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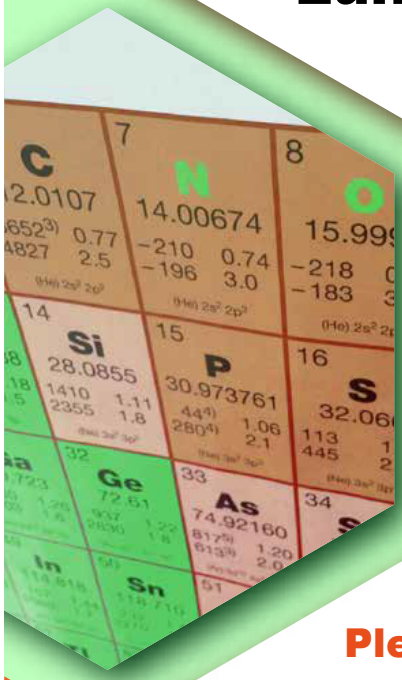

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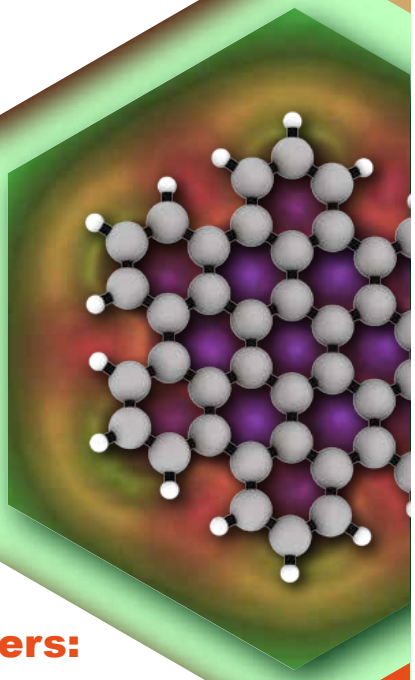

Plenary

Annamaria Lilienkampf
University of Edinburgh

Jan van Maarseveen
University of Amsterdam

Uwe Grether
Roche, CH

Marta Artola
Leiden University

Speakers:

John Overington
Exscientia, UK

Ilja Voets
Technical University Eindhoven

Marc Baggelaar
Utrecht University

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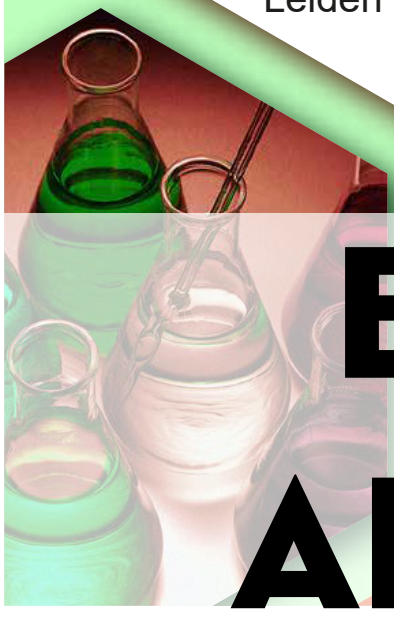

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10:35	**Luuk Stringer (UU) - O-02** *Reversible metal-binding with the flick of a light switch*	**Qi Wang (RU) - O-05** *Supramolecular Templates as a New Strategy for the Design of Click Reactions*
10:50	**Lukas Veth (AMC) - O-03** *[^{18}F]Trifluoromethylation of Thianthrenium Salts via Copper-Mediated Radical-Radical Coupling*	**Edith van der Nol (UL) - O-06** *Barcode-free hit discovery from massive libraries enabled by automated small molecule structure annotation*
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Program Tuesday March 25 2025

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15:15	*Announcement and Lecture winner The MCCB thesis prize 2025 – Iwan de Esch*	
15:45	**John Overington (DrugHunter, UK)** *Data for drug discovery - how to feed the need for data*	
16:30	**SOC Prizes for best oral and poster presentations** **Closing followed by drinks**	

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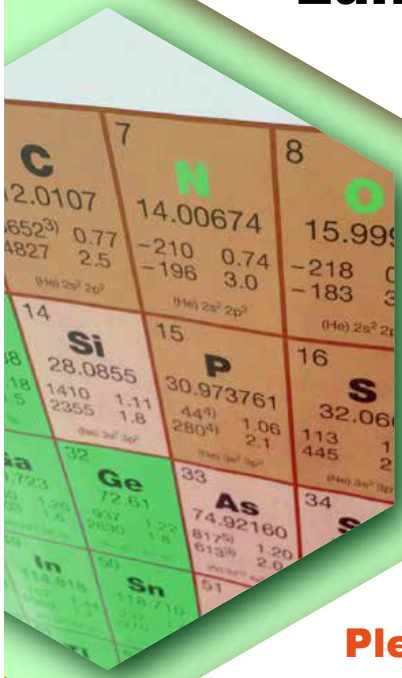

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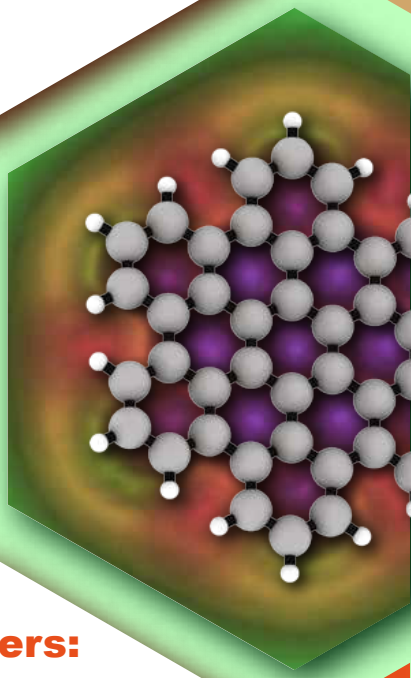

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ORAL PRESENTATIONS

O-01

DESIGN AND SYNTHESIS OF INHIBITORS AND PROBES TARGETING FUCOSE-PROCESSING ENZYMES

Roy Steneker[a], Jeroen D.C. Codée[a], Hermen S. Overkleeft[a]

[a]Leiden Institute of Chemistry, Leiden University, 2333 CC Leiden, The Netherlands

Fucose, an unusual 6-deoxy L-configured sugar, is a highly abundant component of many important oligosaccharides and glycoconjugates in both pro- and eukaryotic organisms.[1] Accordingly, fucosylation plays a key role in numerous biological and pathological pathways.[2] Therefore, studying the enzymes that process and regulate these sugar moieties is crucial. The enzymes that transfer L-fucose residues to acceptor molecules (e.g., oligosaccharides, glycoproteins and glycolipids) are known as fucosyltransferases, while those responsible for cleaving fucose moieties from glycoconjugates are referred to as fucose hydrolases, or fucosidases. The biological and biomedical relevance of fucose-processing enzymes, combined with the limited crystallographic data and poor understanding of their catalytic itineraries warrants the development of inhibitors and probes.[3,4] In the past, our group has been successful at targeting α-L-fucosidases using cyclophellitol-based glycomimetics.[5] Capitalizing on this work, we have designed and synthesized a library of putative inhibitors and probes to target new classes of fucose-processing enzymes.

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2. M. Schneider et al., *Glycobiology*, **2017**, *27*, 601–618.
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5. J. Jiang et al., *Chem. Sci.*, **2015**, *6*, 2782–2789.

O-02

Reversible metal-binding with the flick of a light switch

Luuk Stringer, David Villarón Salgado, Sebastiaan van Elst, Dr. ing. Daniël L. J. Broere

EDTA is well-known for its strong affinity to various metal ions, such as Ca^{2+}, Fe^{3+}, Mn^{2+}, and Cu^{2+}.[1] It has many applications in metal extraction, ranging from detergents to medicine.[2,3] Typically, EDTA is first deprotonated to generate the $EDTA^{4-}$ ligand, which then binds with metal ions to form stable complexes. Once the metal ion is bound to the ligand, it is quite difficult to recover the metal ions from these complexes. One way to decoordinate the metal from its chelator is by using a large excess of acid to protonate EDTA into H_4EDTA, allowing the release of free metal ions into the solution.[4] However, this approach generates large amounts of acidic waste and suffers from non-quantitative recovery of the EDTA ligand.

We hypothesized that an alternative way to release metal ions from strong chelators in a controlled manner can be achieved by inducing large conformational changes in the ligand through an external stimulus such as light. To this end, we designed and synthesized chelating ligands based on photoswitchable moieties. In the Z-isomer, the chelators should bind very strongly to the metal ion, but we hypothesize that upon photoisomerization to the E-isomer the binding strength drastically decreases (Figure 1), allowing for facile dechelation of the metal ion from the chelator, possibly eliminating the need of strong acids.

In this presentation we will discuss new photoswitchable EDTA-inspired chelating ligands. In addition to ligand synthesis, metal binding studies, photoswitching abilities, and dechelation studies will be presented.

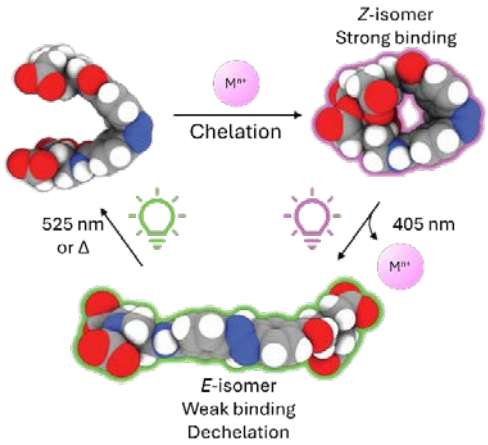

Figure 1: Schematic depiction of a photoswitchable chelator with strong and weak binding modes.

O-03 Title: [^{18}F]Trifluoromethylation of Thianthrenium Salts via Copper-Mediated Radical-Radical Coupling

Authors: Lukas Veth, Albert D. Windhorst, Danielle J. Vugts

Affiliation: Dept. Radiology and Nuclear Medicine, Amsterdam UMC, location Vrije Universiteit, De Boelelaan 1117, 1081 HV Amsterdam, Netherlands

Introduction:

Thianthrenium salts and related compounds have recently emerged as versatile building blocks[1] that can, for instance, be used for the formation of aryl or alkyl radicals. Their use as precursors for radiolabeling reactions has recently been demonstrated in the synthesis of ^{18}F-labeled fluoroarenes[2] and ^{11}C-labeled arylnitriles.[3] We have recently reported the access to ^{18}F-labeled trifluoromethyl radicals for the use in PET tracer synthesis.[4] Herein, we present the [^{18}F]trifluoromethylation of thianthrenium salts via photoredox- and copper-mediated radical-radical coupling for the synthesis of ^{18}F-labeled trifluoromethylarenes and –alkanes.

Methods:

[^{18}F]Trifluoroiodomethane was synthesized according to our reported method[4] and trapped in DMF (1 mL). An aliquot of the solution (100 µL, ca. 25-50 MBq) was added to a vial containing a mixture of CuI, base (DIPEA or DBU), $[Ru(bpy)_3]Cl_2 \cdot 6H_2O$, and the corresponding thianthrenium salt in DMF under nitrogen atmosphere. The resulting reaction mixture was irradiated with blue light (ca. 465-470 nm) while allowing to stir for 10 min. The radiochemical conversion (RCC) was determined by HPLC analysis. The identity of the obtained product was confirmed by co-injection of non-radioactive reference compounds.

Results:

For arenes, model substrate **1a** was chosen bearing a 4-phenyl substitution. Under optimized reaction conditions, trifluoromethylarene **2a** could be obtained in 81±2% RCC. The presence of electron-donating (-OMe, **1b**) and electron-withdrawing substituents (-CN and $–CF_3$, **1c** and **1d**) was well tolerated, delivering the corresponding products in 72-81% RCC. The counterion did not have an influence on the reaction performance. The reaction conditions for alkane **3** were slightly modified (DIPEA instead of DBU) resulting in product **4** in 87±4% RCC. In both reactions, no product formation was observed in the absence of Ru-catalyst, CuI, or blue light.

Conclusions:

A protocol to access ^{18}F-labeled trifluoromethylarenes and –alkanes from their corresponding thianthrenium salts was successfully established. A preliminary evaluation of the substrate scope for the arenes indicated a good functional group tolerance. Further work will be dedicated to establish the full substrate scope for both arenes and alkanes and apply the protocol to the functionalization of bioactive compounds with relevance to PET tracer synthesis.

Acknowledgements:

L.V. thanks the Deutsche Forschungsgemeinschaft (DFG) for a Walter-Benjamin fellowship (project no. 519969214).

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O-04

Affinity-based covalent sialyltransferase probes enabled by ligand-directed chemistry

Tom Wennekes (UU)

Sialyltransferases (ST) are key enzymes found in, among others, mammals and bacteria that are responsible for producing sialylated glycans, which play critical roles in human health and disease. However, chemical tools to study sialyltransferases have been limited to non-covalent inhibitors and probes that do not allow isolation and profiling of these important enzymes. In this talk I will present a new class of covalent affinity-based probes for ST by using ligand-directed chemistry (LDchem).
These affinity-based ST probes are armed with two types of proximity reactive SNAr electrophilic warheads, which are lysine specific. We chemoenzymatically synthesised a series of CMP-Neu5Ac based probes and demonstrate their high specificity in labelling a range of recombinant STs with submicromolar sensitivity. Importantly, with these LDchem ST probes, we successfully labelled the endogenous lipooligosaccharide ST (Lst) in live Neisseria gonorrhoeae, a clinically relevant human pathogen.

O-05 Supramolecular Templates as a New Strategy for the Design of Click Reactions

Qi Wang, Daniela A. Wilson*, Kevin Neumann*
qi.wang@ru.nl
Systems Chemistry, Institute for Molecules and Materials, Radboud University, the Netherlands

Within biological environment, performing synthetic chemistry is often challenging due to the presence of competing reactive groups and the effects of strong dilution. However, enzymes, as highly efficient biological catalysts, overcome this challenge by employing a proximity effect, in which reactants are brought into close spatial arrangement within the active site, significantly accelerating reaction rates.

Inspired by this natural strategy, we present a new supramolecular templating approach that enables to efficiently perform chemical transformations even under strong dilution. Specifically, we utilize a supramolecular anchoring system[1] as a template to facilitate the inverse electron-demand Diels–Alder (iEDDA) reaction, a reaction widely recognized for its high degree of chemoselectivity. In this design, the reactive functional groups – tetrazine and BCN – are conjugated to the pyrene anchor, ensuring their close proximity upon binding to the supramolecular template.[2] This creates a dynamic and localized reaction environment that enhances reaction efficiency, mimicking enzymatic catalysis. The effectiveness of this approach is evident in the reaction kinetics: in the presence of the supramolecular template, the reaction proceeds with a $t_{1/2}$ of 142 minutes, representing a significant ~ 10,500-fold rate increase compared to the untemplated reaction.

In summary, our work describes a novel strategy that allows to perform chemical transformations under strong dilution within aqueous environment, offering a powerful tool for the designs of click reactions.

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O-06

LACDR

Barcode-free hit discovery from massive libraries enabled by automated small molecule structure annotation

Edith van der Nol[1,2]+, Nils Alexander Haupt[3]+, Qing Qing Gao[1], Benthe A.M. Smit[1], Martin Andre Hoffmann[4], Martin Engler-Lukajewski[4], Marcus Ludwig[4], Sean McKenna,[1,2] J. Miguel Mata[1,2], Olivier J. M. Béquignon[1], Gerard van Westen[1], Tiemen J. Wendel[2,5], Sylvie M. Noordermeer [2,5], Sebastian Boecker[3]*, Sebastian Pomplun[1,2]*

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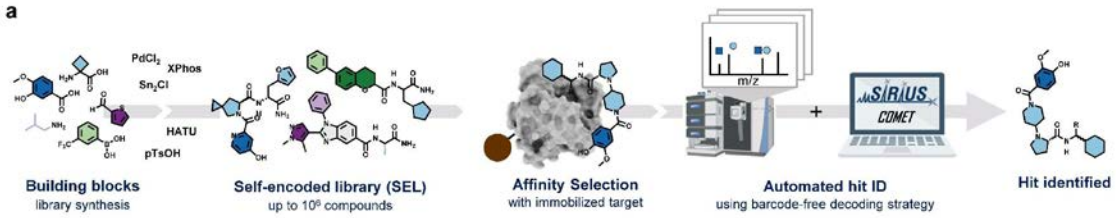
[2]Oncode Institute; Utrecht, 3521 AL, The Netherlands
[3]Chair for Bioinformatics, Institute for Computer Science, Friedrich Schiller University Jena, Jena, 07737, Germany
[4]Bright Giant GmbH, Hans-Knöll-Straße 6, 07745 Jena, Germany
[5]Department of Human Genetics, Leiden University Medical Center; Leiden, 2333 ZA, The Netherlands,

Abstract: The discovery of high affinity ligands is crucial for virtually any drug discovery campaign. Affinity-selection platforms are powerful tools for rapid early drug discovery.[1] Among these, DNA-encoded libraries (DELs) have found widespread application for the identification of small molecule ligands. However, the DNA barcodes required for the decoding of hit-compounds bring challenges in terms of synthesis complexity and reaction scope, and can also influence binding by interacting with the target. We present a self-encoded library (SEL) platform that simultaneously screens up to a million druglike small molecules without barcoding tags. We developed computational methods to automatically decode each query MS/MS spectrum of a selection outcome, matching it against the molecular structures of the library. This combinatorial mass encoding decoding tool (COMET) succeeded in correctly annotating spectra from a wide variety of chemical structures, enabling the screening of druglike libraries with diverse molecular architectures. We developed robust library synthesis approaches with a variety of chemical transformations and validated our platform in affinity-selections, identifying multiple nanomolar binders for the oncologic target Carbonic anhydrase IX. We also succeeded in identifying potent inhibitors for the flap endonuclease 1 (FEN1), a promising drug target for synthetic lethality based cancer treatment. As DNA processing enzymes cannot be addressed with DELs, this example highlights the innovative potential of our SEL platform. Screening barcode-free libraries of this scale is unprecedented and promises substantial impact on both academic and industrial early drug discovery.



