and considering that over 10,000 proteins regulating physiological processes at any given time,[6] it is extremely difficult to distinguish between the production of memory-proteins and other, memory-unrelated, proteins.[4]

We are therefore developing photocontrollable molecular probes[7] for light-activated bioorthogonal non-canonical amino acid tagging (laBONCAT) that provide the required spatiotemporal resolution for the identification of memory proteins.[8] In addition to probe design and synthesis, the project includes photochemical probe characterization as well as *in vitro* and *in vivo* evaluation. In collaboration with the research group of A/Prof. Sadegh Nabavi at the Danish Research Institute of Translational Neuroscience at Aarhus University, Denmark, we will apply these probes in memory-specific *in vivo* experiments (Figure 1).

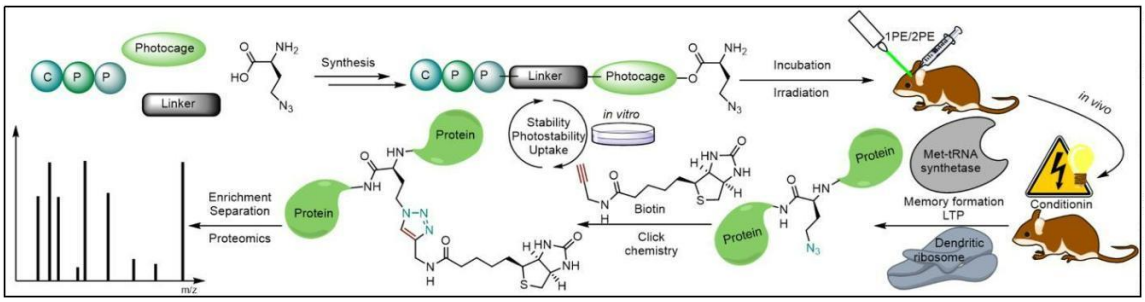

Figure 1. Proposed workflow from synthesis to evaluation of first *in vivo* experiments.

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T9

Human polyphenol exposure explored by targeted LC-MS/MS[1]

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Polyphenols are bioactive phytochemicals known for their beneficial impact on health, due to various properties they exhibit, such as antioxidant, antibacterial and anti-inflammatory. Therefore, being able to monitor their presence, both short and long-term, directly in human samples would be beneficial to both influence health outcomes and to aid individualized medicine. However, this proves to be a challenge as polyphenols are a highly complex class of molecules which are extensively metabolized, majoritarily through conjugation reactions, in the human body yielding numerous biotransformation products. Currently, multiple techniques exist for human biomonitoring of polyphenol exposure, yet many of these assays are not comprehensive, as they tend to only target a limited number of polyphenol metabolites or only focus on a few classes of polyphenols. Hence, the aim of this work was to develop a sensitive broad multi-analyte method. This innovative method involved using a UHPLC-ESI-MS/MS to target roughly 100 different polyphenol metabolites that are the main representatives of the different polyphenol classes. Furthermore, this method also included some sulfated and glucuronidated metabolites, which tend to be omitted in currently published methods. The extraction of these polyphenols was optimized and validated in-house for several human matrices, which are: urine, serum, and plasma. Different analytical parameters, such as limits of detection/quantification, signal suppression and enhancement, and extraction efficiency, were determined for this method. Finally, a short proof-of-principle was performed to develop a kinetic profile of the different polyphenols over 24 hours in urine after the ingestion of a high polyphenol diet in a small sample set.

[1] Similar abstract was submitted to the DOSChem Student Symposium of 2021

T10

Silica encapsulated peptide-antigen conjugates as novel vaccine delivery platforms

Daniela Reichinger[1], Mirjana Drinic[2], Joshua Tobias[2], Manuel Reithofer[3], Meder Kamalov[1], Beatrice Jahn-Schmid[3], Ursula Wiedermann-Schmidt[2] and Christian F. W. Becker[1]*

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Peptide-based subunit vaccines provide a good safety profile and are easy to produce as well-defined modalities. However, they often elicit a weak immune response which is why they require the use of additional stimulants to obtain the desired effects.[1]

Over the past years, increasing focus has been put on biomimetic silica formation for biotechnological applications as well as in biomedical research. Peptide-based systems based on the RRIL motif derived from silaffin proteins in diatoms are employed for the formation of morphologically diverse, nanostructured silica particles *in vitro* under mild, biomimetic conditions.[3,4]

In this work, three different antigens are covalently linked to four different peptides containing the RRIL motif via disulfide bonds. These antigen-RRIL conjugates effectively precipitate silica and the morphology of the resulting particles can be characterized by electron microscopy.

In addition, RRIL-based silica particles induce the formation of neutrophil extracellular traps (NETs) at a similar level as the well-established adjuvant alum as determined by a NETosis assay.[5]

Overall, the described conjugation approach is the first step towards a versatile vaccine adjuvant platform that can be efficiently loaded with a large variety of peptide antigens but also other (bio-)molecules that leads to the stimulation of an immune response.

Acknowledgements
We gratefully acknowledge funding from Austria Wirtschaftsservice (aws, project SILAVAX to CFWB) and University of Vienna as part of a uni:docs fellowship to DR.

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1

Auger electron therapy for cancer treatment

Maximilian Anderla, Thomas L. Mindt

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Radiation therapy utilizing Auger electron (AE) emitters is a promising approach for cancer treatment based on their cytotoxic potential in close proximity to vulnerable cell compartments. AEs have a high linear energy transfer (LET), releasing their energy over a few nanometers distance and producing locally dense clusters of ionisations around the point of decay.[1,2]

Several AE-emitting radionuclides are commonly used for diagnostic imaging in nuclear medicine (e.g. ^{111}In, ^{99m}Tc and ^{123}I) which decay by electron capture and/or internal conversion. These transitions cause vacancies in K-shells that are subsequently filled by electrons from higher shells, thereby transferring their energy to electrons of external layers accompanied by cascades of ejected Auger electrons.[3] In particular DNA is regarded as a preferred target site for AE particle emitters, hence nuclear localization is considered necessary for a distinct therapeutic effect.[2] Thus, the short-ranged delivery of energy by Auger-emitters permits highly targeted therapies with little collateral damage for surrounding tissue.[1]

Conversely, the subcellular range of AE emitters requires delivery systems capable of targeting cancer cells and subsequent translocation to the nuclei of malignant cells.[4] To address these challenges, novel strategies for this so-called dual-targeting approach must be developed. Until today, no AE-based cancer therapies are approved for clinical use. In the course of this PhD thesis, new vectors for efficient AE emitter delivery to the cell nuclei will be developed and investigated.

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2

Synthesis of Chiral PN^3 Pincer Ligands for Transition Metal Catalysed Borrowing Hydrogen Reactions

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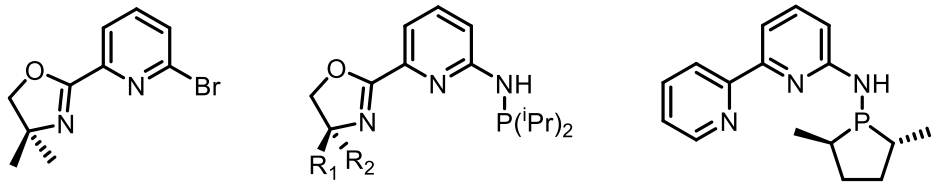
The borrowing hydrogen methodology offers a sustainable alternative for the synthesis of amines.[1] To catalyse these reactions, pincer complexes have been utilised and proved themselves as powerful tools. We hereby report our results on the synthesis of chiral pincer ligands. A 5-step reaction pathway was followed for the synthesis of oxazoline ligands, featuring good overall yield. Second, we report the synthesis of a novel PN^3 bipyridine phospholane ligand.



1 **2a**: $R_1 = R_2 = CH_3$ **b**: $R_1 = {}^iPr$, $R_2 = H$ **3**

Figure 1: The approaches and ligands covered by our research.

To test the reaction procedure for the synthesis of oxazolines provided by Ochoa,[2] an inexpensive, symmetric model compound was used. The pathway reported started with the synthesis of **1** shown in Figure 1. Subsequent amination with NH_3 and Cu powder lead to ring cleavage at the oxazoline moiety, hence significantly reducing the yield. This was circumvented by performing the ring-closure after the necessary amination step.[3] The procedure was successfully adapted to yield the desired oxazoline compound, after which a L-valinol moiety could be introduced. The phosphine was attached to the NH_2 linker to give the final pincer ligands (**2a** and **2b**).

Additionally, initial NMR-scale experiments were performed to gain a bipy-phospholane pincer (**3**) from TMS-protected 2,5-dimethylphospholane. After an Umpolung reaction with C_2Cl_6 the reactive Cl derivate was obtained,[4] which could be attached to the NH_2-linker with standard procedures.

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3

Triapine Analogues and Their Copper(II) Complexes: Synthesis, Characterization, Solution Speciation, Redox Activity, Cytotoxicity, and mR2 RNR Inhibition

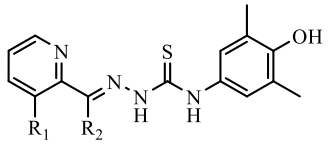
Besleaga I., Stepanenko I., Petrasheuskaya T.V., Darvasiova D., Breza M., Hammerstad M., Marć M.A., Roller A., Spengler G., Popović-Bijelić A., Enyedy E.A., Rapta P., Shutalev A.D., Arion V.B.

