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March 30th & 31st

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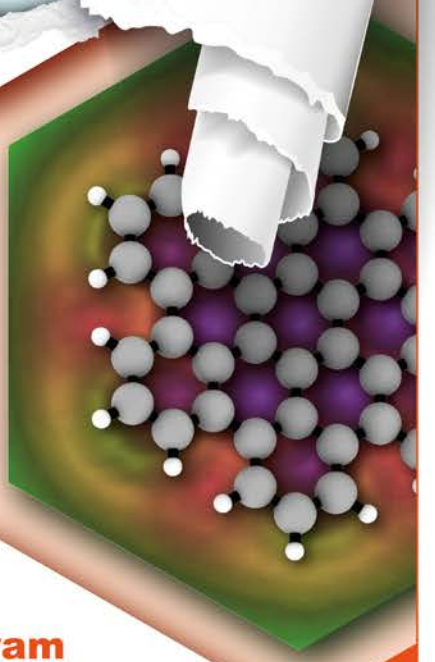

For students, academia and industry

2023 National Symposium

Organic Chemistry Division

MCCB
Medicinal Chemistry & Chemical Biology

Program

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Program Thursday March 30 2023

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10.50	**Jordy Saya (UM)** *Enhancing the speed of the Passerini reaction*	**Erianna Alvarado Melendez (UU)** *Glycoengineering lipooligosaccharides on bacterial pathogens*
11:10	**Wouter Remmerswaal (LEI)** *Competing reactive intermediates in stereoselective glycosylation reactions*	**Icaro Simon (VU)** *The PhotoSwitch Workflow: A computational workflow to design and virtually screen photoswitchable molecules*
11:30	**Michiel Uiterweerd (RUG)** *Total synthesis of lugdunomycin by a biomimetic reaction cascade*	*Margot van Weijsten (RU)* *The effect of antigen valency on B-cell targeting in Rheumatoid Arthritis*
11:50	**Lunch (in FIRE) & MCCB ALV (ALV starts at 12.30 (in AIR))**	
	KEYNOTE II (in AIR) Chair: Kim Bonger	
13:00	**Gonçalo Bernardes (Cambridge University – Online Lecture)** *Translational Chemical Biology*	
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14:05	**Daan Bunt (RUG)** *Divergent Total Synthesis Of Meroterpenoids From Ganoderma Mushrooms*	**Keiko Oike (TUD)** *Immobilisation of oleate hydratase on solid supports*
14:25	**Thomas Roose (VU)** *Iron-catalyzed carbene transfer to isocyanide*	**Jun Yang Ong (UU)** *Chemoenzymatic Synthesis of 13C Enriched Sialic Acids*
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18:00	**Dinner**	
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Program Friday March 31 2023

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10.05	**Brendan Horst (VU)** *Total Synthesis Of Complex Indole Alkaloids By A Nitroaryl Transfer Cascade Reaction*	**Enebie Ramos Cáceres (RU)** *Lightening up NETosis*
10:25	**Benjamin Spitzbarth (TUD)** *Redox-controlled shunts in a synthetic chemical reaction cycle*	**Chuanbao Zheng (WUR)** *Modular design for proteins assembling into antifouling coatings: case of gold surfaces*
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12:20	**Qiang Zheng (RUG)** *The isocyanide SN2 reaction*	**Lifeng Sun (UU)** *Well-defined Heparin Mimetics can Inhibit Binding of Trimeric Receptor Binding Domains of SARS-CoV-2 in a Length Dependent Manner*
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14:25	*Announcement and Lecture winner The MCCB thesis prize 2023 – Iwan de Esch*	
15:00	**Ilja Voets (TuE)** *Ice-cold and crystal-clear: resolving the interfacial dynamics of individual ice-binders by nanoscopy to engineer novel cryoprotective compounds with modular activity*	
15:45	**SOC & MCCB Prizes for best oral and poster presentations**	
15:55	**Closing followed by drinks (in FIRE)**	

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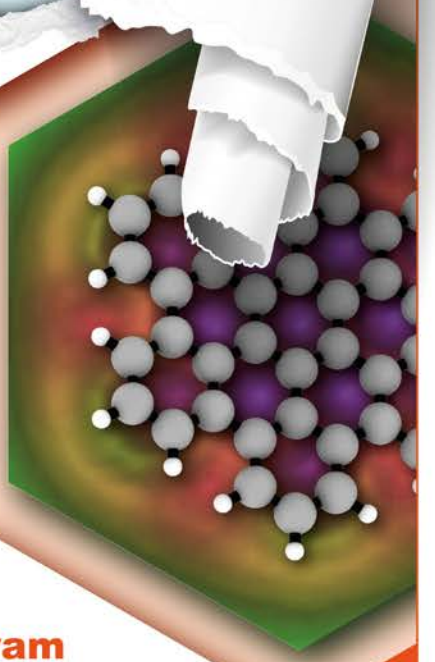