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O-07

Frontside S_N2 Glycosylation Reactions

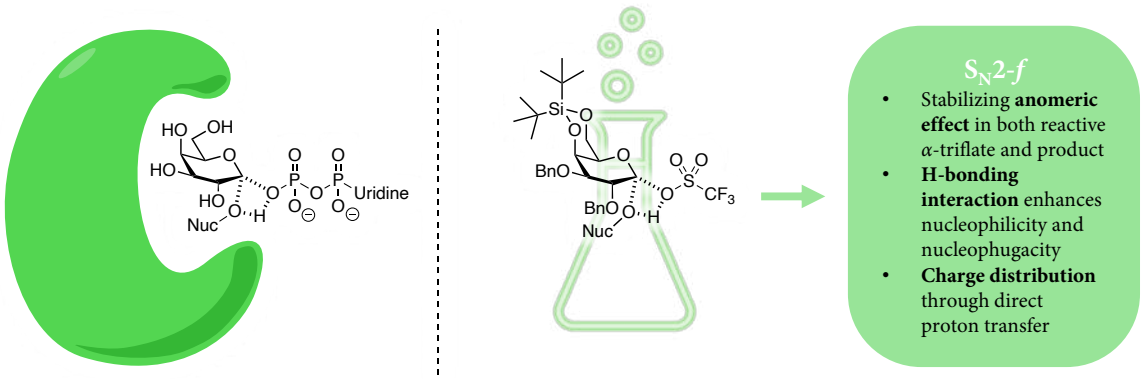
Daan Hoogers[a], Koen N.A. van de Vrande[a], Frank F. J. de Kleijne[b], Jacob M. A. van Hengst[a], Wouter A. Remmerswaal[a], Paul B. White[b], Thomas J. Boltje[b], Thomas Hansen[c], Jeroen D. C. Codée[a]

[a] Leiden Institute of Chemistry, Einsteinweg 55, 2333 CC Leiden, The Netherlands.
[b] Institute for Molecules and Materials (IMM), Synthetic Organic Chemistry, Radboud University, 6525 AJ Nijmegen, The Netherlands
[c] Department of Theoretical Chemistry, Amsterdam Institute of Molecular and Life Sciences (AIMMS), Amsterdam Center for Multiscale Modeling (ACMM), Vrije Universiteit Amsterdam, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands

Controlling the stereochemical outcome of glycosylation reactions remains one of the fundamental challenges in carbohydrate chemistry. Mechanistic models generally describe chemical glycosylation reactions as proceeding via S_N1 or backside S_N2 (S_N2-*b*) pathways.[1] Notably, retaining glycosyl transferases operate via a different mechanism, and substitution reactions on nucleotide diphosphate sugar donors can take place through a front face substitution mechanism (termed S_Ni).[2] This mechanism has been largely ignored to play a role in chemical glycosylation reactions, but we here provide evidence for a concerted frontside S_N2-like (S_N2-*f*) displacement mechanism in glycosylations of 4,6-*O*-di-*tert*-butylsilylene (DTBS)-protected galactosyl donors.

Through ^{19}F EXSY and ^{1}H CEST NMR spectroscopy, we demonstrate that steric hindrance introduced by the DTBS group suppresses triflate exchange, restricting glycosylation reactions to the α-triflate and α-face of the donor. Acceptor concentration-dependent kinetics and primary ^{13}C KIE values support an associative mechanism featuring an “exploded” transition state with retention of stereochemistry. Density functional theory (DFT) calculations further reveal that strong hydrogen bonding between the nucleophile and the triflate leaving group stabilizes the transition state, making this frontside displacement pathway favour more acidic nucleophiles. This was substantiated by acceptor competition experiments, in which the more electron poor *O*-nucleophiles provided faster glycosylation reactions.

Our findings establish a new paradigm in chemical glycosylation chemistry, demonstrating that triflates can be substituted in a stereoretentive manner by exploiting the S_N2-*f* reaction pathway. This work provides new insights to understand the outcome of glycosylation reactions and offers new perspectives for future mechanistic exploration.



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O-08

A quantitative approach to assess neuraminidase activity on glycan surfaces

Qianqian Wang, Daniel Tambuwun, Jurriaan Huskens

Department of Molecules & Materials, MESA+ Institute for Nanotechnology, Faculty of Science and Technology, University of Twente, 7500 AE Enschede, The Netherlands

Abstract

Influenza viruses are covered with hemagglutinin (HA) and neuraminidase (NA) proteins that recognize and infect host cells by forming multivalent interactions with sialic acid-terminated glycans on the host cell surface. Whereas HA is the main binder, NA plays an important role in the infection of host cells and in the escape of the virus from the infected cell after reproduction of the virus inside the cell. In seasonal flu, mutations in both HA and NA occur as a response of the virus against host immune reactions. Therefore, it is important to determine the activity of NA in the presence of HA to assess viral pathogenicity and infectivity.

Here, we present the development of an approach to quantify the activity of viral NA on a glycan surface. When binding to and cleavage of terminal sialic acid occur on the virus-receptor surface, the receptor density and viral coverage on the glycan surface decrease in parallel. We measured the residual sialic acid after cleavage using periodate oxidation and aniline-catalyzed ligation (PAL) methods to obtain the receptor density on the glycan surface. Thereafter, the receptor density threshold on the surface of the glycan at the time of dramatic reduction or even complete escape of the virus can be used to quantify NA activity. Thus, this quantitative approach may be useful in predicting influenza infectivity and answering other biological questions.

O-09

Encounters in Synthesis of ADP-Ribose Analogues

Koen J. Rijpkema[a], Jeroen D.C. Codée[a], Dmitri V. Filippov[a].

[a] *Bio-Organic Synthesis Group, Leiden Institute of Chemistry, 2333 CC Leiden, The Netherlands.*

Adenosine diphosphate ribosylation (ADP-ribosylation) is a post-translational modification crucial for a proper immune response.[1] Accordingly, several viruses encode glycosidases that reverse native ADP-ribosylation.[2] Potent inhibitors for these glycosidases are in high demand, a need primarily addressed through the high-throughput screening of small molecules.[3] In contrast, we aimed to design and synthesize potent inhibitors by structurally mimicking the enzymatic target, namely ADP-ribosylated substrates. By employing an iterative approach,[4] we were able to produce several highly potent (low nanomolar) inhibitors for which we applied various organic transformations, such as the stereoselective establishment of *C*-glycosides via distant Cram chelation control followed by regioselective tosylation and ring closure. Furthermore, during our synthetic explorations we overcame several peculiar side reactions such as intramolecular reductions and the fragmentation of protective groups. Rather than focussing on the successful total syntheses of the ADP-ribose analogues themselves, we would like to put these unusual reactions on center stage.

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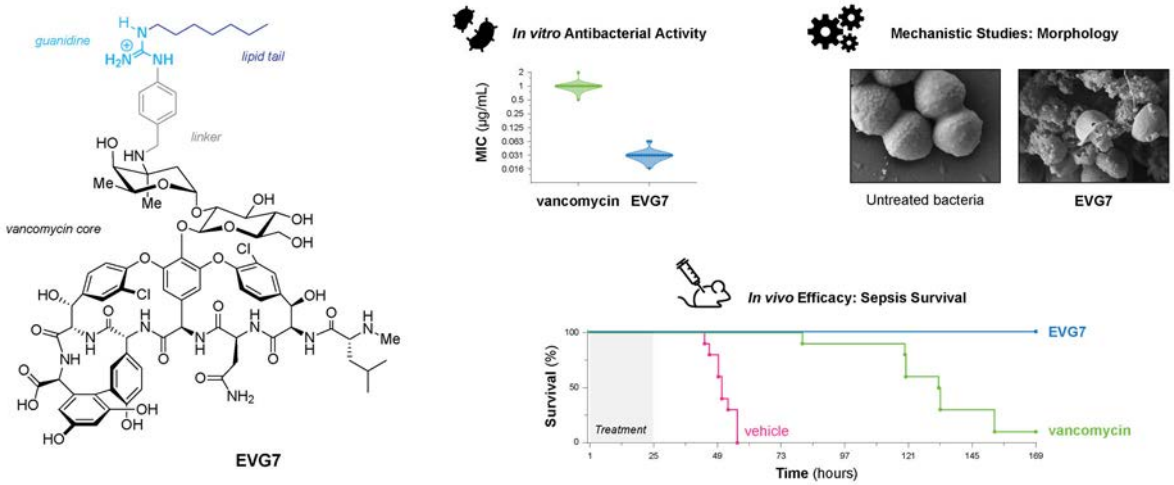
O-10 Preclinical Evaluation of Guanidino Lipoglycopeptide Antibiotic EVG7 with *Best-in-Class* Potential

Elma Mons, Emma van Groesen, Ioli Kotsogianni, Vladyslav Lysenko, Nathaniel I. Martin

Infections caused by methicillin- and vancomycin-resistant bacteria account for more than 0.5 million antimicrobial resistance-associated deaths globally per year. Development of next-generation antibiotics with enhanced activity, reduced toxicity, and the capacity to overcome such infections is crucial. Here, we present the guanidino lipoglycopeptides, a novel class of highly potent semisynthetic glycopeptide antibiotics recently developed in the Martin group.[1,2] Our lead guanidino lipoglycopeptide **EVG7** is active against a range of Gram-positive pathogens, including clinically relevant methicillin-resistant *S. aureus* (MRSA) and various vancomycin-resistant strains. **EVG7** exhibits dramatic enhancements in antibacterial activity of up to >1000-fold compared to vancomycin and other clinically used (lipo)glycopeptide antibiotics. Furthermore, **EVG7** is also able to overcome vancomycin resistance while having a low propensity to induce resistance itself. Evaluation of **EVG7** in validated *in vivo* infection models also demonstrate its superiority compared to vancomycin. The therapeutic potential of **EVG7** is further supported by a recently completed 7-day repeat-dose study which showed a lower risk of nephrotoxicity at relevant dose levels.

Guanidino lipoglycopeptide antibiotic **EVG7** has the potential be a safer alternative to vancomycin. Further preclinical evaluation – including biodistribution studies, efficacy in other infection models, and IND-enabling toxicity studies – is ongoing at this moment. These studies are expected to result in a spin-off company or licensing of the technology to interested pharmaceutical industry partners that will continue the development of **EVG7** towards first-in-human trials.



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O-11

Title:

Targeted photodynamic therapy for imaging and treatment of cancer

Authors:

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Abstract:

Pancreatic ductal adenocarcinoma (PDAC) patients have a dismal 5-year survival of only 8%. A specific feature of PDAC is the dense stroma, produced by cancer associated fibroblasts (CAFs). This stroma causes poor delivery of systemic therapies to tumour cells and an immune-suppressive micro-environment, contributing to poor survival. Current chemo- and immunotherapies are therefore ineffective, and alternative targeted treatment options are an urgent need. A promising target is the fibroblast activation protein (FAP), which is heavily overexpressed by CAFs.

We describe the synthesis and biological evaluation of small peptide based FAP-binding ligands functionalized with phthalocyanine-based photosensitisers for specific imaging of CAFs and targeted photodynamic therapy. The molecules are also equipped with a chelator for radiolabelling to yield bimodal constructs. The radionuclide labelled compounds have been employed for quantification in *in vitro* binding assays using a murine fibroblast cell line overexpressing murine FAP. In addition, we studied the internalization of our compounds using live cell confocal laser scanning microscopy. Finally, we studied the theranostics *in vivo* in mice.

O-12

Genetic and pharmacological inactivation of glycerophosphodiesterase GDE4 promotes oligodendrocyte differentiation and remyelination

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Myelin is essential for effective nerve signaling. The primary cells responsible for myelination in the central nervous system are oligodendrocytes (OLs), which originate from oligodendrocyte precursors cells (OPCs) and undergo a complex differentiation and maturation process to acquire a myelinating phenotype. Since various neurological diseases are associated with loss of myelin and, as a consequence, impaired neuronal function, new approaches to boost remyelination are of great therapeutic interest. Here, we report that inactivation of the glycerophosphodiesterase GDE4, an enzyme part of the biosynthetic machinery to generate *N*-acylethanolamine (NAE) signaling lipids in the brain, leads to increased oligodendrocyte differentiation and myelination. Through a focused screen of in-house synthesized phospholipase inhibitors, we identified a first-in-class inhibitor of GDE4. Inhibition of GDE4 activity results in accumulation of its GP-NAE substrates, which act as a novel class of signaling lipids that promote OPC differentiation and maturation *in vitro*. In line with these results, GDE4 knockout mice have increased levels of GP-NAE lipids and elevated oligodendrocyte and myelin marker proteins in the hippocampus. Both genetic and pharmacological inactivation of GDE4 in primary OPCs subjected to differentiation results in OLs with a more mature myelinating phenotype. Finally, we show that our GDE4 inhibitor is effective in promoting remyelination in acute brain slice cultures. Together, our findings support targeting GDE4 as a novel potential strategy to combat demyelinating diseases.

O-13

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Title: Unveiling the Potential of a Cobalt-Based Metal-Organic Framework as a Catalyst in Carbodiimide Synthesis.

Keywords: nitrene transfer, isocyanide, carbodiimide, ZIF-67, MOF

The synthesis of carbodiimides via nitrene transfer to isocyanides has garnered significant attention in recent years. However, this reaction predominantly relies on homogeneous catalytic systems with high catalyst loadings. In this study, we employed ZIF-67 MOF as a heterogeneous catalyst for carbodiimide synthesis and conducted an in-depth analysis of its stability. Our findings reveal the non-innocent role of catalyst leaching, demonstrating that even as little as 0.04 mol% of leached cobalt species is sufficient to catalyze this reaction. This result is in contrast with previous reports, where 5–10 mol% of cobalt-loading is required. Furthermore, this study highlights that lower catalyst loadings are more efficient, particularly in cases where isocyanides exhibit limited stability.

Figure 1: General scheme

O-14 Development of Chiral Chemical Libraries for Chemical Proteomics Driven Drug Discovery

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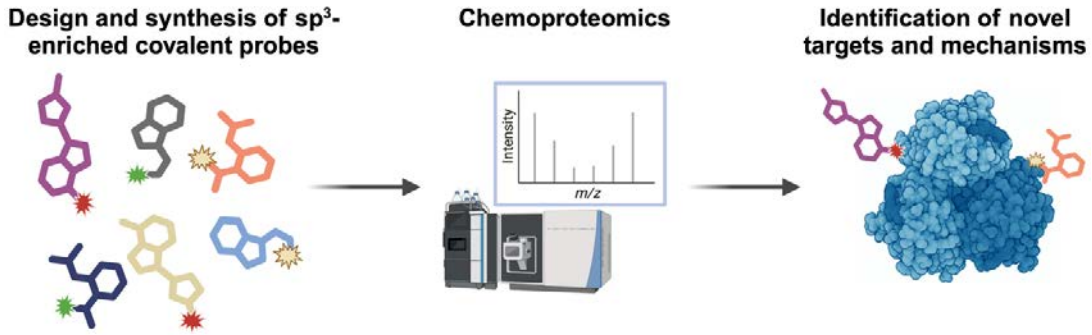

A significant proportion of the human proteome remains intractable to modulation with small molecule drugs, which limits both basic biological research and therapeutic development.[1] Covalent drugs are a re-emerging class of compounds that are gaining traction in the pharmaceutical industry because of their potential to target proteins that have historically been considered undruggable.[2] A key technology enabling the development of covalent chemical probes and drugs is chemical proteomics, which can be used to directly identify the binding sites and targets of small molecules in living systems.[1,3,4] To date, several studies have been published illustrating the power of using chemical proteomics to identify novel binding sites and develop chemical probes with unique mechanisms of modulating protein function. However, to date, these studies have largely been performed using a limited number of highly reactive, low molecular weight, aromatic electrophiles.[4,5] These "fragment-like" compounds are often highly promiscuous, difficult to optimize into potent and selective tool compounds, and lack the functional groups necessary to perform subsequent validation experiments. Furthermore, extensive use of these commercially available compounds means that only a limited proportion of chemical and biological space has been explored using chemical proteomics thus far. Our research aims to address these limitations by developing a library of sp^3-enriched chiral chemical probes that are specifically designed to facilitate the discovery and validation of novel drug targets using chemical proteomics. In this presentation, I will describe the design and synthesis of representative examples from this library. Our methodology enables the rapid diversification of core scaffolds with different electrophiles and biorthogonal functional groups, and importantly, access to both enantiomers of each compound. I will describe the proteomic analysis of these compounds in human immune cells, including the identification of novel binding sites on disease relevant proteins that are stereoselectively engaged by our library. The subsequent validation and functional characterization of these targets will provide proof-of-concept for the potential of our chiral chemical library to expand the druggability of the human proteome.