Thiosemicarbazones are known as biologically active compounds with a broad spectrum of pharmacological properties, including anticancer activity. [1]

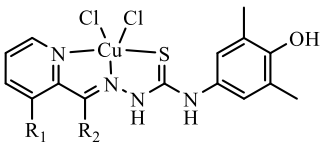
In this work we report on the synthesis of three new thiosemicarbazones (TSCs) **HL^1**–**HL^3** as triapine analogs bearing a redox-active phenolic moiety at the terminal nitrogen atom, and of copper(II) complexes **Cu(HL^1)Cl$_2$ (1)**, **[Cu(L^2)Cl] (2´)** and **Cu(HL^3)Cl$_2$ (3)**. The presence of *E*- and *Z*-isomers with predominance of the first one in DMSO has been disclosed by 1D and 2D NMR spectroscopy. These data along with DFT calculations suggested the mechanism of *E/Z* isomerization with inversion at the nitrogen atom of the imine bond as suggested previously.[2]

Solution (equilibrium) studies revealed that the metal-free ligands are stable as **HL^1**–**HL^3** at pH 7.4, while being air sensitive in the basic pH range. The monocationic complexes **[Cu(L$^{1–3}$)]$^+$** are the most abundant species in aqueous solutions at pH 7.4. Electrochemical and spectroelectrochemical studies of **1**, **2´** and **3** confirmed their redox activity in both the cathodic and the anodic region of potentials. The one-electron reduction was identified as metal-centered by EPR spectroelectrochemistry. Electrochemical oxidation pointed out on the ligand centered oxidation, while chemical oxidation of **HL^1** and **HL^2**, as well as **1** and **2´** afforded several two-electron and four-electron oxidation products, which were isolated and comprehensively characterized.

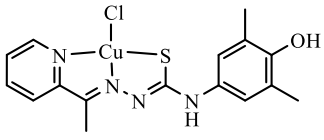
The anticancer activity of the obtained products was tested against two human cancer cell lines (doxorubicin-sensitive Colo205 and the multidrug resistant Colo320 human colonic adenocarcinoma) and normal human embryonal lung fibroblast cells (MRC-5) along with their mR2 RNR inhibiting ability. Complexes **1** and **2´** showed antiproliferative activity with IC_{50} values in the low micromolar concentration range, while **3** with the most closely related ligand to triapine displayed the best selectivity for cancer cells vs normal fibroblast cells (MRC-5). **HL^1** and **1** in the presence of DTT are as potent inhibitors of mR2 RNR as triapine.



R_1 = H, R_2 = H (**HL^1**)
R_1 = H, R_2 = Me (**HL^2**)
R_1 = NH_2, R_2 = H (**HL^3**)



R_1 = H, R_2 = H **Cu(HL^1)Cl$_2$ (1)**
R_1 = NH_2, R_2 = H **Cu(HL^3)Cl$_2$ (3)**



R_1 = H, R_2 = Me **[Cu(L^2)Cl] (2´)**

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4

Development of a N-borylation reaction for the preparation of BN-doped PAHs

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The supreme properties that characterize graphene make it a promising candidate in nanomaterials and technology. Its electronic band structure, however, prevents the application of this exceptional material as semiconductor. One of the most efficient approaches to obtain a functional single-layer material with a tunable bandgap consists in replacing C=C bonds with isostructural and isoelectronic Boron-Nitrogen (BN) couples. This strategy allows the tailoring of bandgap properties without disrupting the honeycomb structure of graphene nor introducing peripheral functional groups.

In this work, we report the results of a one-year synthetic methodology study into the preparation of BN-doped molecular graphenes.

We hypothesized the synthesis of such BNC materials happening via borylation of polyamino starting materials. Indeed, a high-yielding one-step N-borylation reaction was developed on simple "model" substrates, such as 2-aminobiphenyl and [1,1':3',1"-terphenyl]-2,2"-diamine, making use of BBr_3 as borylating agent. No Lewis acid or additive is needed for promoting the reaction.

The photophysical properties of the simple BN-phenanthrene (product of the borylation of 2-aminobiphenyl) were investigated. Interestingly, the compound was found to produce Thermally Activated Delayed Fluorescence (TADF) in solution, and it is currently being analysed for its emission in solid state, thin films and devices at the Technical University of Munich (TUM).

In the near future, the developed synthetic methodology will be applied for the preparation of BN-doped molecular graphenes. We foresee that more complex and extended BN-doped Polycyclic Aromatic Hydrocarbons (PAHs) will have photoluminescence features that would make them good candidates for the implementation in optoelectronic devices, such as Light-Emitting Electrochemical Cells (LECs), Organic Photovoltaics (OPVs) and Electrochromic Devices (ECDs).

5

New substrates to study the biodegradation of P-C compounds

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The high environmental importance of phosphonates as alternative phosphorus source for microorganisms, especially in marine ecosystems, has led to an increased scientific interest in their degradation.[1] Today, three general degradation pathways are known. One of them is the hydrolytic P-C bond cleavage route to which the so-called phosphonoacetaldehyde hydrolase belongs.

This hydrolase uses 2-aminoethylphosphonic acid (AEP) to form acetaldehyde and inorganic phosphate in a two-step process catalyzed by PhnW/X over the intermediate phosphonoacetaldehyde (PnAA).[2] Recently yet another enzyme belonging to this biodegradative cluster, PbfA, was found in several bacterial strains. It was shown to catalyze an elimination reaction on (*R*)-1-hydroxy-2-aminoethylphosphonate [(*R*)-OH-AEP)] to form PnAA and thus expand the substrate scope of this pathway.[3]

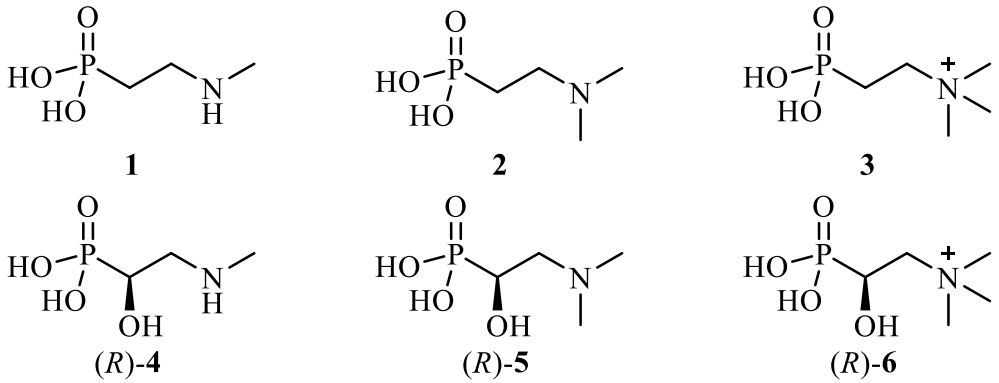

Figure 1: Potential substrates for PbfB/C/D.

Now other putative FAD-dependent oxidases were found, namely PbfB/C/D, which are also 'recurrent' in close proximity to the genes encoding PhnX/W. The presence of these genes in the AEP degradation cluster suggests there might be even more possible substrates for this pathway. Presumably these are closely related to AEP. Thus, we synthesize a set of mono, di and trimethylated analogs to AEP (**1**-**3**) and (*R*)-OH-AEP (**4**-**6**) to test them as substrates for Pbf B/C/D and study the function of these enzymes.

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6

Formation and evolution of nanoscale calcium phosphate precursors under biomimetic conditions

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Simulated body fluids (SBFs) mimic the ionic concentration of human blood plasma; therefore, they are widely employed in biomineralization studies. Despite the popularity of SBF, its highly dynamic behavior is still not completely understood. This study presents an approach combining real-time ^{31}P NMR, Ca-ISE, Cryo-TEM, and computer simulations to characterize modified SBF (mSBF - a variant of SBF).

Using ^{31}P NMR we could identify some calcium phosphate nanoscale inhomogeneities that form 5 hours after mSBF preparation. These inhomogeneities grow from a size of ~2 nm into prenucleation species (PNS) – considered as precursors of the final CaP crystals –, to reach a final dimension of ~200 nm after 24 hours. (Fig. 1) To corroborate the NMR data, we also generated a theoretical model explaining the exchange behavior of phosphate in solution.

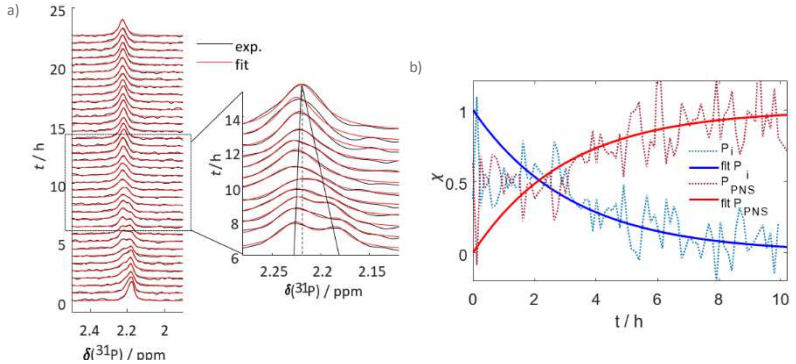

Figure 1: a) ^{31}P NMR signals detected for mSBF over a period of 24 h (black) and corresponding fits to two Lorentzian functions (red). **b)** Time-dependence of the fractional contribution χ of the two lines to the overall spectrum. The contribution of free phosphate is shown in blue and that of PNS-bound phosphate in red. The dotted lines indicate the experimental data, while the solids lines represent the fit of the experimental data.

Thus, we show that mSBF can be considered as a stable or metastable solution only after ~24 hours from preparation. Moreover, our approach can help tracking P_i to P_{PNS} conversion in other biological solutions, shedding light on the still unclear process of biomineral prenucleation.

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7

Targeting Tyrosine Kinase Inhibitors – an insight into overcoming drawbacks of targeted anticancer therapy

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With the approval of imatinib (Gleevec®) in 2001, the substance class of tyrosine kinase inhibitors (TKIs) debuted in clinical application and two decades later marks an indispensable contribution to the treatment of various cancers. Other than traditional chemotherapy, TKIs are directed towards molecular targets involved in specific signal transduction pathways and therefore are referred to as targeted therapeutics.[1]

As of 2021, there are 55 protein kinase inhibitors approved for anticancer therapy, targeting transmembrane receptors like the epidermal, vascular endothelial and fibroblast growth factor receptors (EGFR, VEGFR, FGFR), but also downstream signaling proteins like Bcr-Abl, MEK and ALK.[2] Yet despite their success, TKIs frequently entail major adverse effects.[3] The explanation is that protein kinases are also expressed in various healthy organs and are not solely confined to malignant cells. This, causes off-target effects, which often even lead to dose reduction.[4]

Consequently, the impact of TKIs with increased selectivity for malignant over healthy tissue, would greatly improve drug tolerance and treatment response. One possibility to achieve an increased on- to off-target ratio is the conversion of a drug into a prodrug, which by definition is a pharmacologically inactive compound that has to be converted into its active form *via* specific activation mechanisms *in vivo*. Hereby certain characteristics in cancerous tissue like lower pH-levels, hypoxia or overexpressed proteases can be exploited.[5]

In the course of this PhD thesis, one strategy is the development of prodrug analogues to reduce side effects with the aim to increase the selectivity for cancerous cells and minimize off-target effects.