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ORAL PRESENTATIONS

O-01

Enhancing the speed of the Passerini reaction

Jordy M. Saya, Claudio Ferdeghini, Minghui Wu, Prabhat Ranjan, Martien A. Wurdeman, Romano V. A. Orru

Multicomponent reactions (MCRs), in which three or more reagents are incorporated in the skeleton of the product, are an effective tool to create high molecular diversity and complexity in an efficient manner. Within this field, isocyanide-based multicomponent reactions (IMCRs) have claimed a dominant position as a result of the ambiphilic character of the isocyanide functionality. In 1921, Passerini discovered the first IMCR in the reaction of isocyanides, aldehydes, and carboxylic acids giving α-acyloxy carboxamides. Even though the first discovery of the reaction dates back a century, current research continues to provide new applications and new variations of these flexible reactions.[1-2] In this studies, we demonstrated that 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as a cosolvent in organic solvents enhances the speed of the classical Passerini reaction. We are currently investigating if we can use these conditions in Passerini polymerizations to generate poly(ester amide)s with higher molecular weight.

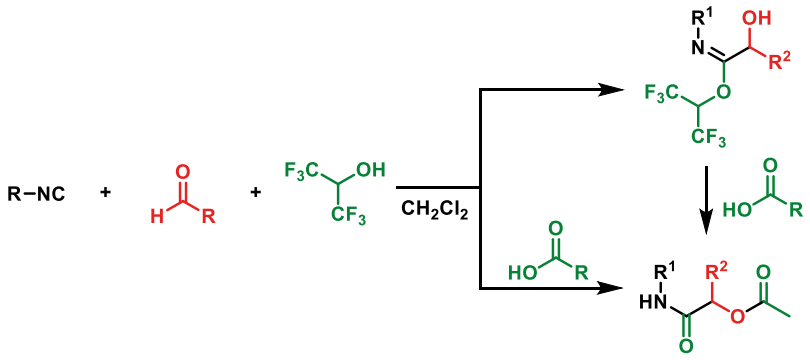

Figure 1: The influence of HFIP in the Passerini reaction.

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O-02 Competing reactive intermediates in stereoselective glycosylation reactions

Wouter A. Remmerswaal,[1] Gijsbert A. van der Marel[1] & Jeroen D. C. Codée[1]

[1] Leiden Institute of Chemistry, Leiden University, Einsteinweg 55, 2333 CC Leiden, The Netherlands.

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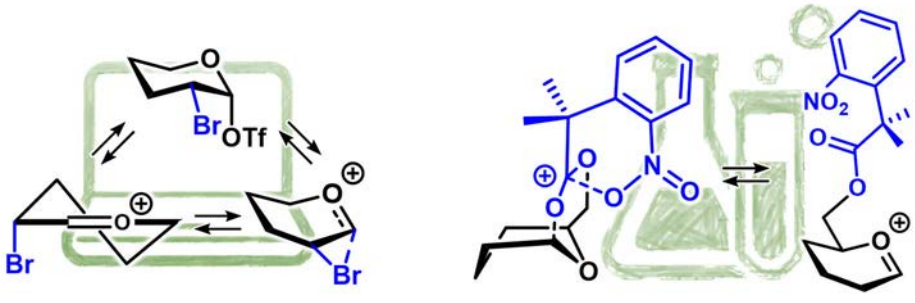
The synthesis of glycans is of paramount importance in understanding their role in biological processes. However, the stereoselective synthesis of complex glycans is challenging due to a lack of understanding of the central reaction of carbohydrate chemistry, the glycosylation reaction. The stereoselectivity of this reaction strongly depends on which reactive intermediates can form from the parent glycosyl donor.[1] These reactive intermediates generally can rapidly interconvert and each intermediate participates in a unique reaction pathway. The competition between the various pathways dictates the overall stereoselectivity of the glycosylation reaction.[2] We have studied these scenarios through a combinatory approach of experimental and computational chemistry. We will here present our recent results on the stereodirecting effect of C-2-halogens. Upon activation of 2-halo glycosyl donors, oxocarbenium ions and halonium ions may form. The ratio between these cations depends on the hyperconjugative capabilities of the halogen and the ring strain in the halonium ions.[3] We also report on our studies on glycosyl donors bearing distal acyl groups. [4] These donors can form both oxocarbenium ions and bridged dioxolenium ions and the competition between these drives the stereoselectivity of the reaction.[5] The stereodirecting capacity of these groups can be further tuned through functionalization. The 2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl protecting group provides stereoselective reactions through the formation of dioxolenium ions stabilized by nitro-participation. These 'double participation' dioxolenium ions are in competition by direct stabilization of the oxocarbenium ion by the nitro-moiety.[6] The characterization of these competitive reaction pathways will enable the rational design of synthesis routes towards complex oligosaccharides.