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O-15

The Marvel Chemistries of PolyBorylated Alkenes

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Polyboron-containing alkene species have recently attracted significant attention as versatile polymetalloid building blocks in organic synthesis. Their unique electronic structure, featuring a double bond and multiple carbon–boron (C–B) bonds, enables precise control over carbon–carbon (C–C) and carbon–heteroatom (C–heteroatom) bond formation, as well as other transformations. In this talk, I will present my group's recent research on exploring new reactivities and developing advanced methodologies for the stereoselective synthesis and versatile applications of polyborylated alkene motifs in synthetic chemistry.

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O-16

Photoaffinity-based protein profiling reveals the target of clock-enhancing small molecule 3

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The circadian clock regulates the behaviour, molecular and physiological processes in a wide range of species including humans. Despite close coordination between the 'master clock' and cellular clocks in peripheral organs, the circadian rhythm can be disrupted. This is associated with diseases such as cancer, metabolic syndromes, and neurodegeneration. Small-molecule modulators can stabilize circadian rhythm, one of these molecules is clock-enhancing small molecule 3 (CEM3). Although previous studies have demonstrated the amplitude-enhancing effects of CEM3 on mammalian cells, tissue explants, and mouse suprachiasmatic nucleus (SCN) slices, its intracellular target remains unknown. In this work, we developed a photoaffinity probe for CEM3 to identify its molecular target. Using a sequential approach that combined proteomics and circadian reporter assays - employing real-time circadian gene reporter (*Bmal1:Luc2P*) in fibroblasts and circadian protein reporter (PER2::LUC) in mouse SCN slices - we identified the target of CEM3. This discovery provides new insights into the molecular regulation of circadian rhythms and highlights a novel potential therapeutic target for diseases associated with circadian disruption.

O-17

Title: Mucus-mimicking PEG hydrogel for studying the effect of multivalent interactions on virus migration

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Abstract:

The airway mucus can block influenza A viruses (IAV) and other pathogens through multivalent decoy interactions, mainly involving sialoglycan-hemagglutinin (HA) interactions. These interactions aim to prevent the pathogens from reaching the host cell surface where they could lead to an infection. Elucidating these interactions between viruses and receptors in the mucus can be explored by studying the specificity of multivalent interactions in an artificial 3D structure, thus to reveal how the mucus layer protects cells from infection.

Therefore, finding a hydrogel that can both mimic and regulate biophysical properties could serve as a potential artificial mucus model for mucus research. Among many synthetic hydrogels, poly(ethylene glycol) (PEG) hydrogels are protein-resistant and uncharged. Using it as a substrate can eliminate other interactions, allowing us to focus on the specific interaction motif of the virus-mucus interface.

We prepared an artificial mucus using 4-arm poly(ethylene glycol) (PEG)-thiol and 4-arm PEG-norbornene in an off-stoichiometric way in order to tune the degree of crosslinking and to give room for the controlled introduction of receptor groups. The mechanical properties and internal structure can be regulated by adjusting the polymer content. After functionalization to covalently bind sialoglycans in controlled densities, this artificial mucus can be used to specifically investigate the effect of sialoglycan-HA interactions on virus diffusion.

O-18

Synthesis of ^{18}F-labeled radioligands for PET imaging of GABA transporter 1 (GAT1)

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As the main inhibitory neurotransmission system, the GABAergic system is involved in the pathogenesis of various neurological disorders, such as epilepsy, schizophrenia, Parkinson's disease, and Alzheimer's disease. To further understand the role of the GABAergic system in these diseases and allow more effective diagnosis and treatment options, non-invasive imaging of the GABAergic system is highly desired.

Despite several research attempts, *in vivo* imaging of GABA transporters is not yet possible due to a lack of appropriate radioligands.[1] Therefore, several ^{18}F-labelled lipophilic nipecotic acid derivatives were synthesized in this research as radioligands addressing GABA transporter 1 (GAT1) (**Figure 1**).[2] The applicability of the final candidate radiotracer employing an ethyl ester prodrug approach was investigated in a rodent model.

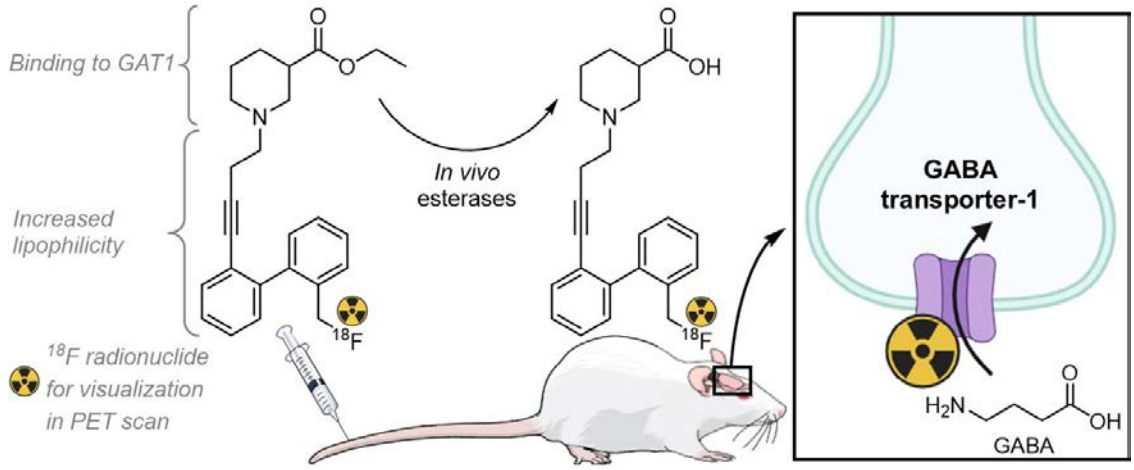

Figure 1. Structure of the developed radioligand and its use as imaging agent for GAT1.

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2 N. Knippenberg *et al.*, *ACS Chem. Neurosci.,* **2025**, *16* (4), 711

O-19 Development of DuoMYC: a synthetic cell penetrant miniprotein that efficiently inhibits the oncogenic transcription factor MYC

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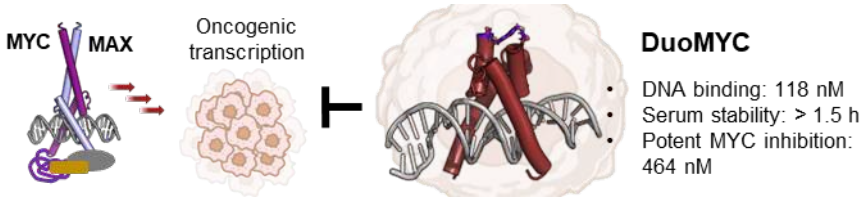
The master regulator transcription factor MYC is implicated in numerous human cancers, and its targeting is a long-standing challenge in drug development. MYC is a typical 'undruggable'target, with no binding pockets on its DNA binding domain and extensive intrinsically disordered regions. Rather than trying to target MYC directly with classical modalities, here we engineer synthetic miniproteins that can bind to MYCs target DNA, the enhancer box (E-Box), and potently inhibit MYC-driven transcription. We crafted the miniproteins via structure-based design and a combination of solid phase peptide synthesis and sitespecific crosslinking. Our lead variant, DuoMYC, binds to E-Box DNA with high affinity (K_D ~0.1 µM) and is able to enter cells and inhibit MYC-driven transcription with submicromolar potency (IC_{50} = 464 nM) as shown by reporter gene assay and confirmed by RNA sequencing. Notably, DuoMYC surpasses the efficacy of several other recently developed MYC inhibitors. Our results highlight the potential of engineered synthetic protein therapeutics for addressing challenging intracellular targets.



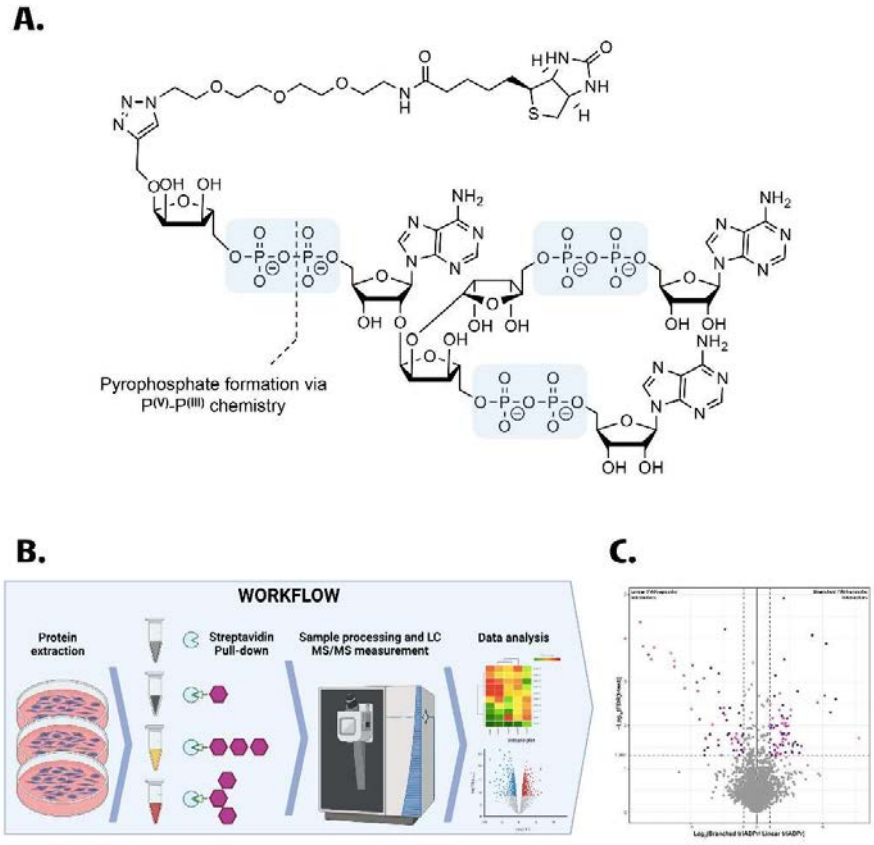
From: B. D. Ellenbroek, J. P. Kahler, D. Arella, C. Lin, W. Jespers, E. A. Züger, M. Drukker, S. J. Pomplun, *Angew. Chemie Int. Ed.* **2024**, DOI 10.1002/ANIE.202416082.

O-20

Elucidating the Branched ADP-ribose Signaling Pathway

Femke L. A. M. van der Heijden (Leiden University, Leiden, Netherlands), Suzanne A. Weijers (Radboud University, Nijmegen, Netherlands), Katarzyna Kliza (Radboud University, Nijmegen, Netherlands), Sven Wijngaarden (Leiden University, Leiden, Netherlands), Michiel Vermeulen (Radboud University, Nijmegen, Netherlands), Dmitri V. Filippov (Leiden University, Leiden, Netherlands).

ADP-ribosylation is a post-translational modification crucial for signaling in various cellular processes, including DNA damage repair. Dysregulation of this pathway is associated with a variety of diseases, including viral infections and cancer, underscoring the importance of understanding this pathway. Three forms of ADP-ribosylation; monoADP-ribosylation, linear polyADP-ribosylation, and branched polyADP-ribosylation influence the ADP-ribose signaling pathway. However, branched polyADP-ribosylation remains the least studied due to its low natural abundance and complex molecular structure. Consequently, there is a lack of appropriate research tools to study this modification. While numerous proteins (readers) have been identified that interact with mono- and linear ADP-ribose, only a single protein, APLF, has been identified for branched ADP-ribose. To overcome this limitation, we synthesized a new affinity-based probe using a complementary liquid- and solid-phase approach based on P(V)-P(III) chemistry. This probe, a branched ADP-ribose trimer with a biotin tag, facilitated the identification of multiple previously unknown readers of branched ADP-ribose through interaction proteomics. These findings significantly contribute to the elucidation of the branched ADP-ribose signaling pathway.



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O-21

Non-Innocent Behavior of Aromatic Isocyanides under Visible Light: A Pathway to Thioformimidates

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Thioformimidates play an important role in peptide modifications as the protection group [1]. The most common method for the synthesis of thioformimidates involves *S*-alkylation of thioformamides with aryl or alkyl halides. However, these processes often suffer from several limitations and purification problems due to the instability of thioformamides and limited substrate scope. Alternatively, thioformimidates can also be synthesized from isocyanides and thiols triggered by UV-light or AIBN initiator [2]. Generally, this reaction proceeds with the formation of a thiyl radical in the presence of UV-light or AIBN followed by thiyl radical addition on the isocyanide to generate an α-thioimidoyl radical [3]. This radical can then undergo H-abstraction from thiols to form the final thioformimidates product. Despite the convenience of this method, less attention has been directed to this pathway due to the following reasons: a) the requirement of UV-light; b) poor reaction efficiency; c) the formation of unwanted side products such as 1,1-bisthiolation; d) C-S bond scission of the intermediate α-thioimidoyl radical, leading to the generation of isothiocyanates.

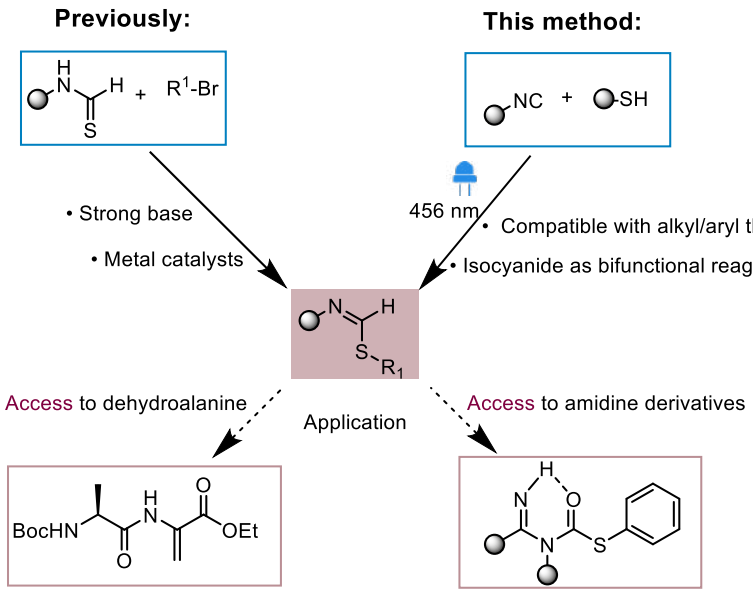

Figure 1. Visible light-mediated synthesis of thioformimidates.

Previously, we desighed a photocatalyst-free pathwy to spirocyclic scaffolds from tryptamine-derived isocyanides by employing blue light [4]. Given the significance of thioformimidates and the current limitations in versatile, sustainable synthetic methods, we focused on developing an innovative, photocatalyst-free, visible-light-driven approach for their synthesis. This study marks a significant advance in the field, as it not only improves existing methods for accessing thioformimidates but also reveals a previously camouflaged role of isocyanides in generation of thiyl radicals.