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8

MULTIFUNCTIONAL ELECTROCHROMIC COVALENT ORGANIC FRAMEWORKS

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Covalent organic frameworks (COFs) are three-dimensional organic solids with extended structures that are constructed from molecular organic building blocks composed of light elements (H, B, C, N, and O) joined by covalent bonds.[1]

Through careful consideration of the choice of linkage and precise control of the reaction conditions, it is possible to balance the thermodynamic and kinetic control of COF formation, yielding crystalline solids with permanent porosity.[2]

In this project, a library of precursor molecules bearing two (linker) and three (knot) functional groups was synthesized. Initially the incorporation of amino and aldehyde groups was pursued in order to later on synthesize COFs using the well-known imine condensation reaction.

Molecules with electrochromic behaviour were target, as well as molecules with other desirable properties (*i.e.* oxygen sensing). The goal is to combine these properties in a well organize structure (*i.e.* COF) that not only adds up the individual properties of each precursor molecule but also increases their performance and stability.

Several strategies were already implemented for the COF synthesis: a) hydrothermal; b) solid-liquid interfacial; c) liquid-air interfacial; d) liquid-liquid interfacial; and e) colloidal nanoparticle assembly. From these, the liquid-liquid interface approach seems to be the best to directly obtain COF thick films that can be deposited in conductive substrates for use in optoelectronic devices.

The future directions in this research are going to focus on the further development of the liquid-liquid interface COF synthesis and in the colloidal COF nanoparticles given their potential for high processability.

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9

Developing chemical probes and inhibitors for SOS-response activated proteases via proteomic metabolite profiling

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Bacteriophages have been found to play an important role in growth and function of microbial populations, ultimately influencing human health and disease. (*1*) However, the complex chemical interactions between microbe and phage still remain scarcely investigated, particularly regarding bacterial pathogenicity. (*2*) Serine hydrolases, such as SOS-response activated proteases LexA and CI as well as assemblin-like or ClpP-like prohead proteases, are important enzymes involved in phage induction and maturation. (*3*) (*4*) Thus, the development of phage-selective probes and inhibitors for these enzymes represents a promising approach to monitor and control lysogney-lytic decisions and hence formation processes of the virus particle.

In this study, a diverse set of activity-based probes equipped with serine reactive electrophilic warheads was designed to covalently label the active-site residue of LexA/cI proteins as well as prohead proteases of bacterial and phage homologues from *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Ligand selection activity-based protein profiling (LS-ABPP) was performed to assess site selective and target specific probe binding. (*5*) Despite high sequence similarities of SOS-response related proteins in bacteria and respective bacteriophages, preliminary results strongly point towards mutually exclusive labelling preferences. In the future, LS-ABPP probes will be further optimized to guide the development of potent covalent inhibitors by live cell competitive inhibitor profiling. These inhibitors will provide novel tools for silencing SOS-response based induction mechanisms, prevent phage maturation, and reduce the release of toxins and virulence factors.

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10

The distinct fragrance of a potential new class of anti-malarials – Synthesis of natural product-derived isocyanides and preliminary binding studies

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Malaria is still one of the most menacing diseases in the world, especially in the developing countries. The parasite *Plasmodium* (transmission by *Anopheles* mosquitos) is responsible for this disease. With increasing resistances against various established drugs (chloroquine and artemisinin-based combination therapies) new anti-malarials are required. [1] Marine natural diterpene isocyanides may represent a novel potential class of drugs, since anti-plasmodial activity by binding to heme (key-step of many current drugs) could already be demonstrated. [2]

Therefore, in this work, the aim was the preparation of smaller isocyanides based on cyclic monoterpenoid and carbohydrate scaffolds as well as the spectroscopic investigation of possible anti-malarial activity. In case of the monoterpenoids two steps were necessary to obtain the desired products. Starting with ketones, a Leuckart reaction led to the corresponding formamides, which were then further converted into isonitriles by dehydration. The functionalization of carbohydrates required several protection and deprotection steps first.

Initial binding studies of some selected compounds were already conducted via mass spectrometry. Monoterpenoid isonitriles based on norbornane scaffolds do not seem to be ideal binding partners for heme, since no complexes were observed so far. However, 1:1 and 2:1 complexes (compound : heme) could be identified using functionalized glucose. Future UV-vis binding studies and *in vitro* assays are planned to gain further insight of its potential activity.

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11

Deciphering the impact of posttranslational modification on function and structure of Heat shock protein 90

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Heat shock proteins (HSPs) play a pivotal role in retaining cellular function by assisting in the folding, transport and maintenance of proteins under stress and normal conditions [1]. The ubiquitous heat shock protein 90 (Hsp90) is highly regulated by PTMs including phosphorylation, acetylation, SUMOylation, ubiquitination and *S*-nitrosylation [2]. To examine the regulatory function of specific N- and C-terminally located PTMs on essential properties of Hsp90 including its ATPase activity, drug affinity and protein-protein interactions, we aim to generate homogenous site-selective modified variants of human Hsp90α by utilizing a semi-synthesis strategy (**Figure**). Synthetic peptide segments are ligated to recombinantly expressed protein domains utilizing chemoselective ligation techniques, including native chemical ligation (NCL) [3]. We report the successful synthesis of several modified peptide variants of the N- and C-terminal domain of Hsp90. We report preliminary data for the recombinant expression of the complementary N-terminal domain (NTD) as well as successful ligations of a modified N-terminal peptide to generate a first posttranslationally modified NTD variants. Currently we are optimizing the generation of Hsp90 NTD bearing site-selective modifications while preparing the recombinant segment for the ligation to modified C-terminal peptides in order to generate full-length Hsp90.

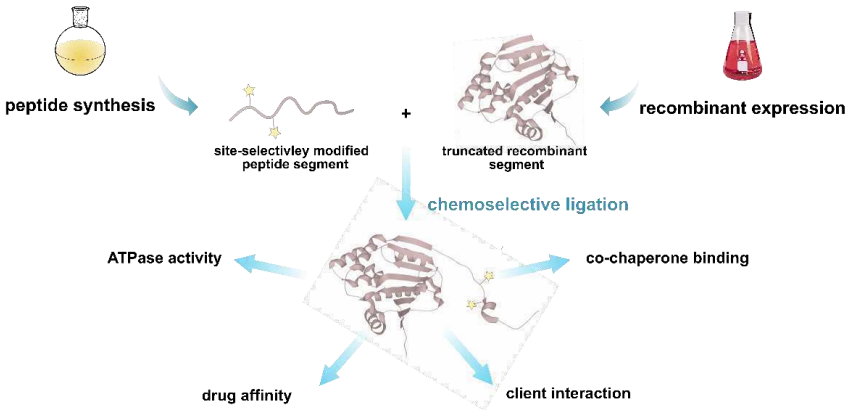

Figure. Overview of the semi-synthesis strategy for elucidating the impact of PTMs on Hsp90.

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12

Chemical strategies to target mucosal biofilms in patients with gastrointestinal disorders

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Gastrointestinal disorders (GI), including inflammatory bowel diseases (IBD) and irritable bowel syndrome (IBS), affect 10–15% of the Western population and represent a substantial socio-economic burden to our society.[1,2] IBD and IBS are progressive diseases related to our lifestyle and the improper and overuse of antibiotics.

Biofilm-forming bacteria are an adherent prokaryotic community embedded in a protective layer of extracellular substances and prone to develop antibiotic resistance.[3] Recently, it was reported that GI biofilms occur in ~60% of IBS patients and ~28% of IBD patients, yet little is known about their function and disease relevance.[4]

Antimicrobial peptides (AMPs) of natural origin represent valuable alternatives for treating bacterial infections since they have retained and optimized their activity throughout evolution and triggered little or no resistance.[5] However, their full potential against biofilms has not been revealed yet.

We want to report our key results of the first year of the PhD project to develop biofilm-specific tools and therapeutic agents for the study and treatment of mucosal biofilms in patients with GI disorders. Our approach and results include (i) synthesis and screening of AMPs from various natural sources for biofilm-specific activity, (ii) chemical strategies to optimize lead compounds as molecular probes and therapeutic candidates, and (iii) characterization of bacterial biofilm isolated from IBD and IBS patients.

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13

Blocking the maturation of Autoinducing Peptide-Quorum Sensing Signals of Human Pathogens

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The human pathogen *Staphylococcus aureus* uses the *agr* quorum sensing system to coordinate the production of a broad spectrum of virulence factors to facilitate infection of its host. Hereby, the enzyme AgrB, a cysteine endopeptidase, possesses a central role in this quorum sensing system since it catalyses the biosynthesis of the autoinducing peptide (AIP) the *agr* QS signal.[1] We hypothesize that an inhibition of the protease AgrB of *S. aureus* would be feasible to block AIP maturation and secretion. In absence of the signal molecule, the *agr* response system would not be activated and the pathogen will not be able to produce virulence factors. Further on we hypothesize that this interference in QS systems can also be achieved in a variety of different pathogens. We will use activity-based probes to label the target AgrB and establish a suitable competitive assay to screen for potential inhibitors. The probes will be developed based on recent findings of α-chloroacetamide warheads and ligand selection strategy for rapid probe scaffold tailoring. Electrophilic inhibitor libraries targeting cysteine will be developed based on the steric and electronic demands of AgrB.[2–4] As a future perspective the developed toolbox will subsequently be applied towards other pathogens. *Agr*-like or similar QS signalling systems controlling the virulence have been discovered in various species of *Staphylococcus*, *Clostridium*, *Bacillus*, *Enterococcus*, and *Streptococcus* and also play a role as a phage encoded infection sensing system.[5]

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14

Peptide-based Radiotracers for PD-L1 PET imaging

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The programmed death receptor1 (PD-1) and its ligand PD-L1 are an immune checkpoint that are involved in many important disease pathways. The interaction between PD-1 and PD-L1 leads to the deactivation of T-cells and the shut-down of an immune response. Inhibitors of different classes of biomolecules have been developed to block either PD-1 or PD-L1. Among the developed inhibitors, antibodies have found immense success and are currently used as diagnostics and therapeutics. However, peptides are more advantageous when it comes to developing the next-generation PD-L1 radiotracers and have been thoroughly investigated in the past years. [1]

We present a general overview on the recently developed peptide-based radiotracers that target PD-L1. PD-L1 is an important receptor that is overexpressed on many tumor cells and currently difficult to quantify with the standard methods (i.e. immunohistochemistry of biopsy samples). [2] Predicting the type of therapy or response is a crucial clinical step for the management of diseases. Therefore, peptide-based, non-invasive PET imaging of PD-1/PD-L1 is a successful alternative and currently an expanding field. Different peptide conjugates under investigations will be discussed for their physicochemical and biological properties that makes them promising candidates for PD-L1 imaging. Furthermore, the outcome of some promising candidates will be discussed based on their current preclinical and clinical trials outcomes.