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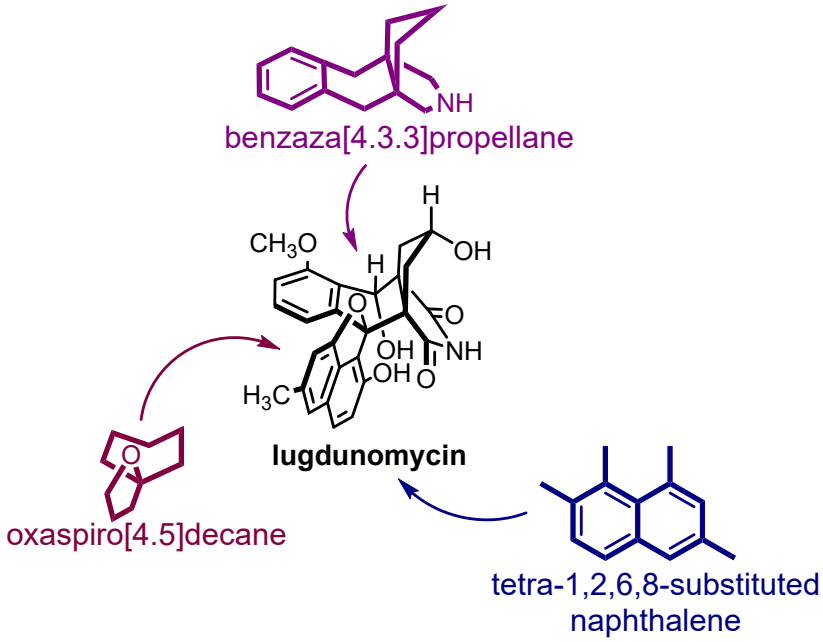
O-03 Total synthesis of lugdunomycin by a biomimetic reaction cascade

Michiel T. Uiterweerd and Adriaan J. Minnaard

The actinobacterial genus *Streptomyces* is associated with the production of a wide plethora of structurally diverse and medicinally important secondary metabolites.[1] A large number of these compounds are the angucyclinones, some of which have undergone enzymatic rearrangements and have complex structures.[2,3] Lugdunomycin is a rearranged angucyclinone derivative, it is produced in small amounts by *Streptomyces* sp. QL37.[4] Its structure poses a formidable synthetic challenge, since it contains highly functionalised aromatic functionality, a rare propellane-motif and five stereocenters. In our lab we have executed the first total synthesis of lugdunomycin by performing a biomimetic Diels-Alder reaction cascade between two natural product precursor compounds. In my talk I will discuss our endeavours in the synthesis of the precursor natural products and show how we constructed lugdunomycin using the reaction cascade.[5]



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O-04

Glycoengineering lipooligosaccharides on bacterial pathogens

Erianna I. Alvarado Melendez[a]*, Hanna de Jong[a], Marc Wösten[b] & Tom Wennekes[a]

[a] Department of Chemical Biology and Drug Discovery, Utrecht Institute for Pharmaceutical Sciences and Bijvoet Center for Biomedical Research, Utrecht University, Utrecht, The Netherlands.

[b] Department of Biomolecular Health Sciences, Division Infectious Diseases and Immunology, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands.

Bacterial glycans play an important role in the interaction with their host. Lipooligosaccharides (LOS) are the most abundant cell surface glycoconjugates on the outer membrane of most Gram-negative bacteria. They contribute to the rigidity and impermeability of the cell wall and can stimulate the host immune system. Some bacteria display LOS capped with sialic acid as terminal epitopes to mimic host glycans. This phenomenon, known as molecular mimicry, can help bacteria hijack host biological mechanisms to facilitate infection and evade the host's immune system. To further investigate the functional role of sialic acid-capped LOS at the molecular level, it is important to have tools readily accessible for the detection and manipulation of Neu5Ac on glycoconjugates of live bacteria.