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O-22

Orthogonal Site-Specific Dual Bioconjugation of Aryl and Alkyl Thiols

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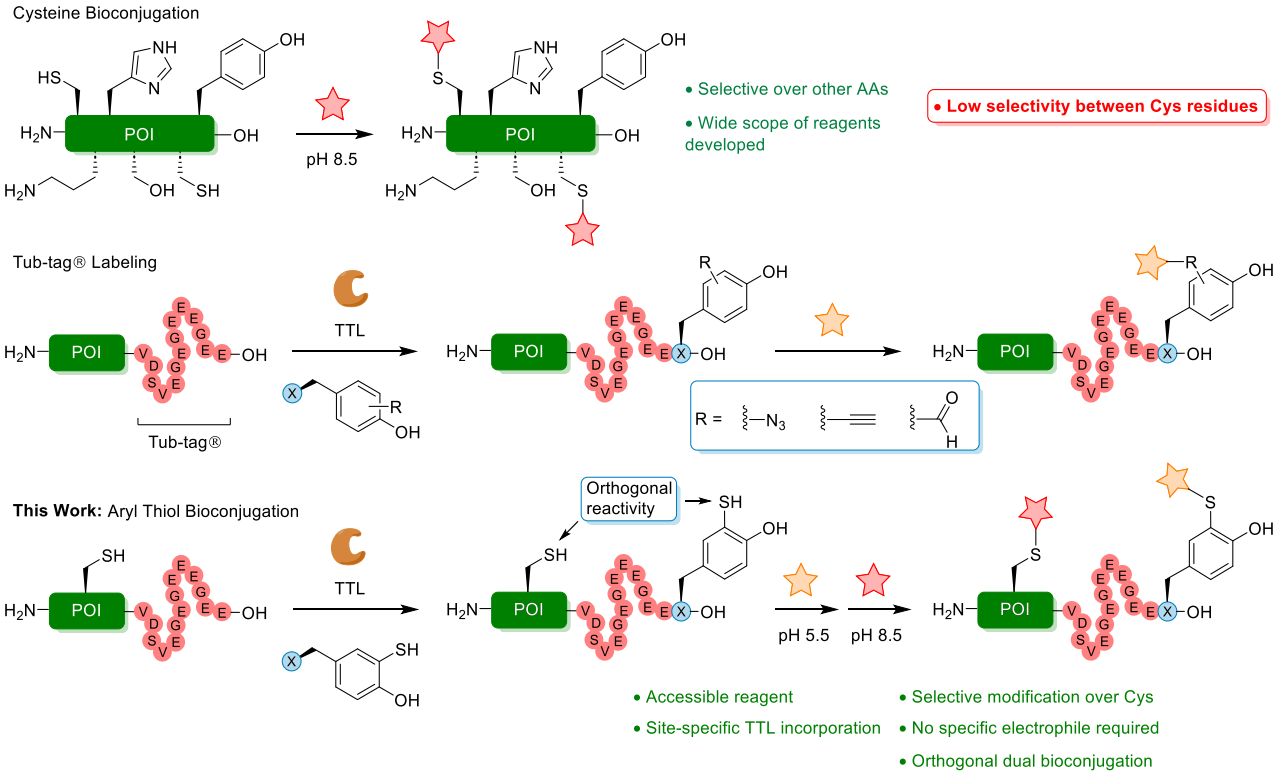
ABSTRACT: We introduce aryl thiols as nucleophiles for site-specific protein and antibody bioconjugation which allows the orthogonal labeling of native cysteines for double modification strategies. In a high-yielding synthesis we introduce aromatic thiol substituents in two amino acids (4-SH-*L*-Phe and 3-SH-*L*-Tyr), which can be site-specifically incorporated into the *C*-terminus of a protein using the enzyme *tubulin tyrosine ligase* (TTL, Tub-tag® labeling). In particular, we found that 3-SH-*L*-tyrosine shows excellent water solubility and incorporation rates, similar to previously described Tyr-derivatives. 2D NMR experiments revealed a pK_a value of 5.5 for the aryl thiol modality of 3-SH-*L*-tyrosine, which matches the pH-dependent reactivity profile towards thiol-selective ethynyl-triazolyl-phosphinate (ETP) electrophiles. Most importantly, we found that the addition of glutathione had no significant effect on the reaction between ETPs and the aryl thiol at pH 7.0 and below, supporting orthogonal reactivity between the aryl and alkyl thiols. We utilized these findings to develop an orthogonal thiol-selective dual bioconjugation protocol for proteins, featuring TTL-ligation to site-specifically incorporate the arylthiol-containing amino acid derivative, followed by aryl thiolate functionalization at pH 5.5 and subsequent conjugation of cysteines at pH 8.3. This dual bioconjugation strategy was used to generate a highly fluorescent photostabilized nanobody, and a fully functionalized antibody-drug conjugate (ADC) carrying two different cytotoxic payloads, which displays potent cytotoxicity towards cells carrying the target antigen in addition to a strong bystander effect.



O-23

Enhancing Intracellular Activity of Synthetic Transcription Factors via reCHEMbinant Protein Engineering

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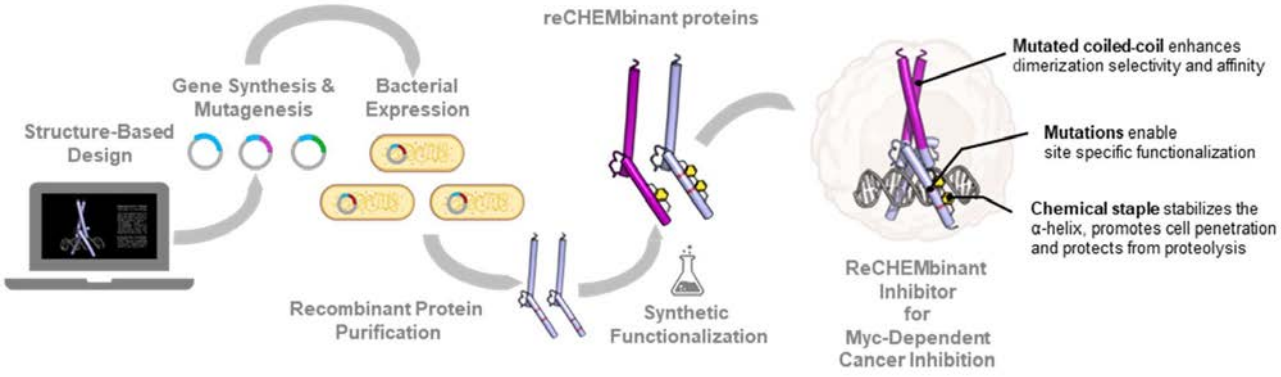
Protein therapeutics have revolutionized drug discovery, offering treatments for challenging targets that small molecules cannot address. However, typically, proteins cannot penetrate cells, where many critical drug targets are located. Here we present the development of a reCHEMbinant protein engineering platform, designed to create synthetically enhanced protein-based MYC inhibitors with potent intracellular activity. This platform combines structure-based design, recombinant expression of precursor proteins, and synthetic modifications to enhance bioactivity. Biophysical analysis demonstrated that all reCHEMbinant variants were functional and exhibited low nanomolar affinities to the MYC DNA target site. Most strikingly we identified a specific biphenyl *i, i* + 7 staple modification that boosted cellular uptake and activity of the reCHEMbinant protein variants HeloMYC 714 and HeloMYC 1421. Both show enhanced cell permeability compared to their unmodified counterparts and are more potent in inhibiting MYC-driven transcription. Our study highlights how integrating synthetic chemistry with protein therapeutics can lead to novel modalities for tackling challenging intracellular drug targets.



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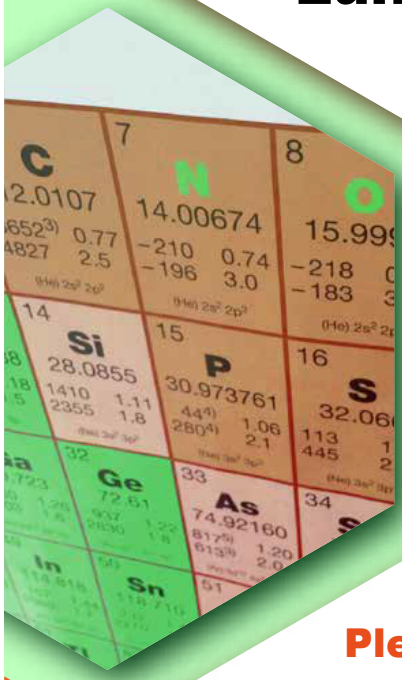

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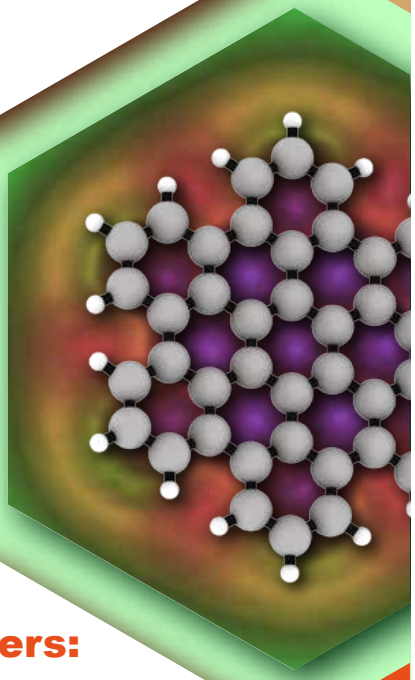

Plenary

Annamaria Lilienkampf
University of Edinburgh

Jan van Maarseveen
University of Amsterdam

Uwe Grether
Roche, CH

Marta Artola
Leiden University

Speakers:

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Exscientia, UK

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POSTER PRESENTATIONS

P-01 **SOC MCCB Symposium 2025**

Modular Synthesis of Lignin Model Compounds

Eman Abdelraheem[1], Tom Ewing[2], Gijs van Erven[2,3,*], Fedor Miloserdov[1,*]

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Abstract:

Lignin is the most abundant aromatic substance in nature and holds great potential for valorization in the biobased economy. The predominant structural feature of the lignin biopolymer is a complex network of methoxylated aromatic subunits linked through various etherand C-C bonds. Studying and developing strategies for the catalytic modification and selective conversion of the lignin polymer into value-added chemicals and materials hence, heavily relies on appropriate structural lignin model compounds including dimers, trimers, and small oligomers. Therefore, access to different model compounds containing specific subunits and β-O-4, β-5 or β-β linkage motifs is crucial and targeted at here, ultimately aiming to build a structural library. We report a protocol for exploring the chemistry of bromoketoethers to realize the first modular synthetic approach toward lignin model compounds, and present insight into the further development of this platform for synthesizing other structurally relevant oligomeric models.

P-02

Palladium catalyzed cascade cyclization towards the enantioselective total synthesis of (+)-Aspidofractinine

Theodora Athanasiadou, Cristiano Cassinera, Eelco Ruijter*

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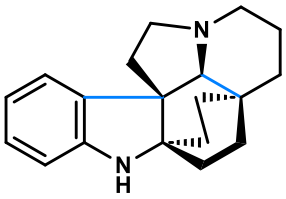
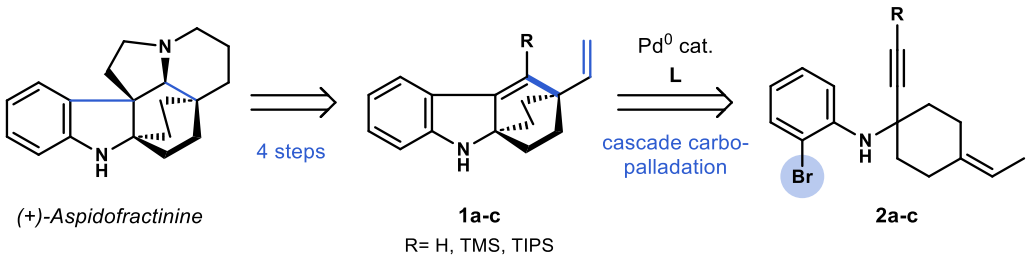


The monoterpene indole alkaloid (+)-Aspidofractinine was first isolated in 1964 from the leaves of *Pleiocarpa tubicina* of the family of *Apocynacae* by Schmid and coworkers[1]. Many monoterpene indole alkaloids have proven to be an important source of drugs in the modern medicine, such as treatment of cardiovascular diseases, malaria, diabetes, fever and rheumatism[2]. (+)-Aspidofractinine bears a bicyclo[2.2.2]octane motif with three all-carbon quaternary stereogenic centers that has proved a challenging synthetic puzzle. In this poster, we present our synthetic plan towards the enantioselective total synthesis of this hexacyclic indole alkaloid through a carbopalladation of an alkyne followed by a cascade cyclization. The advantages of this plan include that enantioselectivity can be implemented in the later stages of the synthesis providing possibly higher enantioselective ratio and diversification towards different scaffolds. For our retrosynthesis plan, we envisioned an efficient asymmetric total synthesis of (+)-Aspidofractinine from an achiral late-stage intermediate(**1**) which in turn can result from a cascade cyclization of a simple precursor(**2**) (*Scheme 1*).



Scheme 1: Retrosynthetic plan of (+)-Aspidofractinine from simple precursors **2**

[1] Schmid, H. et al. Weitere Alkaloide aus den Blattern von *Pleiocarpa tubicina*; Umwandlung von (–)-Quebrachamin in (+)-1,2-Dehydroaspidospermidin. *Helv. Chim. Acta.* **1964**, *47*, 1147–1152.

[2] de Almeida, V. L. et al. *Aspidosperma species*: A review of their chemistry and biological activities. *J. Entomol.* **2019**, *231*, 125-140.

P-03

ChemoPar-db: A Structural Chemogenomics Database for Chemokines and their Binding Partners

Bas de Boer[1], Albert J. Kooistra[2], Iwan J.P. de Esch[1] and Barbara A. Zarzycka[1].

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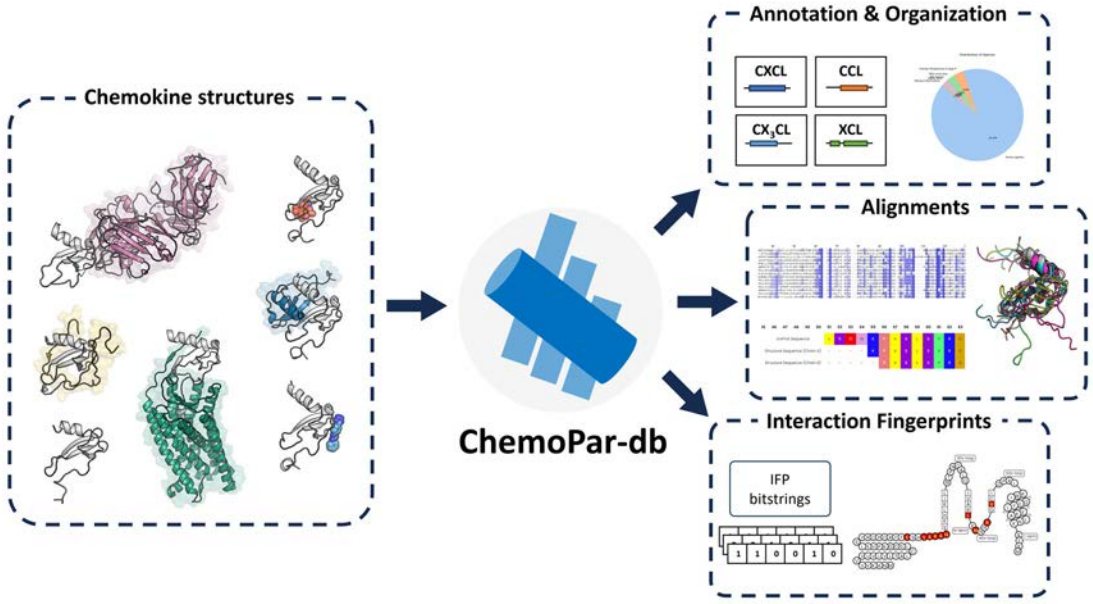


Abstract

Chemokines play a central role in the organization of the immune system in both homeostatic and inflammatory processes.[1] As highly versatile scaffolding proteins, chemokines bind a diverse range of partners. This includes binding to chemokine receptors, other chemokines, glycosaminoglycans, antibodies, and various chemokine binding proteins, indicating their important role in highly specific and complicated cellular communication.[2,3] Considering that chemokines engage with a multitude of other interaction partners, targeting the diverse scaffolding properties of these chemokines could lead to the discovery of drugs that have unprecedented control over their physiological action. Here we present ChemoPar-db, a database in which we compiled all publicly available structural data on chemokines. By using a Python-based workflow, ChemoPar-db collects and processes chemokine 3D structures from the Protein Data Bank. This workflow involves the alignment of sequences to a reference multiple sequence alignment, preparing structures by protonation and separation of structural elements, structural alignment onto a common template, and calculation of chemokine-partner interactions. By leveraging generic chemokine residue numbers and molecular interaction fingerprints, we enable rapid comparison of chemokine complexes, allowing us to systematically map the chemokine interaction space. Utilizing the Django framework, we integrated all this information into an organized online database which is freely accessible at https://chemopar-db.net. By providing a focused structural overview of chemokines and their molecular interactions, we expect ChemoPar-db to aid in efforts targeting the chemokine signaling axis. Specifically, the database can help structure-based drug discovery efforts, leading to more small-molecule modulators of chemokines.