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15

Dynamic, Real-Time Insights Into Assembly And Silicification Activity Of Silaffine R5 Peptide

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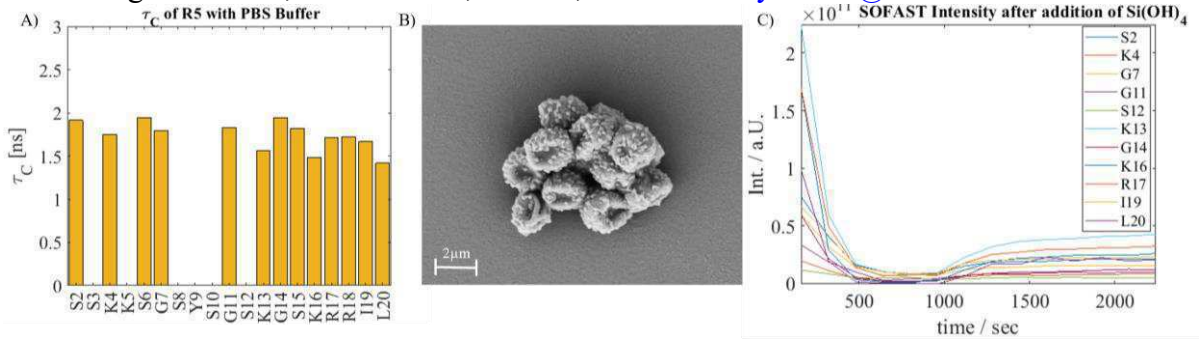

Figure 1. A) Residue resolved correlation time τ_c of R5 with PBS Buffer, residues without bars are not accessible due to aggregation and low signal amplitudes. B) SEM measurement of silica particles yielded by silica precipitation with R5 peptide. C) Residue resolved, real-time intensity traces during silica precipitation by R5 followed by SOFAST.

Silaffine peptides gained interest by their ability to precipitate silica in different morphologies from silicic acid under mild, biomimetic conditions, paving the road to facilitating design of tailored bone graft substitutes. One of the first peptides to be derived from Silaffine 1A, isolated from diatom species *Cylindrotheca fusiformis,* is the peptide R5.[1] Herein we report extensive dynamic and structural analyses to further elucidate the processes that lead to the ordered precipitation of silica by R5 in phosphate buffer. Through the integration of state of the art liquid state NMR techniques and molecular dynamic simulations, a multidimensional picture of the processes leading to precipitation can be drawn. Simulations show significant changes in secondary structure, which can be confirmed by HSQC as well as T_1, T_2, ^{1}H-^{15}N heteronuclear NOE and DOSY measurements. These results additionally demonstrate assembly of R5 molecules [2,3] upon the addition of phosphate buffer prior to precipitation to be necessary for controlled silica formation. After all residues have been assigned and those most affected identified, the precipitation was followed by real-time SOFAST-HMQC measurements, and the kinetics assessed at residue resolution. Indeed, different crosspeak intensity behaviour, depending on the nanoscale environment of the residues involved was detected. Thus enabled the monitoring of the precipitation event and provides a new perspective on biomineral prenucleation species in liquid phases.

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16

HFIP mediates a direct C–C coupling between Michael acceptors and Eschenmoser's salt

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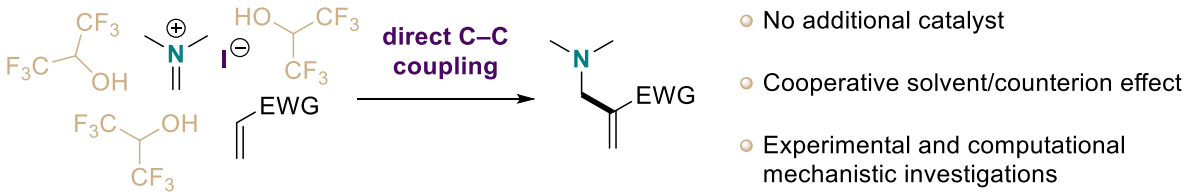
Over the last decades, hundreds of scientific publications have employed the Morita-Balyis-Hillman (MBH) reaction as a powerful method to forge C–C bonds.[1] Traditionally, MBH reactions couple Michael acceptors with aldehydes, taking advantage of a Lewis basic catalyst – recently, however, Nguyen and coworkers have shown that a similar reaction, in which the aldehydes are exchanged with tropylium halides, yields □-functionalized products without the need for a catalyst.[2] Intrigued, we sought to develop a method using an iminium iodide (specifically Eschenmoser's salt) as the electrophile. Notably, we found that the counteranion and the highly polar solvent hexafluoroisopropanol (HFIP) are crucial for the reaction and allow smooth conversion without any additional catalyst. We investigated the reaction scope, explored the application of the produced aminocarbonyls and examined the mechanism using NMR experiments, isotopic labeling and quantum chemical calculations.[3]



Scheme 1: An aza-Morita-Baylis-Hillman reaction without added Lewis base catalyst.

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17

Peptide based drug delivery systems

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With the term drug delivery system, we refer to formulation and system for transport a pharmaceutical compound in the body to archive the desired therapeutic effect. Drug delivery systems modify drug release profile: absorption, distribution metabolism, and elimination (ADME) for improving efficacy and safety as well as patient convenience and compliance.[1]

Current efforts in the area of drug delivery include the development of targeted delivery, where the drug is only active in an area of the body or is active only to a particular tissue (for example, in cancer cells) where the drug is released over a period of time controlled by the formulation itself. In the last year, different types of formulations were developed including the peptide-based formulation].[2] Peptides based delivery systems have significant advantages over others as they are relatively low cost and their synthesis is easily scalable and does not encounter potential immunogenicity compared to proteins [3].

Today, there is no clinically approved peptide-drug or peptide-conjugated drug delivery system. There will be a great need to develop well-characterized and reproducible peptide-based carriers. The project focus is to develop novel peptide-based drug delivery systems for anti-rheumatic and anti-inflammatory drugs, with the aim to improve drug efficacy and safety as well as patient convenience and compliance. The system will be characterized using multinuclear NMR spectroscopy and HR-MS while release profiles will be evaluated using HPLC-MS. Further detailed biological studies will be carried out using appropriate *in-vitro* conditions.

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18

Investigations on an unexpected side reaction during the synthesis of a cytotoxic diaminedicarboxylatoplatinum(II) complex

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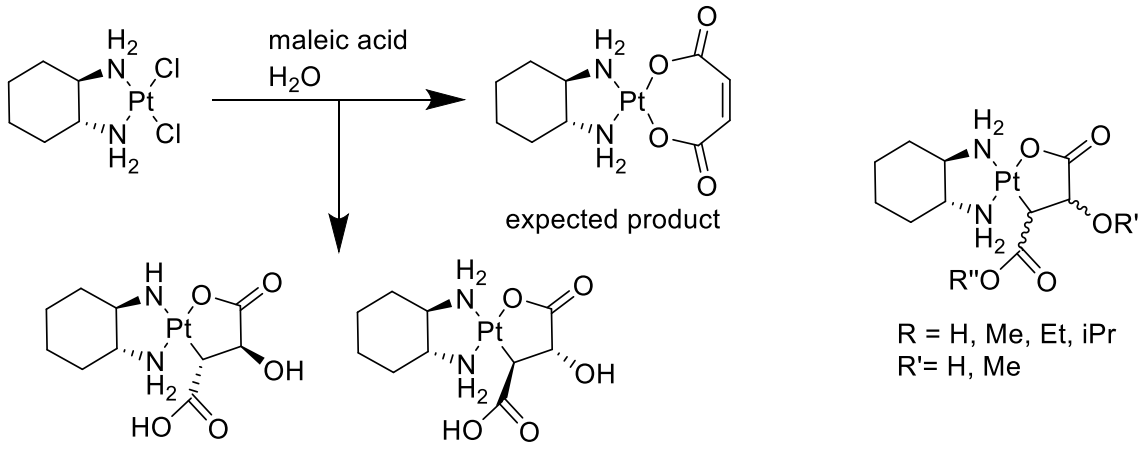
During the synthesis of a Pt(II) complex according to standard literature methods[1], we observed the formation of an unexpected by-product (Scheme 1) featuring a metal carbon bond.



Scheme 1: The planned reaction pathway, the unexpected side reaction and the general structure of the new complexes

To the best of our knowledge, there is only one report dealing with this substance class in the literature.[2] Starting from either maleic or fumaric acid, the inventor was able to produce either a mixture of the RR and SS or of the SR and RS carboxylato ligand. Based on these findings, we report on the synthesis of new complexes, where R equals different alkyl moieties and R' equals H or OMe, respectively. Additionally, the complexes were characterized *via* multinuclear NMR spectroscopy, elemental analysis and HR-MS. Crystallographic analyses, stability assassments *via* NMR and HPLC, and determination of cytotoxic properties is still ongoing as of now.