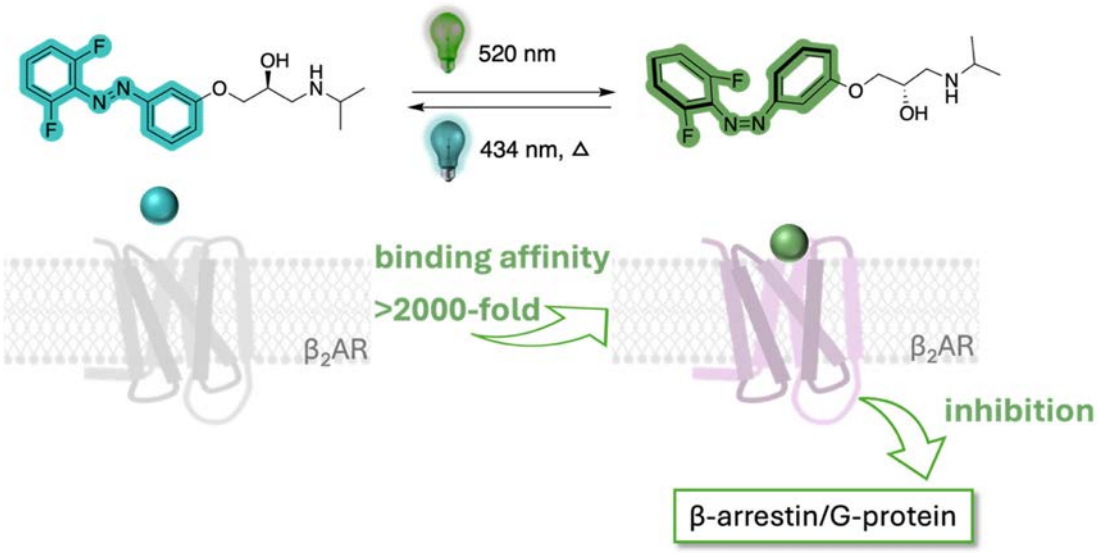
[1] Gerard *et al. Nat Immunol*, **2001**, *2*:108-115
[2] Proudfoot *et al. Pharmaceuticals*, **2017**, *10*:70
[3] Handel *et al. J Histochem Cytochem*, **2021**, *69*:87-91

P-04 VUF26782: A red-shifted photoswitchable *cis*-on antagonist for β_2-adrenergic receptor photopharmacology

Yangzhi Cao, Shuang Shi, Lars P. Binkhorst, Simone A. H. Does, Valeria Turina, Henry F. Vischer, Maikel Wijtmans, Rob Leurs

Division of Medicinal Chemistry, Amsterdam Institute of Molecular and Life Sciences (AIMMS), Vrije Universiteit Amsterdam, The Netherlands. Email: y.cao@vu.nl

Photopharmacology can achieve a high level of spatial and temporal control of protein signaling by using light as an external trigger. G protein-coupled receptors (GPCRs) constitute one of the most preferred families of drug targets and ~34% of the currently used drugs act on GPCRs. Application of photopharmacology to GPCRs has attracted considerable interest.[1] Adrenergic receptors (ADRs) are GPCRs that recognize the endogenous signaling molecules adrenaline and noradrenaline. Among the subtypes of ADRs, the β_2 adrenergic receptor (ADRB2) is an important target that mediates physiologic responses such as smooth muscle relaxation and bronchodilation. Recently, we developed a first-generation photoswitchable ligand using an "*azologization*" strategy applied to propranolol, a well-known β_2 antagonist. The most effective compound, (*S*)-Opto-prop-2, exhibits a large shift in binding affinities at the β_2-AR, with a 1000-fold increase upon illumination with 360 nm.[2,3] In the current study, red-shifted analogues of (*S*)-Opto-prop-2 were explored to allow photoswitching with visible light. Among them, VUF26782 shows good photochemical properties and good thermal stability of the *cis* isomer ($t_{1/2}$ ~ months). Importantly, VUF26782 can be photoswitched using 520 nm illumination to obtain the *cis* isomer, which displays a large difference in β_2-AR binding affinity compared to the *trans* isomer (>2000-fold).



(1) Wijtmans et al. *Curr. Opin. Pharmacol.* **2022**, *63*, 102192.
(2) Bosma et al. *iScience* **2022**, *25*, 104882.
(3) Shi et al. *Biochem. Pharmacol.* **2024**, *226*, 116396.

P-05

Synthesis and study of photoswitchbles nucleosides

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RNA plays a crucial role in regulating cellular processes, making it a key target for therapeutic applications. However, a major challenge in RNA-targeting drug development is achieving precise spatial and temporal control over their activity.[1] Such control is essential for understanding the mechanisms underlying these processes. In this context, incorporating a switchable moieties into an RNA binder, enabling its properties to be controlled by an external stimulus, is highly desirable. Light, as a versatile and non-invasive tool, has emerged as an invaluable asset for this purpose. Its unique ability, such as high spatial and temporal resolution, make it an attractive alternative to conventional chemical or electrical stimuli.[2] Photoswitchable molecules that undergo significant geometric changes have been covalently attached to DNA oligonucleotides, creating photochromic oligonucleotides that can regulate biological processes using light.[3] However, linking photoswitches to RNA remains underdeveloped. In addition, some photoswitchable small-molecule RNA binders have been reported, they lack target specificity and rely on UV light (200–400 nm).[4] However, UV light is unsuitable for biological applications due to its low tissue penetration and potential damage to biomolecules.

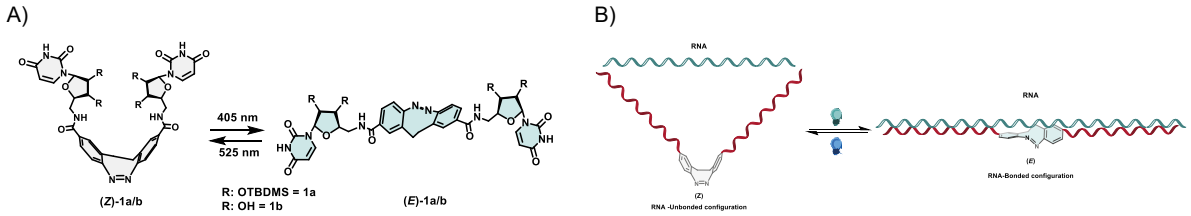

Figure 1 : A) Photoisomerization of diazocine base nucleoside. B) Representation of the photoswitching control of RNA-bonding activity

In this context, we are designing new photoswitchable oligonucleotides based on diazocine, which has emerged as a promising candidate for controlling biological activity with light.[5] Its incorporation into oligonucleotides enables visible-light photoisomerization and induces significant geometrical changes. In addition, diazocine undergoes photoswitching between a thermally stable bent (*Z*) isomer and a metastable linear (*E*) isomer. Since the (*E*) state is often the biologically active form, light irradiation allows precise control over biological function, making diazocine an ideal tool for tuning biological activity.

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P-06 Synthesis and Structural Characterization of Ru(MOP)L Complexes

Kathleen Cheasty

Coordination chemistry and homogeneous catalysis rely on the development of effective strategies to stabilizing low-valent transition metal complexes. To this end, herein, a novel Ru(0)(MOP)(PPh_3) catalyst is described. Starting from $[Ru(cymene)(Cl_2)]_2$, the complex was synthesized by first coordination of the MOP ligand and subsequent reduction by Zn metal. The high thermal stability and lack of intramolecular C-H activation this complex displays is unusual for carbonyl-free phosphine complexes of Ru(0).

These characteristics are the result of the σ-P/π-arene coordination mode of the MOP ligand, which stabilizes the complex. It is anticipated that simultaneously as stabilizing the metal center, the MOP ligand also increases its reactivity by its ability to slide from an η^6 coordination mode to an η^4 coordination mode, revealing vacant sites for incoming substrates.

To assess this hypothesis, Ru(MOP)(PPh_3) was observed by ^{31}P NMR in the presence of various potential substrates, such as styrene, methyl methacrylate, indene and N-ethylpyridin-2-amine, revealing interesting substitution behavior.

Tofurtherinvestigate this, crystallization efforts of the Ru(MOP)(PPh_3) complex are currently ongoing and some experiments for C-H activation will be carried out.

P-07 Development of DuoMYC: a synthetic cell penetrant miniprotein that efficiently inhibits the oncogenic transcription factor MYC

Brecht D. Ellenbroek[1, 3], *Jan Pascal Kahler*[1, 3], *Damiano Arella*[1], *Cherina Lin*[1], *Willem Jespers*[1], *Eliane Ann-Katrin Züger, Micha Drukker, and Sebastian J. Pomplun*[1, 3]

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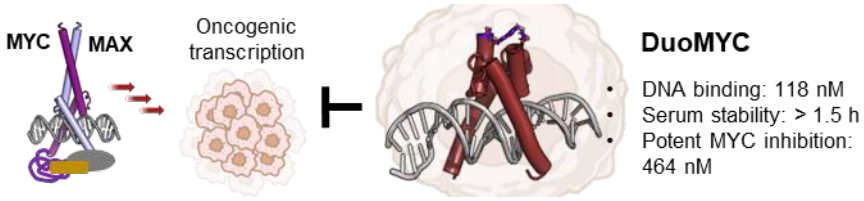
[2] Cell Systems and Drug Safety, LACDR, Leiden University, 2333 CC Leiden, The Netherlands

[3] Oncode institute, 3521 AL Utrecht, The Netherlands

The master regulator transcription factor MYC is implicated in numerous human cancers, and its targeting is a long-standing challenge in drug development. MYC is a typical 'undruggable'target, with no binding pockets on its DNA binding domain and extensive intrinsically disordered regions. Rather than trying to target MYC directly with classical modalities, here we engineer synthetic miniproteins that can bind to MYCs target DNA, the enhancer box (E-Box), and potently inhibit MYC-driven transcription. We crafted the miniproteins via structure-based design and a combination of solid phase peptide synthesis and sitespecific crosslinking. Our lead variant, DuoMYC, binds to E-Box DNA with high affinity (K_D ~0.1 µM) and is able to enter cells and inhibit MYC-driven transcription with submicromolar potency (IC_{50} = 464 nM) as shown by reporter gene assay and confirmed by RNA sequencing. Notably, DuoMYC surpasses the efficacy of several other recently developed MYC inhibitors. Our results highlight the potential of engineered synthetic protein therapeutics for addressing challenging intracellular targets.



From: B. D. Ellenbroek, J. P. Kahler, D. Arella, C. Lin, W. Jespers, E. A. Züger, M. Drukker, S. J. Pomplun, *Angew. Chemie Int. Ed.* **2024**, DOI 10.1002/ANIE.202416082.

P-08 Sustainable Biopolymers via Passerini Reaction: Valorization of Biomass-Derived Phenolic Acids and Succinic Anhydride

Claudio Ferdeghini

The transition towards sustainable materials calls for innovative approaches to polymer synthesis. In this work, we exploit a variation of the Passerini multicomponent reaction (PMR)[1] to develop novel biopolymers using diacids derived from phenolic acids extracted from biomass waste. Phenolic acids, widely recognized for their availability in agricultural residues and their potential as bio-based chemical feedstocks[2], serve as key building blocks in our approach. These naturally occurring compounds will be used in combination with aldehydes, succinic anhydride, and isocyanides to enable the formation of structurally diverse and potentially biodegradable polymers. The valorization of agricultural and industrial waste streams through polymer chemistry aligns with the principles of circular economy and sustainable development. This study underscores the versatility of PMR in biopolymer development and highlights the potential of waste-derived phenolic acids as renewable polymer precursors.

[1]Passerini, M.; Simone, L. *Gazz. Chim. Ital.* **1921**, *51*, 126-29.

2Panzella, L.; Moccia, F.; Nasti, R.; Marzorati, S.; Verotta, L.; Napolitano, A. *Front. Nutr.* **2020**, *7*.

P-09 A New Class of Antibacterial Allosteric Inhibitors of DNA Gyrase

Meg Ferguson

Given the increasing threat that antimicrobial resistance poses to global healthcare, identifying new antibiotics is a priority. With some highly resistant bacteria now displaying resistance to nearly all known antibacterials, finding antibiotics that target bacteria via novel mechanisms is desirable.[1] Recently, our group conducted a phenotypic screen that identified a new class of antibacterial allosteric inhibitors of DNA gyrase, an essential bacterial topoisomerase.[2] Following this, an extensive structure-activity relationship (SAR) study lead to compound LEI-800 (**Fig. 1**) which inhibits DNA gyrase with an IC_{50} of 35 nM. While LEI-800 is one of the most potent DNA gyrase inhibitors reported to date, its antibacterial activity was found to be limited due to poor penetration through the Gram negative outer membrane. Recent studies from the Hergenrother group have led to the so-called eNTRy rules which describe physicochemical properties of small molecules that can enhance uptake by Gram negatives (unhindered primary amine (N), low three-dimensionality ($T \leq 0.25$), and $R \leq 5$).[3,4] By applying the Hergenrother rules, alongside the insights gained from extensive SAR studies in the development of LEI-800, our current work involves developing derivatives of LEI-800 with improved Gram negative cell permeability and antibacterial activity.

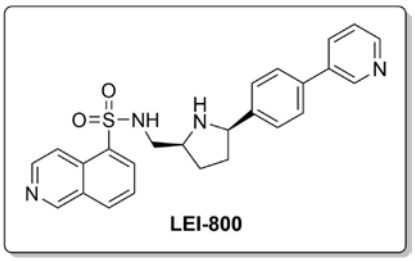


Figure 1. Structure of isoquinoline sulfonamide compound LEI-800, a new inhibitor of DNA gyrase.

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P-10 Gold screen-printed electrodes coupled with molecularly imprinted conjugated polymers for ultrasensitive detection of streptomycin in milk

Margaux Frigoli*[a], Manlio Caldara[a], Jeroen Royakkers[a], Joseph W. Lowdon[a], Thomas J. Cleij[a], Hanne Diliën[a], Bart van Grinsven[a]

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Abstract:

Antibiotic resistance is a global health threat, challenging traditional treatments and complicating the food safety process. This study introduces an electrochemical detection method for streptomycin sulfate, utilizing gold screen-printed electrodes (Au-SPE) functionalized via electropolymerization of a custom-made naphthalene diimide-based conjugated monomer (Th_2-NDI-PIA). This modification creates specific binding sites for streptomycin, allowing rapid detection of the antibiotic. The sensor's response to different concentrations of streptomycin was studied via Differential Pulse Voltammetry (DPV) in a wide linear range from 10^{-13} M to 10^{-9} M, with a limit of detection (LoD) of 0.190 ± 0.005 pM. The imprinted electrode demonstrates selectivity to other antibiotics, but also to common interferents that can be found in milk such as lactose, glucose, riboflavin, and bisphenol A. Successful proof-of-principle in whole cow milk highlights the sensor's efficacy in detecting antibiotic residues in food samples, offering a promising alternative for a rapid and portable detection technique.

P-11

Synthesis and evaluation of carbapenem/metallo-β-lactamase inhibitor conjugates

Mei-Ling Gao, Ioli Kotsogianni, Foteini Skoulikopoulou, Nora C. Brüchle, Paolo Innocenti, Nathaniel I. Martin

Abstract

The increasing prevalence of bacterial resistance to β-lactam antibiotics, particularly through the production of metallo-β-lactamases (MBLs), represents a critical challenge in modern medicine. MBLs, such as NDM-1 and IMP-1, can hydrolyze a broad spectrum of β-lactam antibiotics, including carbapenems, rendering them ineffective. This study aims to develop and evaluate novel conjugates that combine a carbapenem antibiotic (meropenem or ertapenem) with an indole carboxylate-based MBLs inhibitor. These conjugates are designed to overcome MBL-mediated resistance and restore the efficacy of β-lactam antibiotics. We synthesized carbapenem/MBL inhibitor hybrids and assessed their enzymatic inhibitory activity against key MBLs, including NDM-1 and IMP-1, as well as their antibacterial potency. The synthesized conjugates exhibited potent MBLs inhibition with IC_{50} values in the low nanomolar range. Despite this, their overall antibacterial activity was limited. Mechanistic investigations suggested that while the conjugates effectively inhibited MBLs within live bacterial cells, they showed reduced interaction with the primary bacterial target of β-lactams. These results highlight the challenges associated with successfully designing β-lactams conjugates.

P-12

S,O ligand promoted C-H activation of anisoles for thiolation and tosylation using palladium catalysis

Thijs de Groot, Soma Rudi and dr. Tati Fernandez Ibanez
Universiteit van Amsterdam

Abstract

The introduction of functional groups in (aromatic) molecules can be challenging and may require large amounts of (energy intensive) reagents. Classically, substitution is achieved through pre-functionalization of a C-H bond (by introducing e.g. a halogen or boronic ester), whereafter it is reacted with another functionalised molecule, resulting in the formation of a C-C or C-heteroatom bond. These two steps may be reduced to one step via Pd catalysis, where C-H activation can be achieved, followed by the installation of a functional group. Earlier research within the group found that S,O ligands facilitate aromatic substitution of non-prefunctionalized substrates, allowing to form C-C bonds selectively in the ortho, meta or para position. Meta functionalisation is achieved via a Catellani-type reaction, where norbornene is added to facilitate the activation of the C-H bond next to the para position, which is activated first.[1] Via this reaction, arylation of anisoles has been achieved. The meta activation of such substrates is highly interesting, as they are usually ortho and para directing, whereas the meta position is relatively unreactive. This opens the possibility for late-stage meta functionalisation of complex molecules, which is highly difficult to achieve otherwise. In my project, I try to expand the scope of functional groups that can be installed, such as thiolation using thiosulfonates or alkynylation using alkynyl halides.