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19

Triggering Self-assembly and Function of Yeasts by External Stimuli

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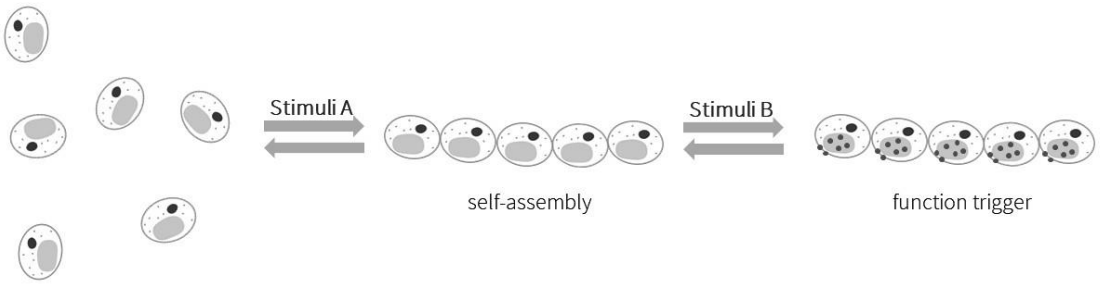
Yeasts are known as a microbial factory that can produce recombinant proteins as pharmaceuticals, so-called biopharmaceuticals. Yeast is a single eukaryotic microorganism and its mating reaction is very important for cell-cell communication studies.[2] The fission yeast S. pombe possesses two haploid mating cells P and M cells, that can be differentiated under nitrogen starvation. The M type cells express the Mam2 receptor, which recognizes the p-factor released from P cells.[1,2]

Constructing multicellular assemblies to form a tissue or aggregate with controlled cell-cell interaction is remaining a great challenge. To create the irreversible controlled cell-cell assembly there has been some techniques as modifying the surfaces with single-stranded DNA molecules that are complementary to each other, or using highly specific biotin-streptavidin interaction6. Lately, the focus has been moved to create reversible cell-cell interaction. For this purpose, the supramolecular interaction has been used as photo-switchable azobenzene with β-cyclodextrin.[3-5]

In our project we are focusing on Mam2 receptor and p-factor interaction. We are using only one-type of yeast that are genetically modified to express the Mam2 receptor independently of the external conditions. Our idea is to modify the p-factor, that is 23 amino acid peptide, and by this modification to attach there a motive that can trigger self-assembly or function by external stimuli. The modified p-factor-like-peptide has to have similar interaction behaviour to the Mam2 receptor as the natural p-factor, therefore most of the work is currently focused on this topic.



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20

Synthesis of BN-doped polycyclic aromatic hydrocarbons for applications in optoelectronic devices.

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During this last decade the interest on in the obtention of semiconductive graphene considerably increased in the scientific community. Due to its properties, such as a high carrier mobility and flexibility, graphene is one of the most attractive organic material for electronic application.[1] However, the lack of a bandgap makes graphene unsuitable for many applications. One of the possible approaches for the obtention of semiconductive graphene is the heteroatom doping.[2] One of the most promising doping consists in the inclusion of borazine (B_3N_3) units in the honeycomb lattice of graphene. In fact, borazine is known to be isoelectronic and isostructural to benzene, but its bonds are way more polarized.[3] This makes borazine one of the most attractive building blocks for the production of semiconducting graphene. In this work we report a one-year study on the synthesis of borazine-doped PAHs, and our future plans for the obtention of a borazine-doped graphene layer.

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Simple carbonyl a-deuterations via keteniminium intermediates

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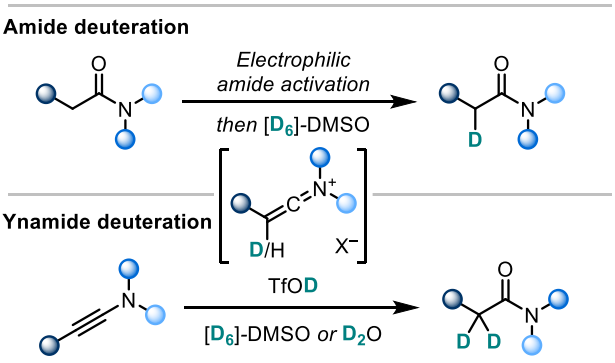
Isotope labelling is a powerful tool that enables the precise monitoring of specific atoms and as such, constitutes a common strategy to study and elucidate reaction mechanisms.[1] Importantly, the introduction of isotopic labels is also employed for the investigation of behavior and metabolic pathways of drug candidates.[2] Due to the kinetic isotope effect, deuterium incorporation in specific sites of drug molecules can slow down cytochrome P450 metabolism, optimize pharmacokinetic properties or reduce toxicity.[3] Expanding the synthetic toolbox to enable convenient and mild deuterium incorporation in organic molecules is, therefore, highly desirable.

Here, we present two recent methodologies developed in our team for the synthesis of deuterated amides and imides.[4,5] In both cases, the transformations hinge on transient keteniminium ions, formed either by electrophilic amide activation or by treatment of ynamides with a (deuterio)-Brønsted acid. As will be shown, the deuterated products were obtained in good yields with high degrees of deuterium incorporation.



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22

Characterization of the androgen receptor in androgen-sensitive and androgen-independent human prostate cancer cell lines

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The androgen receptor (AR) displays a key therapeutic target and diagnostic biomarker in prostate cancer. This *in vitro* study aimed at the characterization of the AR in prostate cancer progression using (i) 16β-[^{18}F]fluoro-5α-dihydrotestosterone ([^{18}F]FDHT), a radiotracer for positron emission tomography targeting the AR [1], as well as (ii) specific antibodies for immunofluorescence (IF) and Western blot (WB).
[^{18}F]FDHT uptake was investigated in androgen-sensitive (LNCaP [2]) and androgen-independent (PC-3 [3]) human prostate cancer cell lines by means of collecting membrane-bound, internalized and nuclear cell fractions. WB analyses as well as IF were employed to determine target expression and receptor localization in support to obtained data.
Results showed significantly higher specific [^{18}F]FDHT membrane binding and uptake in LNCaP cells than in PC-3 cells, suggesting androgen-dependence as the driving force for higher expression of androgen-binding membrane proteins. Moreover, significantly higher specific nuclear uptake was detected in LNCaP cells, in contrast to PC-3 cells. This meets the expectation that androgen-sensitive cells quickly translocate the tracer-receptor complex to the nucleus in order to initiate gene transcription and consequent tumor growth. In contrast, androgen-independent cells are suggested not to require androgens for gene transcription. In this cause, WB analyses and IF confirmed the presence of ARs of different isoforms in both investigated cell lines. Furthermore, localization of the AR was demonstrated in cytoplasm and nucleus, utilizing IF.

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23

Introduction of bioactive ligand scaffolds to tridentate organoruthenium complexes.

Alexander Rosner

Geisler, H.; Westermayr, J.; Cseh, K.; Wenisch, D.; Fuchs, V.; Harringer, S.; Plutzar, S.; Gajic, N.; Hejl, M.; Jakupec, M. A.; Marquetand, P.; Kandioller, W., Keppler, B. K.

The use of bioactive ligands for development of novel metal-based anticancer agents has certain advantages. Known molecular targets, familiar pharmacokinetics and pharmacodynamics, as well as already investigated adverse effects feature evaluation as bioactive moieties. Moreover, synergistic effects have been observed for certain candidates, which might overcome side effects of established drugs.

Recently, an unexpectedly *in situ* formed tridentate ligand architecture of piano stool ruthenium (and osmium) complexes has been established. This novel compound class differs from most literature known organometallic anticancer agents. The tridentate complexes show interesting properties and unexpected selectivity towards certain human cancer cells *in vitro*. Stable derivatives were shown to exert extraordinary cytotoxic impact towards certain cell lines over others.[1] Though being based on bioactive moieties and their literature known properties, the mode of action for cancer cell growth inhibition still remains unresolved. Investigations on the interaction with "classical targets" in chemotherapy (*e.g.* DNA) or considerations of the ligands' anticancer properties have already been carried out. Solution chemistry of these metallodrugs has been examined, aside from interaction studies.[2] However, the exact mode of action of this promising compound class is unknown.

Overall, this project offers a lot of research potential, involving fine tuning of chemical properties and cytotoxic impact. Still, investigations on cellular behaviour, molecular targets and *in vivo* results are critical for further predictions.

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24

Synthesis of 4-deoxy-4-fluoro-D-sedoheptulose

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We report the first synthesis of 4-deoxy-4-fluoro-D-sedoheptulose (**4DFS**) from commercially available methyl 4,6-*O*-benzylidene-α-D-*gluco*-pyranoside (**1**). **4DFS** is of great interest because fluorination of position 4 in D-sedoheptulose-7-phosphate is expected to halt the enzymatic degradation of the sugar phosphate in the pentose-phosphate-pathway. After uptake and phosphorylation in cells[1], **4DFS** would thereby be metabolically trapped within cells and could serve as a promising starting point for further development into a positron-emission-tomography (PET) probe to image tissue types with high proliferation rates (e.g. tumor tissue).

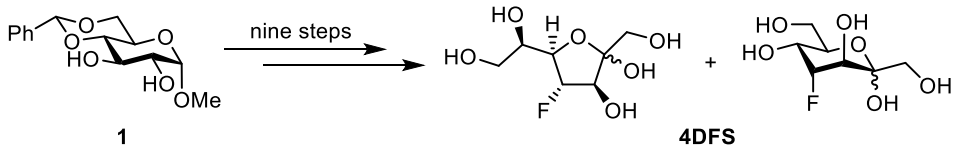

Figure 1: Synthesis of **4DFS**.

The nine-step sequence takes advantage of a combination of two approaches [2], [3]. Key transformations involve a one-step generation of an epoxide from **1** which was then opened in a trans-diaxial fashion by potassium bifluoride and tetrabutylammonium fluoride trihydrate to generate the desired fluorinated altrose core. Subsequently, a series of protecting group manipulations and an oxidation step led to 2,4,6-tri-*O*-benzyl-3-deoxy-3-fluoro-D-*altrono*-1,5-lactone. The lactone was then methenylated using Petasis' reagent [4] giving the elongated C_7 enol ether which was dihydroxylated to yield the protected heptulose. Final deprotection of the benzyl ethers yielded **4DFS** in a total yield of 8% after nine steps.