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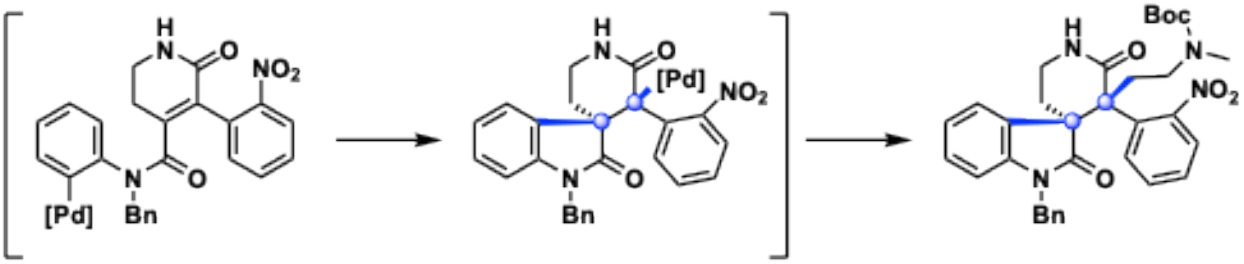
P-13 TOWARD A TOTAL SYNTHESIS OF (+)-PEROPHORAMIDINE THROUGH A CARBOPALLADATION APPROACH

Jaap Harteveld[1], Rutger de Haas[1], Eelco Ruijter[1]

[1]*Amsterdam Institute of Molecular and Life Sciences, VU Amsterdam, Amsterdam, The Netherlands*

Perophoramidine is a complex polycyclic alkaloid isolated from the marine ascidian *Perophora namei* showing promising anticancer activity. These medicinal properties, together with its two vicinal quaternary spiro stereocenters, make it a popular target for total synthesis.

Here, we report a novel synthetic strategy toward the regio- and stereoselective construction of (+)-(dehalo)perophoramidine through an asymmetric carbopalladation approach. In the key step, we envision a Heck – Suzuki coupling cascade to construct the two required vicinal quaternary stereocenters of (+)-(dehalo)perophoramidine. We report our progress in synthesizing suitable substrates and investigating conditions for the envisioned cascade cyclization.



P-14 Exploring ADP-Ribosylation of SUMO2: Synthesis of a Non-Hydrolysable Mimic and Identification of Novel Interactors

Matthew D. Heijne, Cami M. P. Talavera Ormeño, Rishov Mukhopadhyay, Gerbrand J. van der Heden van Noort

Small ubiquitin-like modifier (SUMO) is a small protein post translational modification that is mainly conjugated to proteins that are localized in the nucleus and is important in the regulation of nuclear processes, including DNA damage response, cell cycle progression and proteostasis.[1] Recent unbiased proteomics experiments in HeLa cells under normal physiological conditions identified SUMO2 to be ADPribosylated on His17.[2] Research has shown that the ADPribosylation on several amino acid residues of ubiquitin, a better understood small protein post translational modification that shows similarities with SUMO, are associated with tumor development,[3–5] DNA damage response[6,7] and bacterial infections.[8–10] This implies that ADPribosylation is not limited to ubiquitin, but might also occur more frequently on other ubiquitin-like proteins. It remains unknown what biological relevance this modification has and which proteins interact with ADPribosylated SUMO2. Here, we synthesize a non-hydrolysable SUMO2-ADPr mimic using copper catalyzed click (CuAAC) chemistry to enrich interacting proteins using a pulldown approach followed by tandem mass spectrometry. Validation of our probe via western blot techniques showed a loss of interaction with known interactors MORC3 and RNF4 upon ADPribosylation of SUMO2, while we maintain recognition by Ubc9 indicating our synthetic material can be used to explore such details in cell lysate settings. More notably, our probe shows significant interaction with PARP9, PARP14 and DTX3L which still warrant further studies. The findings of this work will give better insights in the ADPribosylation of SUMO2 and its biological role. It will broaden our understanding of ADPribosylation on ubiquitin-like proteins, potentially leading to novel targets to further study the role of this post translational modification.

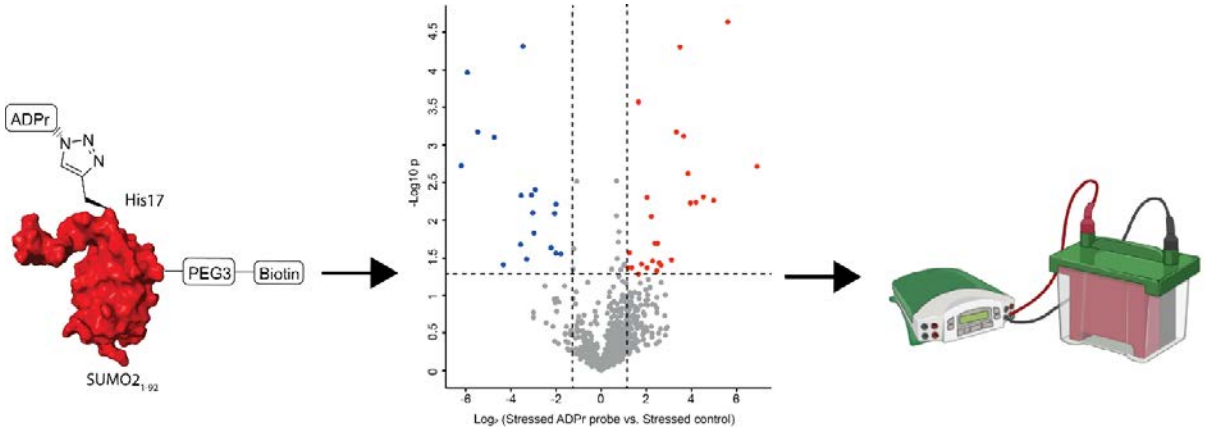


Figure 1) Enrichment of interacting proteins with the non-hydrolysable SUMO2-ADPr mimic shows significant interactors which were validated via western blotting.

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P-15

NEW SYNTHETIC APPROACHES TOWARDS THE ANTI-MALARIAL DRUG GANAPLACIDE

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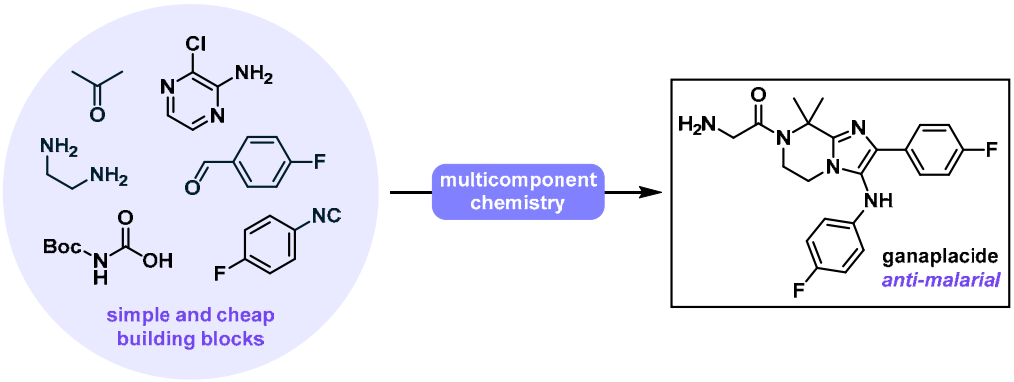
Malaria is a neglected tropical disease that cause about 600 000 deaths each year, mainly on the African continent.[1] As the effective treatment of malaria has stagnated in the past years due to drug resistance, the discovery of new drugs has high urgency. Developed by Novartis, KAF156 (also known as *ganaplacide*) is a new type of anti-malarial of the imidazolepiperazine class that successfully completed phase II clinical trials recently.[2]



The current route to ganaplacide counts 9 linear steps and it is our goal to scout new short and efficient routes towards this drug. We show that the imidazolopiperazine core of ganaplacide can be formed very quickly and efficiently using multicomponent chemistry.[3] This process uses only simple and cheap building blocks and produces minimal waste. We are exploring various routes involving multicomponent chemistry and we currently are working on the final steps to obtain the desired product.

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P-16 Iminosugar-based PROTACs for targeted protein degradation of non-lysosomal glucocerebrosidase (GBA2) and glucosylceramide synthase (GCS)

Authors

Rob F. Lammers, Nicky de Koster, Eva Wan, Saskia Pieters, Ioana Belcin, Maxime Mingot, Julie Fournier-Vaudelin, Akrivi Mela, Laura van Vliet, Rolf Boot, Marta Artola

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Abstract

Targeted protein degradation offers several advantages over ‘classical’ small molecule inhibitors and, in particular, proteolysis-targeting chimeras (PROTACs) technology downregulates enzymes by causing their selective proteasomal degradation. PROTAC research mainly focuses on molecular targets with therapeutic relevance for various forms of cancer. However, new PROTACs targeting other “difficult to target” proteins might open new therapeutic opportunities. Although glycosidases and glycosyltransferases are involved in many diseases, no efficient PROTACs have been described to degrade these targets. Here we aim to develop potent and selective degraders of relevant glycosylases and glycosyltransferases, taking advantage of the catalytic mechanism and protein-protein interaction induced selectivity of non-covalent PROTACs. As model glycosidase and glycosyltransferase targets, we selected non-lysosomal glucocerebrosidase (GBA2) and glucosylceramide synthase (GCS), respectively. These enzymes are therapeutically relevant in the context of various LSDs and potentially Parkinson’s disease, and whereas selective inhibitors of GCS exists, targeting GBA2 in a selective manner is still a challenge that could be solved by engaging specific targeted degradation. Thus, capitalizing on a dual GCS/GBA2 iminosugar ligand, we have synthesized the first library of iminosugar-based PROTACs functionalized with CRBN and VHL E3 ligands through diverse linkers and monitor their degradation potential using activity-based protein profiling, western blotting and proteomic analysis.

P-17

Ultra High-Throughput Screening of RNA-Binding Protein Inhibitors Using Tag-Free Affinity Selection

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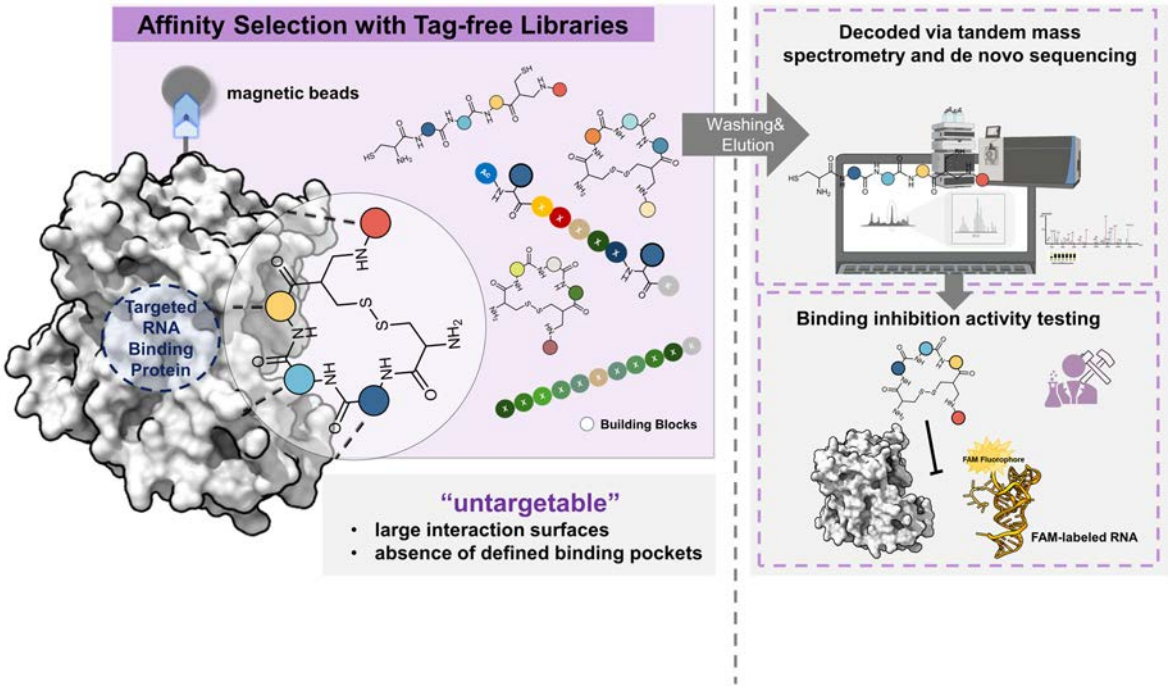
[1]Division of Drug Discovery and Safety, LACDR, Leiden University, the Netherlands

Abstract:

RNA-binding proteins (RBPs) play crucial roles in regulating various aspects of RNA metabolism and cell functions, and dysregulation of RBPs is implicated in severe diseases. However, RBPs remain largely unexplored in drug discovery due to challenges associated with the absence of conventional small molecular binding pockets and the 'untargetable' nature of the large nucleic acid interaction surfaces[1].

In this study, our objective is to develop an affinity selection platform aimed at facilitating the de novo discovery of high-affinity hits targeting RBPs. Existing powerful discovery platforms, DNA-encoded libraries, is not suitable for RBP targets due to interference from DNA decoding tags. We address this challenge by developing fully synthetic tag-free libraries. These libraries, upon screening, can be decoded using tandem mass spectrometry and de novo sequencing, enabling the rapid screening of > 1 million unique sequences.

We envision that our discovery workflow could accelerate the hit discovery process for RBPs and represent a general platform for generating ligands for challenging targets.



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P-18

Title: Synthesis, Structure Optimization, and Evaluation of Antibacterial Activity of Rifampicin-Siderophore Conjugates

Co-authors: Vladyslav Lysenko, Mei-Ling Gao, Fabienne A. C. Sterk, Cornelis J. Slingerland, Paolo Innocenti, Nathaniel I. Martin.

Abstract: The growing concern around antibiotic resistance has sparked increased attention toward the development of new antibiotic strategies. One promising approach, known as the “Trojan horse” strategy, involves using siderophores to hijack the iron transport system of bacteria to deliver antibiotics inside the bacterial cell. This approach is particularly promising against Gram-negative bacteria as they have a thick outer membrane that some antibiotics, such as rifampicin, cannot penetrate. The research presented here describes the development of rifampicin-siderophore conjugates with activity against Gram-negative bacteria. A key factor determining their potency was the nature and length of the linkers used in conjugating rifampicin with established iron-binding moieties. In the course of these studies, we also found that the incorporation of a triazole moiety in the linker, resulting from the use of click-chemistry-based conjugation approaches, can have a detrimental e ect on the antibacterial activity of the resulting conjugates.

P-19

Direct Aziridination for Synthesis of Cyclophellitol Benzenesulfonyl Aziridines and Their Evaluation as Potential Activity-Based Probes for Glycosidases

Qiang Ma, Florian Küllmer, Thomas I. Mather, Gijs Ruijgrok, Jianyun Guo, Liping Zhao, Roy Steneker, Thijs Voskuilen, Jeroen D. C. Codée, and Hermen S. Overkleeft

Activity-based probes (ABPs) are powerful chemical tools for studying complex biological process, including glycosidase activity.[1] Cyclophellitol aziridine ABPs, designed as mechanism-based inhibitors, are typically synthesized from protected polyhydroxyled cyclohexene. However, conventional synthetic strategies require multiple steps and yield low efficiency, excluding the latter incorporation of a linker and reporter tag.[2–4] Recently, Codée and colleagues introduced a photochemical aziridination method using *p*-methyl benzenesulfonyl azide, enabling direct aziridination of alkenes, including a D-galacto-configured cyclophellitol analog.[5] Inspired by this, we designed a specialized phenylsulfonyl azide featuring a C-8 linker including a terminal azide, facilitating later reporter attachment *via* azide-alkyne Huisgen cycloaddition. This project explores both applications of this strategy to synthesize cyclophellitol aziridine ABPs with different configurations and their evaluation on labeling efficiency *via* competitive ABPP with in-house ABPs. This approach enables the streamlined aziridination of cyclophellitol hexene and subsequent fluorescent reporter assembly, providing an efficient route to potential ABPs for glycosidase targeting.