Future enzymatic stability and cell-based uptake assays will assess the ability of **4DFS** to be metabolically trapped within cells.

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25

Synthesis of a Selenium-based Ligation-Auxiliary for Traceless Native Chemical Ligation

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Native chemical ligation (NCL) is an incredibly valuable tool for peptide chemists to join two unprotected peptide chains under mild conditions, leaving no ligation scar. Historically, two requirements must be fulfilled to use NCL: The respective peptides need to be equipped with a C-terminal thioester on one and an N-terminal cysteine on the other peptide segment. [1]
For NCL reactions where these requirements cannot be met, multiple strategies have been developed to sidestep them, including the use of radical desulfurization, thiolated amino acid analogues or cleavable ligation auxiliaries.[2-3]
Lately, the use of N-terminal selenocysteine residues in combination with C-terminal selenoesters in diselenide-selenoester ligations (DSL) led to improved reactions kinetics and higher yields, even at very low peptide concentrations.[4]
Here we present the combination of two of these concepts, namely a photocleavable selenium based ligation auxiliary to provide a highly versatile solution for DSL at almost any ligation site. Starting from the three-component Petasis reaction, synthesis of this auxiliary could be realized with satisfactory yields in 5 steps.
Employing standard SPPS coupling and deprotection reagents, the auxiliary could be attached to a peptide, ready for ligation. Preliminary results show the ligation of two test peptides and further photocleavage indicates the successful removal of the auxiliary.

In summary, we developed a concise route for the synthesis of a selenium-based, photocleavable ligation auxiliary for native chemical ligation. Initial experiments show promising results, and warrant further investigation concerning ligation sites, additives and concentrations used.

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26

A Redox-neutral Selenium-catalysed Isomerisation of Hydroxamic acids into *para*-Aminophenols

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One of the oldest pharmaceutical compounds still in use today is the century-old analgesic *paracetamol* (*para*-acetylaminophenol), the synthesis of which can be achieved through different routes. Nevertheless, synthetic approaches to *para*-aminophenols generally suffer from low regioselectivity, high step count or harsh conditions, limiting the chemical space accessible for this family of compounds.[1] Recently, interest in more selective reactions to form the title compounds has grown and led to interesting novel synthetic approaches.[2-4]

Earlier this year, our group disclosed a selenium-catalysed rearrangement of hydroxamic acids into *para*-aminphenols. This reaction is carried out under mild conditions and affords a broad scope of *para*-aminophenols in good yields and with perfect regioselectivity through an intriguing double [2,3]-sigmatropic rearrangement process (Fig. 1).[5] The proposed reaction mechanism is supported by quantum chemical calculations as well as ^{18}O-labeling experiments. Different *para*-aminophenols with applications in the treatment of heart disease and infection, as well as *paracetamol* itself can be readily synthesized by this novel methodology.

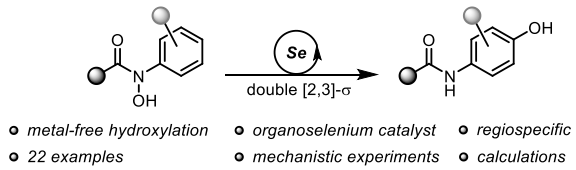

Figure 1: an organoselenium-catalysed regioselective rearrangement to form *para*-aminophenols.

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Direct Synthesis of Enamides via Electrophilic Activation of Amides

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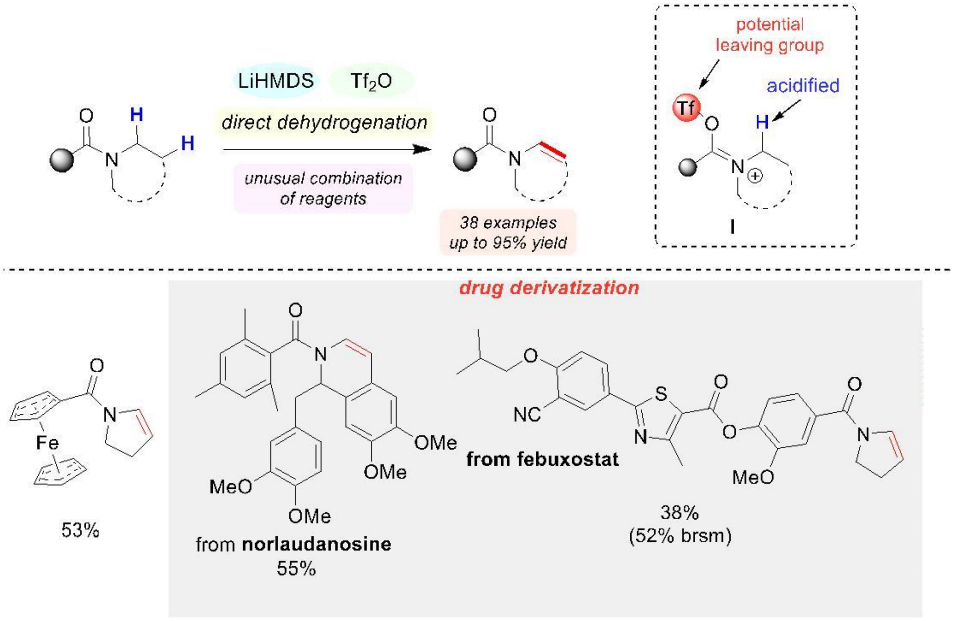
Enamides are highly versatile synthetic building blocks which can be seen as stable enamine surrogates. As reactants, enamides can be applied in a variety of settings, including transition-metal (asymmetric) catalysis or photochemistry.[1] However, the preparation of enamides has remained a major challenge, relying to a large extent on prefunctionalized starting materials.[2] In order to address this issue, a direct *N*-dehydrogenation of an amide is a highly desirable scenario. However, only a few methods with limitations[3] have been reported to date.

Informed by our group's extensive experience in the field of electrophilic amide activation, we speculated whether the *in-situ* generated species **I** might allow a novel and operationally simple pathway to access enamides.[4] For this, we assumed that the proton α to the nitrogen of **I** is highly acidified (see Scheme) and that combination with a suitable strong, non-nucleophilic base would might trigger the desired N-dehydrogenation event. Ultimately, the unusual combination of triflic anhydride and LiHMDS proved optimal, and the scope of the transformation was explored in depth. In addition, the utility of the synthesized enamides was showcased through a range of downstream transformations, and mechanistic studies shed more light on the reaction pathway.



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28

Towards the synthesis of 3-deoxy-3-fluoro-D-xylulose

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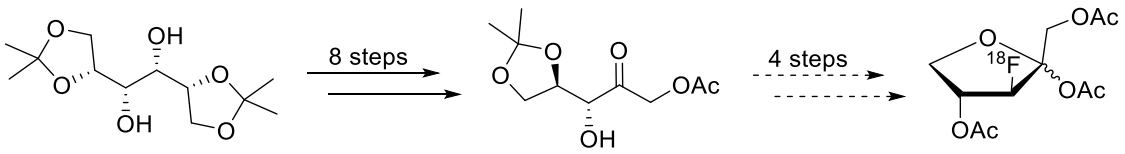
Although sugars are of considerable biological importance, the elucidation of minor metabolic processes, such as the pentose phosphate pathway (PPP) still lags behind in comparison to other classes of functional biomolecules. Despite its involvement in a large variety of pathologies [1] and its strong link to glycolysis, the latter has been studied far more extensively, while the PPP is still poorly explored.
For a long time, it was believed that the PPP is dominated by a variety of complex equilibrium reactions that produce otherwise unimportant reaction intermediates with the mere purpose to generate pentoses for DNA/RNA biosynthesis. [2] However, the recent discovery of sedoheptulose kinase [3], which allows direct uptake of this unconvential carbohydrate by cells, suggests the existence of a variety of specialized kinases for other carbohydrates as well, making them available as alternative carbon sources that can directly enter the cells and influence the enzymatic equilibria of the non-oxPPP [4].
Fluorinated analogues to the carbohydrate intermediates of the PPP can be used as an alternative tool for diagnostic imaging of cancer types with a known upregulation of the PPP. Several of these cancer types, such as colorectal carcinoma (CRC) [5] and different non-small-cell lung cancer types are known to be difficult to diagnose with already established PET tracers [6].
Here I present the synthetic strategy to access a suitable precursor for the synthesis of the [^{18}F]-radiolabeled analogue of D-xylulose.



Scheme 1. Synthetic strategy towards 3-deoxy-3-fluoro-D-xylulose.

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28

Self-assembling peptide based hydrogels

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Self-assembly, a fundamental process in nature, is the spontaneous organization of molecules into ordered structures by non-covalent integration.[1] We have been interested in the development of self-assembling peptides, which can entrap large amounts of water yielding hydrogels.

Typically hydrogels are based on 3D polymer networks that entrap large amounts of water, however, hydrogels based on small self-assembling peptides form supramolecular structures which function in a similar manner; although the single building blocks are typically below 1 kDa.[2] These peptides can be easily chemically modified and are stable in broad range of biological conditions.[3] Further through rational design of metal binding sides the self-assembling properties can be fine-tuned.[4]

We would like to report on the synthesis of self-assembling peptides, which are designed to specifically bind to biological benign metal salts. However, the project is confidential and as such no detailed structures or experimental results can be shared.[3] Based on our current research, the presence of different metal salts indicates an effect on self-assembly leading in significant changes in mechanical properties.

The future directions in this research are likely to focus on characterization of the conformation of the different metal containing peptide hydrogels via a series of studies on Circular Dichroism and SEM. Hence, further studies are performed with focus on rheology thanks to striking mechanical properties (mechanical stiffness and elasticity) of hydrogels. The final goal would be to assess the ability of such hydrogels as primary dressings for partial thickness burns.