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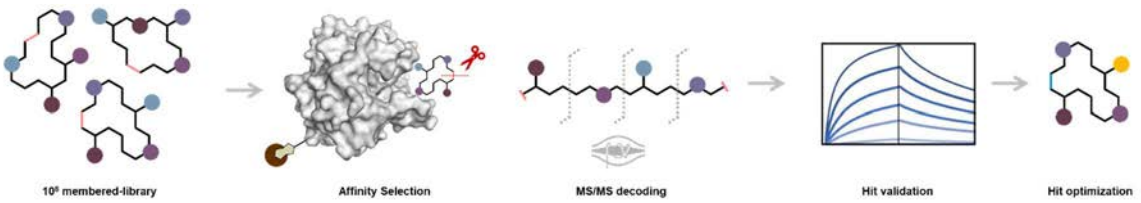
P-20 CycloSEL: A Barcode-Free, Ultra-High Throughput Platform for Synthetic Macrocycle Discovery

J. Miguel Mata[1,2], Jingming Liu[1,2], Sebastian J. Pomplun[1,2]

[1]Division of Medicinal Chemistry, Leiden Academic Centre for Drug Research, Universiteit Leiden, The Netherlands
[2]Oncode Institute, The Netherlands

Synthetic macrocycles are a promising class of therapeutics due to their ability to engage challenging biological targets with high specificity and affinity. However, their large-scale discovery has been largely limited by the established molecular biology based decoding technologies, restricting the explorable chemical diversity and druggable target classes. Here, we report CycloSEL: a barcode-free, fully synthetic ultra-high throughput macrocycle discovery platform that integrates combinatorial synthesis of Self-Encoded Libraries decodable by *de novo* tandem mass spectrometry with affinity selection of high-affinity binders from complex ultra-large mixtures. We established a robust synthesis, cyclization and decoding workflow and prepared several libraries of 'druglike' macrocycles in the beyond rule of five space. We performed affinity selections with ~16million macrocycles against the oncology target Carbonic Anhydrase IX, achieving excellent enrichment of true binders. Our most potent validated hit show a binding affinity of ~1 nM. Current efforts are being applied to expanding the target portfolio to other disease-relevant proteins. Overall, CycloSEL expands the scope of synthetic macrocycle screening, providing a scalable and versatile tool for identifying potent ligands against therapeutic targets.



P-21

Accelerating Hit Discovery Through Combination of *In Silico* Screening with Semi-Automated Synthesis

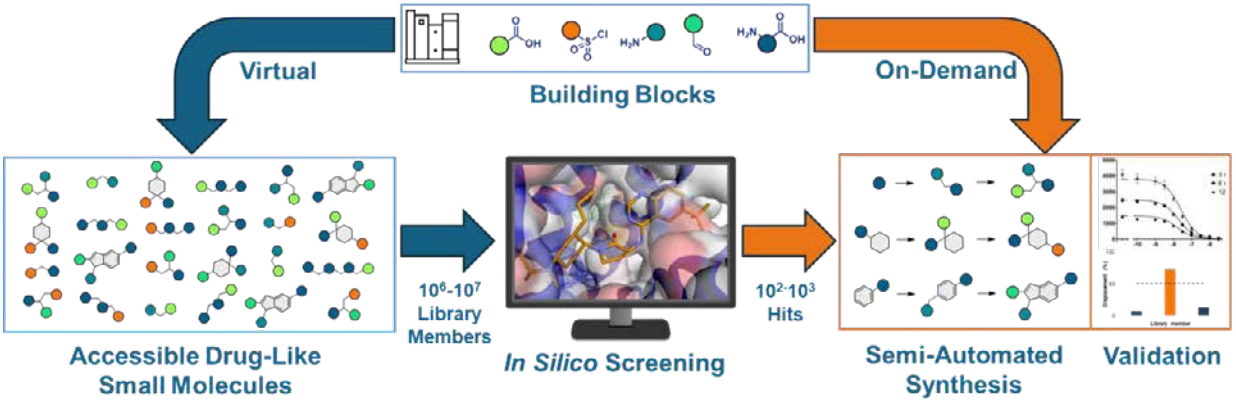
S.M.McKenna, Leiden/NL, M.Šícho, Prague/CZ, W.Jesper, Leiden/NL, A.Bernatavicius, Leiden/NL, E.van der Nol, Leiden/NL, C.van der Horst, Leiden/NL, L.H.Heitman, Leiden/NL, G.J.P. van Western, Leiden/NL, S.Pomplun, Leiden/NL

Dr. Sean M. McKenna, Leiden University, Einsteinweg 55 2333 CC Leiden, NL

Identifying novel ligands for therapeutically relevant proteins of interest is one of the fundamental challenges in drug discovery. Screening multimillion member compound libraries requires massive investment in materials, infrastructure & time.[1] In contrast, *in silico* screening offers a rapid method for hit detection. However, this approach requires significant computing power, typically results in high rates of false positive hits, and is always dependent upon costly and time-consuming preparation of large numbers of compounds for validation.[2]

To overcome this crucial synthetic bottleneck, we expanded upon the combinatorial chemistry toolbox to develop a platform for rapid semi-automated parallel synthesis of drug-like small molecules. Simultaneously, we created virtual libraries of ~10 million compounds based upon application of in-house synthetic building blocks. Leveraging *in silico* screening tools such as molecular docking and pharmacophore modelling, hits can be identified from the virtual libraries, then prepared in a matter of days, streamlining the identification and validation of hundreds of hits at a time.

In this study we showcase the screen-make-test workflow in the identification of ligands for the immuno-oncology target CCR2 and the clotting-related target thrombin.[3,4] Focusing on allosteric antagonists of CCR2, virtual screening followed by parallel synthesis and validation in a radioligand binding assay resulted in identification of two novel and distinct hits. This platform can inform expanded *in silico* screening campaigns of ultra large compound libraries, and has the potential to accelerate the discovery of novel ligands for almost any structurally elucidated protein target.



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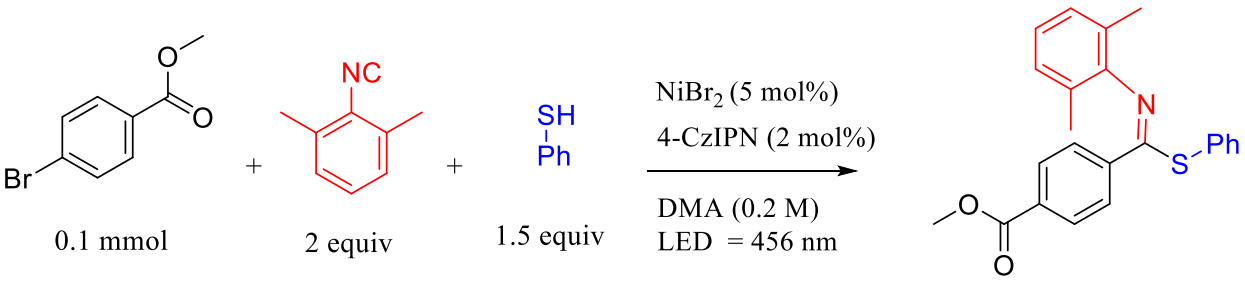
P-22

Using renewable feedstock in dual transition-metal/photoredox catalysis and isocyanide insertion

Diego Meneses

Isocyanides are versatile C1 building blocks due to their ability to react with nucleophiles, electrophiles, and radicals. They are valuable inputs for multicomponent reactions (MCRs) and one-pot cascade processes. In organometallic chemistry, isocyanides often act as ligands for transition metals, altering the electronic distribution of the isocyano moiety and enabling unique reaction pathways. Palladium-catalyzed isocyanide insertion processes have gained prominence in recent years, but the use of earth-abundant and inexpensive base metals in these reactions is underexplored.[1] On the other hand, cross-coupling reactions are essential in organic synthesis, but diverse reaction conditions often require individual optimization. In this context, we want to merge homogeneous catalysis with nickel, under visible-light-driven redox conditions, to adress this challenge. [2]



This approach accommodates a broad range of $C_{(sp2)}$–(hetero)atom coupling reactions with a self-adjustive catalytic system. The system's adaptability allows for the classification of various nucleophile classes in cross-coupling reactions. Sulfur-based nucleophiles are employed with the goal of mimicking disulfide bonds in peptides for their modification.

Following the 12 principles of circular chemistry, it is reasonable to move towards the use of valuable renewable feedstock such as phenolic acids. These are especially valuable, as they can be used as precursors of species that can undergo oxidative addition in the catalytic system.

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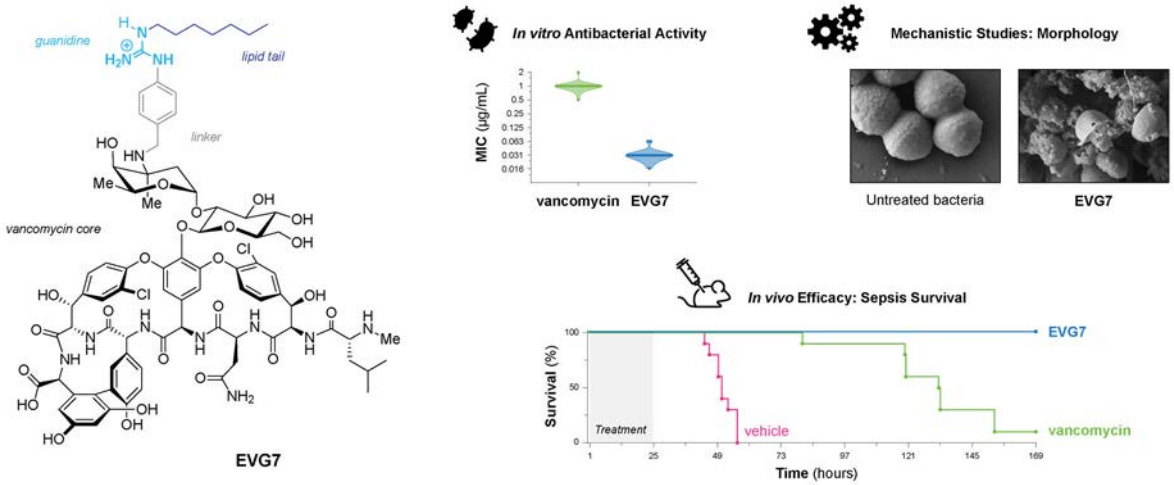
P-23 **Preclinical Evaluation of Guanidino Lipoglycopeptide Antibiotic EVG7 with *Best-in-Class* Potential**

Elma Mons, Emma van Groesen, Ioli Kotsogianni, Vladyslav Lysenko, Nathaniel I. Martin

Infections caused by methicillin- and vancomycin-resistant bacteria account for more than 0.5 million antimicrobial resistance-associated deaths globally per year. Development of next-generation antibiotics with enhanced activity, reduced toxicity, and the capacity to overcome such infections is crucial. Here, we present the guanidino lipoglycopeptides, a novel class of highly potent semisynthetic glycopeptide antibiotics recently developed in the Martin group.[1,2] Our lead guanidino lipoglycopeptide **EVG7** is active against a range of Gram-positive pathogens, including clinically relevant methicillin-resistant *S. aureus* (MRSA) and various vancomycin-resistant strains. **EVG7** exhibits dramatic enhancements in antibacterial activity of up to >1000-fold compared to vancomycin and other clinically used (lipo)glycopeptide antibiotics. Furthermore, **EVG7** is also able to overcome vancomycin resistance while having a low propensity to induce resistance itself. Evaluation of **EVG7** in validated *in vivo* infection models also demonstrate its superiority compared to vancomycin. The therapeutic potential of **EVG7** is further supported by a recently completed 7-day repeat-dose study which showed a lower risk of nephrotoxicity at relevant dose levels.

Guanidino lipoglycopeptide antibiotic **EVG7** has the potential be a safer alternative to vancomycin. Further preclinical evaluation – including biodistribution studies, efficacy in other infection models, and IND-enabling toxicity studies – is ongoing at this moment. These studies are expected to result in a spin-off company or licensing of the technology to interested pharmaceutical industry partners that will continue the development of **EVG7** towards first-in-human trials.



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P-24 Development of peptidomimetic compounds for EVI1-CTBP disruption and acute myeloid leukemia treatment

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Acute myeloid leukemia (AML) is a highly aggressive form of cancer and in particular patient subgroups with overexpression of the transcription factor EVI1 are characterized by poor prognosis. The protein-protein interaction (PPI) between EVI1 and CTBP has been recently shown as essential for AML progression. We leveraged Alphafold multimer to identify a short linear motif from a disordered EVI1 region that drives binding to CTBP. We developed binding and competition assays and showed that peptidomimetic modalities can disrupt the EVI1/CTBP interaction. Via alanine scanning and truncation analysis, we identified hot spot residues within the sequence and developed a short sequence of 7 residues that can disrupt this PPI effectively. Notably, our lead variants have significant stability in human serum with over 80% intact compound after 24h. Via unnatural amino acid scanning and the introduction of a covalent warhead we further boosted the potency of the peptidomimetic. Current research devolves around improving cell penetration of our EVI1/CTBP inhibitor. Taken together we have developed a promising starting point for future AML targeted therapeutics.

P-25

Encounters in Synthesis of ADP-Ribose Analogues

Koen J. Rijpkema[a], Jeroen D.C. Codée[a], Dmitri V. Filippov[a].

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Adenosine diphosphate ribosylation (ADP-ribosylation) is a post-translational modification crucial for a proper immune response.[1] Accordingly, several viruses encode glycosidases that reverse native ADP-ribosylation.[2] Potent inhibitors for these glycosidases are in high demand, a need primarily addressed through the high-throughput screening of small molecules.[3] In contrast, we aimed to design and synthesize potent inhibitors by structurally mimicking the enzymatic target, namely ADP-ribosylated substrates. By employing an iterative approach,[4] we were able to produce several highly potent (low nanomolar) inhibitors for which we applied various organic transformations, such as the stereoselective establishment of *C*-glycosides via distant Cram chelation control followed by regioselective tosylation and ring closure. Furthermore, during our synthetic explorations we overcame several peculiar side reactions such as intramolecular reductions and the fragmentation of protective groups. Rather than focussing on the successful total syntheses of the ADP-ribose analogues themselves, we would like to put these unusual reactions on center stage.

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P-26

Non-Directed *Meta* C─H Amination of Electron Rich Arenes Via Pd/S,O-ligand/Norbornene Cooperative Catalysis

Soma Rudi

The direct C─H functionalization of aromatic substrates without the need for chelating directing groups could allow for the efficient synthesis of complex organic structures including a number of medicinally relevant compound. By using a catalytic norbornene mediator together with a palladium/S,O-ligand catalyst system, the natural site selectivity of the C─H functionalization can be reversed and the electronically disfavoured *meta* position of electron rich arenes can be functionalized. This orthogonal site selectivity can provide a simple, one-step route towards the functionalization of positions that would otherwise be challenging to directly access.

P-27 Design, synthesis and evaluation of fluorinated pyrazolidine-3,5-dione derivatives as potential PET tracers for the $P2Y_{12}$ receptor

E. Johanna L. Stéen[a,b], Anne van der Schatte Olivier[a], Berend van der Wildt[a], Pedro Pereira[a], Robert C. Schuit[a], Khaled Alkayal[a], Leopoldo J. Gabella Carena[a], Sjors van Klaveren[a], Barbara Zarzycka[b], Wissam Beaino[a], Iwan J.P. de Esch[b] and Albert D. Windhorst[a]

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Introduction: The $P2Y_{12}$ receptor ($P2Y_{12}R$) plays an important role in neuroinflammation and is a promising biomarker for PET imaging of anti-inflammatory microglia. However, a key challenge with developing PET tracers for the $P2Y_{12}R$ is identifying high affinity ligands with ideal properties for brain permeability. The aim of the present study was to develop a series of fluorinated pyrazolidine-3,5-dione derivatives, designed based on a lead structure (**1**, Figure 1) and evaluate their potential as $P2Y_{12}R$ PET tracers.[1]

Methods: Structural modifications of lead **1** were guided by molecular docking studies in a crystal structure of $P2Y_{12}R$ in complex with the antagonist AZD1283 (PDB code: 4NTJ)[2] using an energy-based docking protocol implemented in ICM-Pro (version 3.9-1c, Molsoft L.L.C.). Likelihood for brain uptake was assessed with the CNS PET MPO and the BBB score. Binding affinities were determined in *in vitro* radioligand binding assays for both the human and rat $P2Y_{12}R$.[3] Radiolabeling was performed and PET imaging, *ex vivo* biodistribution and metabolism studies were performed in healthy female Wistar rats.

Results: The compounds were synthesized in moderate to good yields (13-83%) and showed high affinities for the receptor. K_i values were ranging from 1.21 to 5.66 nM for the human receptor, and between 36.8-77.0 nM for the rat receptor. Compound **2c** (K_i = 5.26±3.66 nM) was selected for ^{18}F-labeling and subsequent *in vivo* evaluation. [^{18}F]**2c** was synthesized in a radiochemical yield of 4.1±0.2%, and a high radiochemical purity (≥99%). PET imaging revealed low brain uptake and this was further confirmed by *ex vivo* biodistribution. The tracer showed a rapid metabolism with only 17% intact tracer remaining in the blood pool 15 min post-injection.

Conclusions: A series of fluorinated pyrazolidine-3,5-dione derivatives were designed and synthesized, demonstrating strong affinity for the $P2Y_{12}R$. The tracer candidate selected for evaluation showed sub-optimal behavior *in vivo* with low brain uptake, which might be a result of the rapid metabolism or poor properties for brain permeability due to a potential deprotonation. On-going work is directed toward finding new chemical entities via virtual screenings.