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29

Revealing the chemical diversity of plants – New alkaloids from *Tabernaemontana divaricata* and *Tabernaemontana peduncularis*

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As plants cannot run away from herbivores they have developed sophisticated chemical defense strategies. The natural products involved therein are evolutionary designed to exhibit strong biological activity and are therefore a great source for drug discovery candidates. As a matter of fact, many common drugs are derived from natural products [1].

We isolated several interesting new alkaloids from two *Tabernaemontana* species (Apocynaceae), a genus known for its diverse monoterpenoid indole alkaloids. A large variety of known alkaloids was isolated from *T. divaricata*, but also javanisides previously unknown in the Apocynaceae family. Furthermore, we were able to isolate javanisides from *T. peduncularis* including a derivative containing uronic acid as glycoside. Although glucuronidation of molecules is a relatively common process in animals, such glycosides are rarely found in plants. Additionally, we isolated several new iboga alkaloids from *T. peduncularis*. They show molecular dynamics and reversible rearrangements to similar structures. Further, some of these substances are highly unstable leading to impurities by irreversible rearrangements. Such isolation artefacts could not be completely separated in all cases.

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30

Zooming in on the MTBR of Tau4 by Protein Semisynthesis

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The dysfunction of the microtubule associated protein Tau plays a central role in the pathogenesis of several neurodegenerative diseases.[1] Among others, specific posttranslational modifications (PTMs) located in the microtubule binding region (MTBR) of Tau are of very high importance and have been linked to the development of Alzheimer's disease.[1] Whereas the effects of several site-specific PTMs on microtubule binding and aggregation have been described quite recently[2,3], their impact on structure and dynamics at atomic resolution remains elusive so far. Based on previous studies on the longest Tau variant (Tau4) from our group[3], we now focus on conformational changes of the Tau4-microtubule protein complex and the impact of PTMs on this interaction. This is achieved by assembling different variants of posttranslationally modified Tau with specific segmental isotope labelling patterns for NMR analysis.[4] Our semisynthesis strategy is based on generating synthetic peptide segments with PTMs that comprise the MTBR flanked by two recombinantly expressed Tau4 segments.[3] Both, the N-terminal as well as the C-terminal Tau4 fragments, can be labelled with the required stable isotopes (^{15}N, ^{13}C) for comprehensive NMR experiments.[4] Taken together, these modifications will enable valuable insights into molecular determinants of Tau aggregation and binding to microtubules as well as the impact of specific posttranslational modifications.

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31

Tackling TEAD4 with Entropy Oriented Drug Design

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The dysregulation of the Hippo signalling pathway, a focal point in cell proliferation, plays an essential role in promotion of oncogenesis.[1,2] The main cause for the dysregulation is the mutation of executor proteins YAP [3] or TAZ/WWTR1 [4] and their transcription factors TEAD1-4 (TEADs). The inhibition of this Yap/TAZ-TEAD interaction is therefore a promising strategy to combat tumorigenesis.[5]

Our strategy for drugging this challenging pocket is based on Entropy Oriented Drug Design (EnODD).[6] The introduction of a fused cyclic system minimizes the flexibility of the molecule, leading to a greatly enhanced entropic factor, thus potentially attaining superior affinity for the protein target.[7] Based on internal fragment screening of over 2500 molecules for the transcription factor TEAD4 at Boehringer Ingelheim, a series of rigidified "natural product-like" targets were designed and synthesised. After two generations of Structure Activity Relationship (SAR) studies, a promising drug target for the YAP/TAZ-TEAD interaction was obtained, featuring nearly two orders of magnitude higher potency than the initial hit.

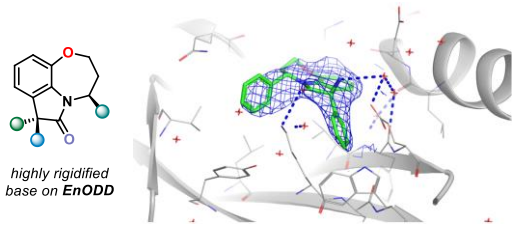

Figure 1. Highly rigidified TEAD4 binders based on Entropy Oriented Drug Design (EnODD).

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33

AUTOMATED SYNTHESIS OF TRIAZOLE BEARING PEPTIDES

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The medical relevance of peptides is often offset by their low *in vivo* stability.[1] Among the many stabilization strategies, 1,4-disubstituted 1,2,3-triazoles have emerged as stable *trans* amide bond surrogates.[2] The incorporation of triazoles on the peptide backbone is usually accomplished by adapting the diazotransfer [3] and the copper-catalysed azide-alkyne cycloaddition (CuAAC) reactions to the solid phase peptide synthesis (SPPS). To the best of our knowledge these reactions have never been implemented into an automated setup for the synthesis of triazolopeptides.

We therefore report the development of the first procedure for the fully automated synthesis of backbone modified triazolopeptides. To accomplish this, the compatibility of the diazotransfer reaction was studied with a microwave assisted automated peptide synthesizer (Biotage® Initiator+Alstra^{TM}). The stability of the diazotransfer reagent imidazole sulfonyl azide (ISA.HCl) was assessed in different solvent systems. The CuAAC reaction was completed under microwave conditions using Tetrakis(acetonitrile)copper(I) hexafluorophosphate complex as copper source.

The preliminary experiments showed promising results. The bombesin derivative [4] with the triazole between the Histidine and Valine residues (Figure 1) was synthesized in 14 hours with purities greater than 90%. This procedure represents a time-saving and cost-effective method for the synthesis of metabolically stabilized peptides.

It is our objective to optimize this methodology so it can be used for the facile synthesis of a wide range of triazolopeptides. For that, different resins will be tested. The synthesis of different clinically relevant triazolopeptides will also be evaluated.

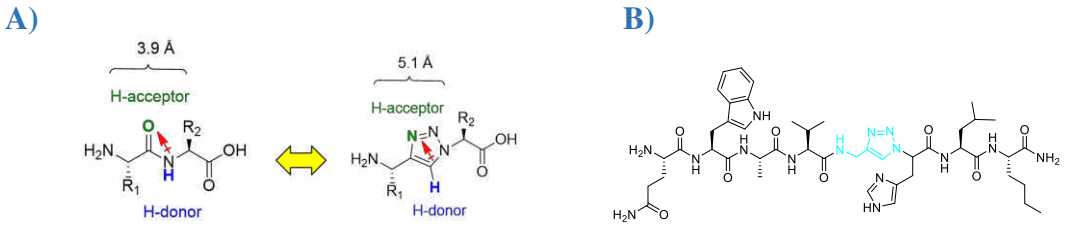

Figure 1. a) 1,4-disubstituted 1,2,3-triazoles as trans amide bond surrogates. b) The triazole bearing minimal binding motif of Bombesin.

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34

Development of oxytocin receptor tracers for imaging applications

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The oxytocin receptor (OTR) is a G protein-coupled receptor that mediates various physiological functions including reproduction and social behaviour.[1,2] It is an attractive target for the exploration and therapy of a number of high-profile disorders including cancer, pain, and autism.[3,4] The design of selective ligands to investigate and visualise OTR is however challenging as OTR shares >80% extracellular sequence homology with the closely related vasopressin receptors.[5] There is also a lack of selective probes (e.g., OTR-specific antibodies) to study OTR expression at the protein level. In this work, we describe the rational design, synthesis, and pharmacological evaluation of a series of peptide tracers for the visualization of OTR. By applying solid phase peptide synthesis and liquid phase labelling methods, we produced a series of OTR-targeting peptide tracers equipped with functional labelling groups such as biotin, fluorophores, near-infrared dyes, and positron emission tomography chelators. We determined the binding affinities of these tracers at OTR and the three closely related vasopressin receptors *via* radioligand displacement assays and identified a promising lead with a 50-fold selectivity for human OTR. Interestingly, we also demonstrated that linker design could be used to tune the selectivity for OTR. The results of the first ligand series were then used for the design and synthesis of a second series, whose pharmacology is to be determined. These tracers hold a powerful application scope for several *in vitro* and *in vivo* studies including positron emission tomography, near-infrared, and fluorescence based imaging techniques that will advance our understanding of the role of OTR in health and disease.

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35

Design and Synthesis of O-doped Polycyclic Aromatic Hydrocarbons Nanoribbons for Applications in Optoelectronic Devices

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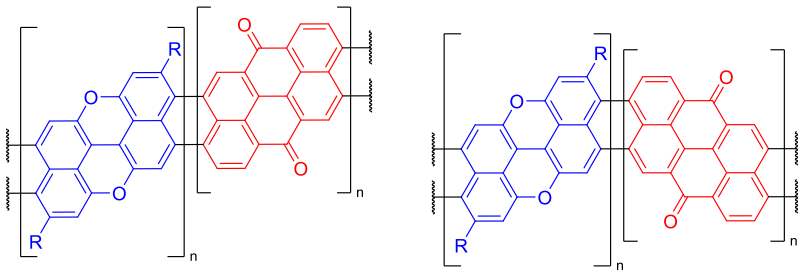
Graphene due to its high mechanical, thermal, and chemical stability and excellent electronic properties has attracted an enormous amount of interest in the area of optoelectronic and composite materials [1].

Polycyclic Aromatic Hydrocarbons (PAHs) can be considered as fragments of graphene with finite size that ranges from 1 to 5 nm.

Having a well-defined structure, PAHs can serve as good model compounds for understanding the fundamental electronic properties of graphene and graphene nanoribbons. Moreover, the polycyclic aromatic hydrocarbons display higher solubility than graphene, providing organic semiconductor solution-processable for OFET (Organic Field-Effect Transistors) preparation [2].

Organic dyes and pigments constitute a large class of industrial products. Recently they have been researched for the utilisation in the field of organic electronics [3].

The aim of this project is to synthetize O-doped nanoribbons. For this purpose, we are using modified organic dyes as PXX (Peri-xanthenoxanthene) and ATT (anthanthrone) (figure).



zig-zag periphery armchair periphery

Semiconductor based on peri-xanthenoxanthene (PXX) has been used by Sony in 2011 for their release of rollable AMOLED display [3].