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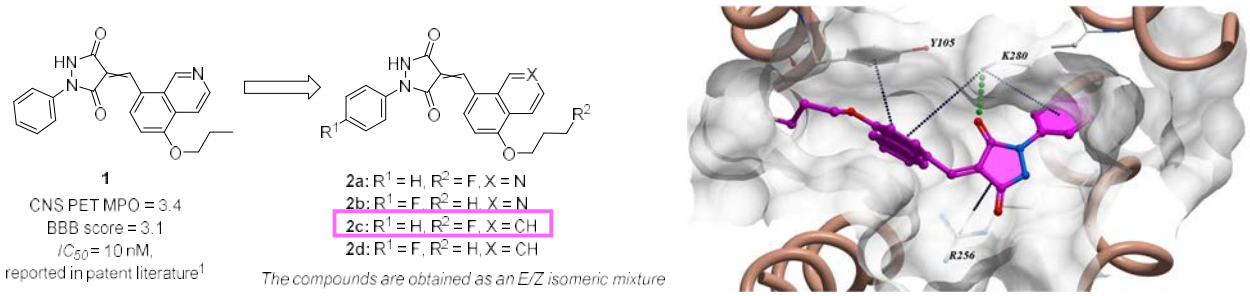

Figure 1. Fluorinated derivatives based on lead **1** and the predicted docking pose for **2c** in the $P2Y_{12}R$.

P-28

Stereoselective Synthesis of Bicyclic Scaffolds by Cu/Ir Tandem Catalysis

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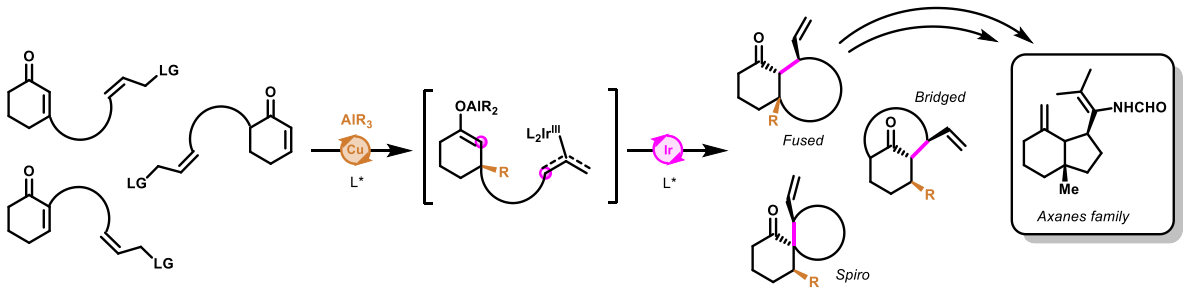
Tandem catalysis refers to a process where two or more closely coupled catalytic steps occur sequentially in one synthetic operation, without isolating intermediates between steps.[1] Each catalytic step produces an intermediate that serves as the substrate for the next one, allowing for the efficient formation of multiple bonds and stereogenic centers in one single procedure. Such strategy has garnered significant attention in recent years due to its capacity to streamline complex reactions and improve both the economics and the environmental acceptability of a process.[2]

Modern transition metal catalysis offers unique opportunities for the chemo-, regio-, and stereoselective construction of new covalent bonds. Notably, the Cu-catalyzed conjugate addition of nucleophiles to cyclic enones generates a metal enolate intermediate which makes it suitable for tandem catalysis in combination with Ir-catalyzed asymmetric allylic alkylation.[3] While the amalgamation of these two independent reactions in an intermolecular fashion has already been reported, no example of an intramolecular version has yet been developed.[4–6]

Our strategy is thus based on the enantioselective Cu-catalyzed conjugate addition of organoaluminium reagents to cyclic enones bearing a tethered chain containing an allylic functionality for subsequent intramolecular asymmetric Ir-catalyzed allylic alkylation. Depending on the position and the length of the tethered chain, bridged, fused, and spirocyclic scaffolds of different ring sizes can be obtained. Moreover, all the stereoisomers of each product are accessible by simply switching the combination of absolute configuration of the ligands. Lastly, many of these bicyclic scaffolds being present in nature, the strategy could be applied to the synthesis of biologically active natural products such as axanes.[7]



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P-29

Reversible metal-binding with the flick of a light switch

Luuk Stringer, David Villarón Salgado, Sebastiaan van Elst, Dr. ing. Daniël L. J. Broere

EDTA is well-known for its strong affinity to various metal ions, such as Ca^{2+}, Fe^{3+}, Mn^{2+}, and Cu^{2+}.[1] It has many applications in metal extraction, ranging from detergents to medicine.[2,3] Typically, EDTA is first deprotonated to generate the $EDTA^{4-}$ ligand, which then binds with metal ions to form stable complexes. Once the metal ion is bound to the ligand, it is quite difficult to recover the metal ions from these complexes. One way to decoordinate the metal from its chelator is by using a large excess of acid to protonate EDTA into H_4EDTA, allowing the release of free metal ions into the solution.[4] However, this approach generates large amounts of acidic waste and suffers from non-quantitative recovery of the EDTA ligand.

We hypothesized that an alternative way to release metal ions from strong chelators in a controlled manner can be achieved by inducing large conformational changes in the ligand through an external stimulus such as light. To this end, we designed and synthesized chelating ligands based on photoswitchable moieties. In the Z-isomer, the chelators should bind very strongly to the metal ion, but we hypothesize that upon photoisomerization to the E-isomer the binding strength drastically decreases (Figure 1), allowing for facile dechelation of the metal ion from the chelator, possibly eliminating the need of strong acids.

In this presentation we will discuss new photoswitchable EDTA-inspired chelating ligands. In addition to ligand synthesis, metal binding studies, photoswitching abilities, and dechelation studies will be presented.

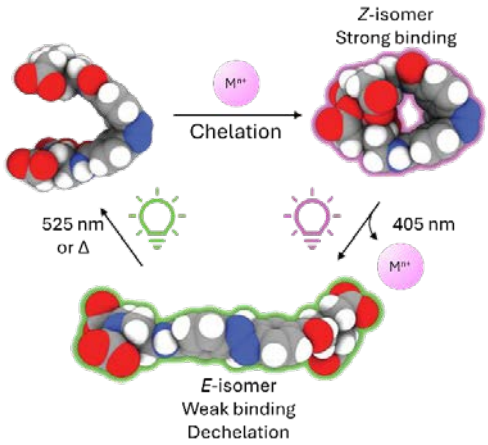

Figure 1: Schematic depiction of a photoswitchable chelator with strong and weak binding modes.

P-30

A Diversified Approach to Functionalized Piperazinone *via* Post Ugi Cyclization and Diastereoselective Nucleophilic Addition

Shashank Tripathi[ab] and Han Zuilhof[ab]*

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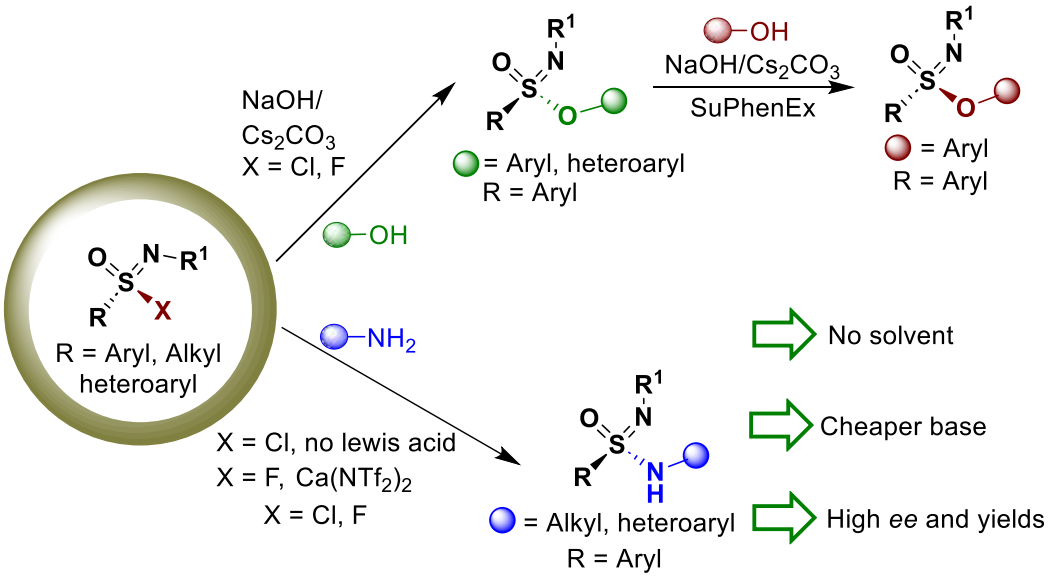
Abstract: Abstract: Mechanochemical S(VI) exchange reactions are developed on chiral S(VI)–F and S(VI)–Cl centers that are fast, solvent-free, high–yielding, and enantiospecific. We use this approach to synthesize a range of sulfonimidate esters and sulfonimidamides from sulfonimidoyl fluorides and chlorides under mild reaction conditions. The broad scope of this method is demonstrated by its successful reactivity with a range of phenols, and both primary and secondary anilines. Furthermore, we also successfully achieve substitution in 4–nitrophenol–derived S(VI) species with substituted phenols (SuPhenEx). We successfully showcased the late-stage functionalization of various drugs. This approach is faster, greener, and reduces the need for the formation of fluorinated species, while retaining many of the advantages of SuFEx and related S(VI) substitution reactions.



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P-31 Title: Probing the interplay between ubiquitination and ADP-ribosylation

Authors: Max C.M. de Vries, Gerbrand J. van der Heden van Noort

Ubiquitination, like PARylation, is a crucial post-translational modification (PTM) primarily known for its role in protein degradation and cell cycle progression. Recent studies have shown that these PTMs can occur in tandem in HeLa cells, with ubiquitin being ADP-ribosylated at multiple amino acid sites. However, the interplay between these modifications remains poorly understood.

To explore this underexplored part of the ubiquitin code, we synthesized hydrolase-stable Ub-ADPr conjugates. These probes were created using solid-phase peptide synthesis (SPPS) enabling the incorporation of non-natural amino acids at desired positions combined with copper-catalyzed azide-alkyne cycloaddition (CuAAC), to mimic the native Ub-ADPr isotypes but rendering them non-susceptible to hydrolase or protease activities. These probes can be used for future interactome identification through pull-down experiments from whole-cell lysate, followed by tandem mass spectrometry. The outcomes of these experiments could provide valuable insights into the interacting partners of these specific substrates and contribute to a deeper understanding of the functional role of the interplay between ubiquitination and ADP-ribosylation.

P-32

Fragment-based design of dual-activity H_1R and H_4R antagonists with superior efficacy in a mouse model for allergic conjunctivitis.

Peter Weber[1], Rogier Smits[2], Jac Wijkmans[2], Herman Lim,[1,2] Mabel Dekker[1], Tiffany van der Meer[1,2], Mounir Andaloussi[2], Henry F. Vischer[1], Matt J. Chapin[3], Paul Gomes[3], Andy Whitlock[3], Maikel Wijtmans[1], Rob Leurs[1,2], Iwan J.P. de Esch[1,2,*]

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Abstract:

Histamine receptors are G-protein-coupled receptors that play pivotal roles in health and disease and consist of four distinct subtypes (H_1R, H_2R, H_3R and H_4R). The H_1R is a well-established drug target and a plethora of H_1R antihistamines have been marketed to alleviate, with limited success, various pruritic and allergic conditions, including allergic rhinitis and allergic conjunctivitis. Interestingly, the H_4R is also associated with inflammatory processes, but no H_4R-related drugs have so far reached the clinic. The contributions of these histamine receptor subtypes on inflammation have ignited interest in polypharmacological strategies.

Starting from a quinazoline-containing fragment hit[1] and using computer-aided drug design, synthesis, and pharmacological evaluation, we developed quinazoline-containing compounds with different and well-defined activity and polypharmacology profiles across histamine receptor subtypes. In preclinical studies, the challenges of species differences as well as various ADME-tox properties needed to be navigated, ultimately yielding several promising clinical candidates. The dual-activity H_1/H_4 ligands exhibit potent anti-inflammatory effects in several preclinical models. Here, we will focus on the development of GD136, a clinical candidate that shows promising *in vivo* efficacy for the treatment of allergic conjunctivitis and firmly establishes the clinical potential of dual-activity H_1R/H_4R ligands.

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P-33

Non-Innocent Behavior of Aromatic Isocyanides under Visible Light: A Pathway to Thioformimidates

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Thioformimidates play an important role in peptide modifications as the protection group [1]. The most common method for the synthesis of thioformimidates involves *S*-alkylation of thioformamides with aryl or alkyl halides. However, these processes often suffer from several limitations and purification problems due to the instability of thioformamides and limited substrate scope. Alternatively, thioformimidates can also be synthesized from isocyanides and thiols triggered by UV-light or AIBN initiator [2]. Generally, this reaction proceeds with the formation of a thiyl radical in the presence of UV-light or AIBN followed by thiyl radical addition on the isocyanide to generate an α-thioimidoyl radical [3]. This radical can then undergo H-abstraction from thiols to form the final thioformimidates product. Despite the convenience of this method, less attention has been directed to this pathway due to the following reasons: a) the requirement of UV-light; b) poor reaction efficiency; c) the formation of unwanted side products such as 1,1-bisthiolation; d) C-S bond scission of the intermediate α-thioimidoyl radical, leading to the generation of isothiocyanates.

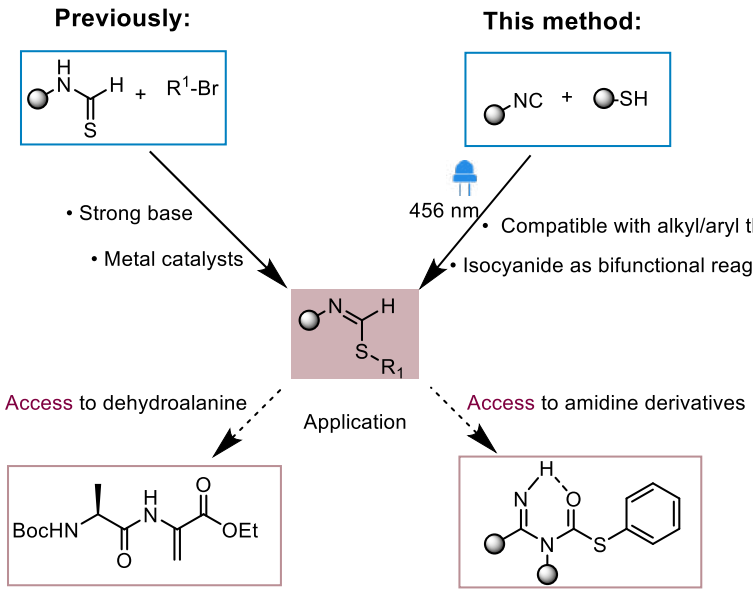

Figure 1. Visible light-mediated synthesis of thioformimidates.

Previously, we desighed a photocatalyst-free pathwy to spirocyclic scaffolds from tryptamine-derived isocyanides by employing blue light [4]. Given the significance of thioformimidates and the current limitations in versatile, sustainable synthetic methods, we focused on developing an innovative, photocatalyst-free, visible-light-driven approach for their synthesis. This study marks a significant advance in the field, as it not only improves existing methods for accessing thioformimidates but also reveals a previously camouflaged role of isocyanides in generation of thiyl radicals.

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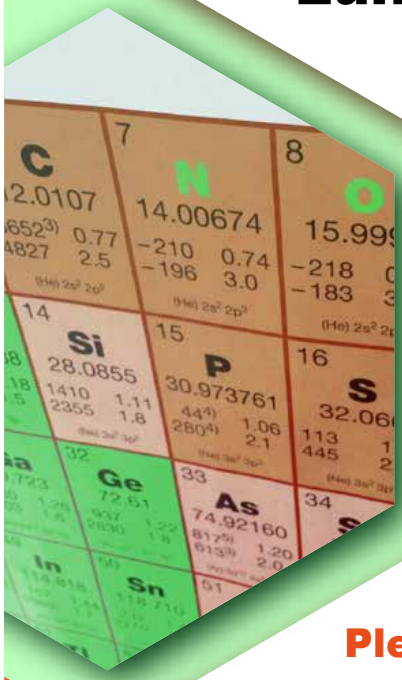

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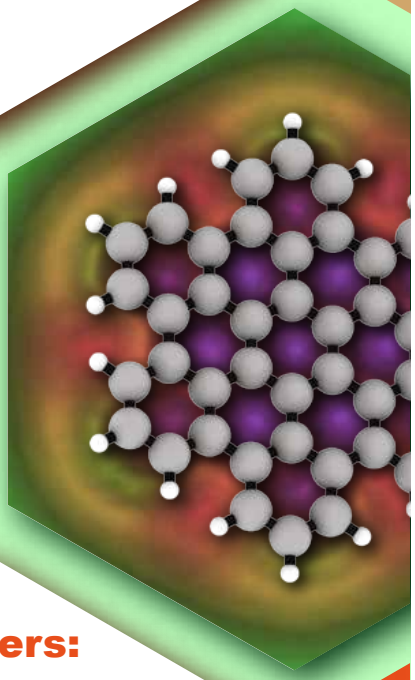

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