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36

New methodologies for the synthesis of BN-doped polycyclic aromatic hydrocarbons

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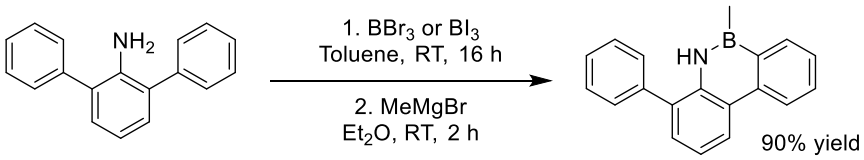
Boron-Nitrogen bond (B-N) is isoelectronic and isostructural to Carbon-Carbon bond (C-C). By replacing a C-C bond with a B-N bond in an aromatic molecule, we can change the optoelectronic properties of the molecule without changing its structure. In particular, the polarization of the B-N bond is able to modify the HOMO-LUMO energy gap, which, depending on the localization of the B-N bond in the molecule, can be opened or closed, causing a blue- or red-shift in the optical properties of the molecule[1].

This strategy, known as heteroatom doping, is well known and has been used in the last years to synthetize various BN-doped polycyclic aromatic hydrocarbons (BN-PAHs), which were implemented in optoelectronic devices such as Light-Emitting Electrochemical Cells, Organic Photovoltaics and Electrochromic Devices. Thanks to the increased stability and tuned properties of the BN-PAHs, in respect to their all-carbon congeners, these devices have also shown improved performances[2].

While the potential of the doping strategy is now well established, the synthesis of BN-doped molecules remains a challenge. The standard procedure for the synthesis of a Boron-Nitrogen bond is not too different from the $AlCl_3$ catalysed synthesis used by Dewar *et al.* in 1958, for the synthesis of azaboraphenantrene[3]. When synthetizing extended BN-doped systems, metal catalysts (or amino bases, which are also widely exploited) become an obstacle to a clean and high-yield reaction.



In this first year, we developed an easy borylation reaction which involves only a Boron halide (BBr_3 or BI_3), under mild temperature conditions. In the near future, we plan to apply this new methodology to polyaminophenylenes, in order to get extended multi-BN-doped PAHs with semiconducting properties, ready to be implemented in organic-based electronic devices.

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[2] (a) Dosso J., Tasseroul J., Fasano F., Marinelli D., Biot N., Fermi A., Bonifazi D., *Angew. Chem. Int. Ed*. **2017**, *56*, 4483−4487.; (b) Fresta E., Dosso J., Cabanillas-González J., Bonifazi D., and Costa R. D., *Adv. Funct. Mater.* **2020**, *30*, 1906830.
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37

Synthesis of epoxide-containing triglycerides and evaluation of its inflammatory effects after *in vitro* digestion

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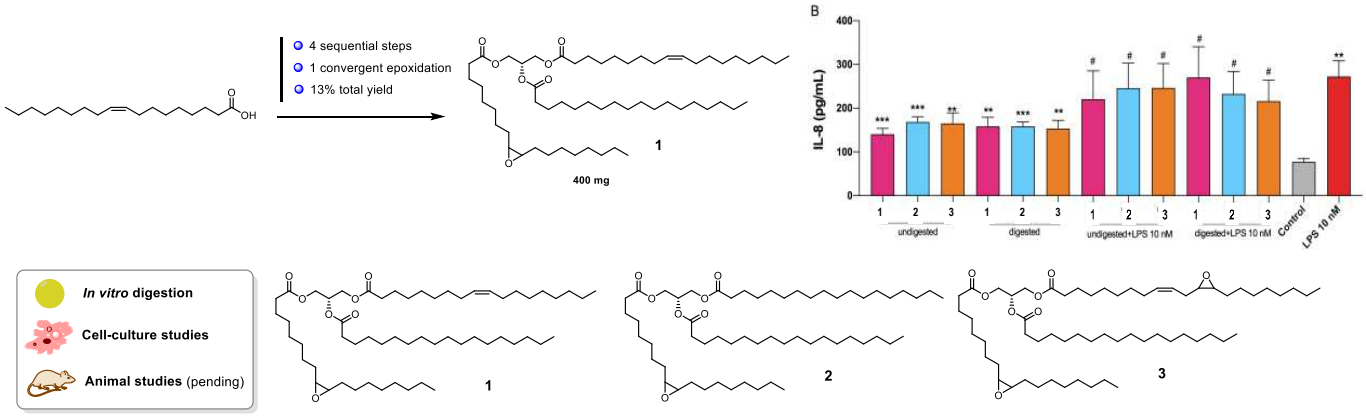
The content of peroxides in food-derived products such as oils, with known deleterious organoleptic and health-related effects,[1] is a well-established parameter to evaluate their rancidity in early decomposition stages. However, the repercussions to the organism which result from the intake of lipid epoxides (also found to be present in the composition of extensively used dietary lipids such as canola oil or margarine [2]) still remain relatively unknown.

For this collaborative study, aiming to shed light into the inflammatory response to epoxidised lipids, triglyceride-epoxide **1** was synthesized. Starting from oleic acid, five total steps, including a convergent epoxidation, were performed to deliver **1** in 13% overall yield.

After in-vitro digestion, **1** was used to treat intestinal Caco-2 cell cultures in order to trigger an inflammatory response. Other similar epoxides (**2** and **3**) were synthesized to identify structure-activity relationship. The studies showed an increased release of IL-8 from the cell cultures after being exposed to the afore-mentioned epoxides, both before and after the *in vitro* digestion (after which the main compounds appeared to be diols), further accentuated with simultaneous treatment with LPS. The results indicate that consumption of epoxidised lipids might lead to intestinal inflammation, thus raising concerns of the health effects from processed oils.

The second part of the investigation, still to be carried out, will be based on an animal study assessing the effect on the organism derived from a high-fat diet presenting **1** as part of its composition.



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38

Design and synthesis of chromogenic materials based on polycyclic aromatic hydrocarbons

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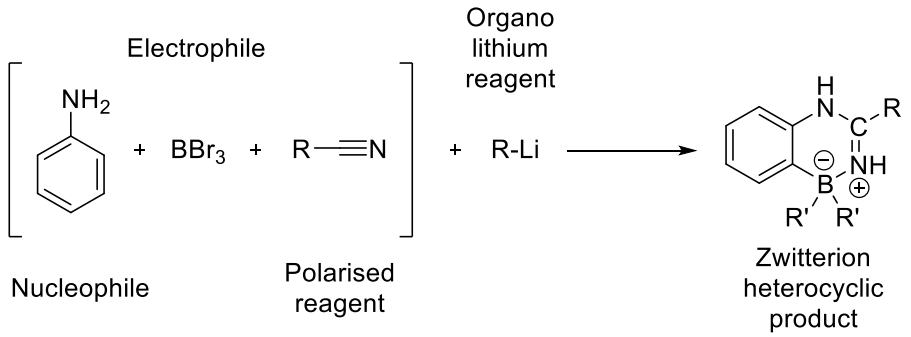
We report designing irreversible electrochromic material based on BN-based polycyclic aromatic hydrocarbons via 3+1 multi-component reaction.



Scheme 1. A new multi-component reaction of Zwitterionic BN based polycyclic aromatic hydrocarbon molecule.

Designed target molecule is zwitterion molecule which will be good condition for redox reaction as electrochromic material. Also, this target molecule includes bond between negatively charged quaternary boron and nitrogen which is easy to be broken by electrical stimulus as an irreversible factor.

So far, preparation of the BN-based zwitterionic molecule via a new multi-component reaction has been developed and its property is exploring to understand this new multi-component reaction. On the process, a new possibility of the metal-free ortho-direct borylation via BBr_3 has been discovered which will help to understand the target multi-component reaction.

39

Abstract

Hydrative Amination of Activated Alkynes using Sulfinamide Reagents

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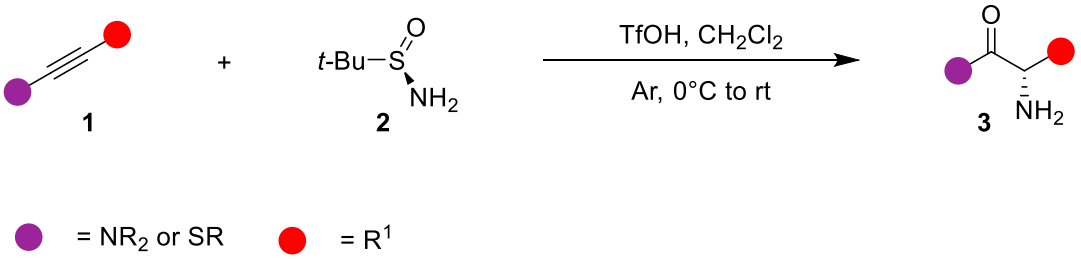
Although the S–N bond might hardly be regarded as common in organic molecules; several reactions throughout the literature shows its involvement in interesting transformations. Unfortunately, the obtaining of high valuable compounds generally requires a second step where the S–N bond is cleaved.

A first example reported the use of sulfur imido compounds as a π-bonds partner in a sequence of two ene-reactions that led, after the S–N bond cleavage, to a protected amine. Further improvements in S–N bond chemistry were achieved when sulphur imido compounds where employed as dienofile in a [4+2]-like cycloaddition. Here, the subsequent S–N bond cleavage allowed the formation of a 1,4-difunctionalised compound. Finally, a very recent work showed a gold catalysed rearrangement of an α–alkynyl ketimine where a consecutive S–O/ S–N bond cleavage led to the formation of an α-azirin carbonyl compound. In spite of the gained S–N cleavage within the rearrangement, the presence of the sulphur atom in the final product caused a smaller interest toward this reaction.[1–3]

As part of our ongoing research into the synthetic utility of electron-rich alkynes and the reactivity of sulfur(IV) species, we developed an interest in the union of ynamides and thioalkynes (**1**) with sulfinamides such as Ellman's auxiliary (**2**) (***Scheme 1***).[4–6] Initial results suggest that this intriguing combination affords α-aminated carbonyl derivatives. Herein, we present the development of this reaction, enabling the direct synthesis of valuable α-aminated amides and thioesters (**3**). Importantly, the use of commercially available chiral sulfinamides allows for an enantioselective process, delivering the products in enantioenriched form.



***Scheme 1**: Hydrative amination of ynamides and thioalkynes.*

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