Here we report a novel strategy to incorporate Neu5Ac with a reporter group onto the lipooligosaccharides of a selection of Gram-negative bacteria. We show that the native sialyltransferases of several pathogens are able to accept extracellular unnatural sugar nucleotides, thereby introducing unnatural sialosides onto their LOS. This new technique, Labeling via Bacterial Native Sialyltransferases, is an efficient and rapid way to screen for bacteria that can decorate their glycoconjugates with exogenous sialic acid. This strategy complements other glycoengineering techniques, such as Metabolic Oligosaccharide Engineering (MOE) and Selective Exo-Enzymatic Labelling (SEEL), and can help to dissect host-bacterial glycan interactions.

O-05

The PhotoSwitch Workflow: A computational workflow to design and virtually screen photoswitchable molecules

Icaro A. Simon[1], Evert J. Homan[2], Maikel Wijtmans[1], Rob Leurs[1], Iwan J.P. de Esch[1], Barbara A. Zarzycka[1]

[1] Division of Medicinal Chemistry, Faculty of Science, Amsterdam Institute for Molecular and Life Sciences, Vrije Universiteit Amsterdam, 1081 HZ Amsterdam, The Netherlands.
[2]Science for Life Laboratory, Department of Oncology-Pathology, Karolinska Institutet, S-171 76 Stockholm, Sweden

Photoswitchables are molecules that reversibly change configuration (*cis*/*trans* or E/Z) upon the incidence of light. This configurational change results in isomers with distinct geometric, electronic, and physical-chemical characteristics, which can be explored to dynamically modulate the activity of biological targets[1]. However, despite extensive efforts, the design of photoswitchable probes remains challenging, as the insertion of the photoresponsive group into a target-optimized molecule can lead to a significant decrease in binding affinity/bioactivity, reduced solubility, and can result in chemical probes with little distinction between isomers, i.e., small isomeric shifts[2]. Thus, here we present a computational workflow to design and virtually screen photoswitchable molecules. This workflow, implemented in Knime Analytics Platform[3], retrieves, filters, and processes bioactivity data for any given target available in the ChEMBL database. Next, it inserts the photoresponsive group in a suitable position at the core (*azologization*) or the periphery (*azoextension*) of the template ligand. Finally, the workflow uses the curated data from the template ligand together with high-throughput ligand-based and structure-based virtual screening tools to assess the photoswitchable ligands and estimate their isomeric binding affinity shifts (ΔpKi). In three retrospective case studies, our workflow was able to accurately predict the active isomer and successfully estimate the ΔpKi of photoswitchables for the β_2-adrenergic and histamine H_3 receptors. Thus, we expect this workflow will facilitate the design of novel photoswitchable probes with enhanced bioactivities and improved isomeric shifts for G protein-coupled receptors and many other targets, enabling the light-induced dynamic control and the enlightening of the pharmacological and physiological mechanisms of these targets.

Acknowledgment: *This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 875510. The JU receives support from the European Union's Horizon 2020 research and innovation program and EFPIA and Ontario Institute for Cancer Research, Royal Institution for the Advancement of Learning McGill University, Kungliga Tekniska Hoegskolan, Diamond Light Source Limited.*

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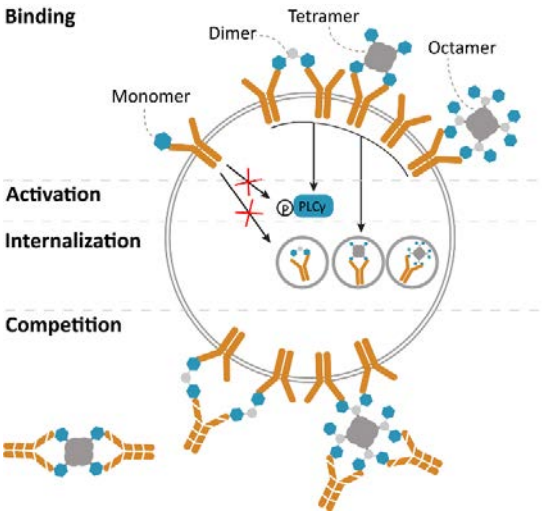
O-06 The effect of antigen valency on B-cell targeting in Rheumatoid Arthritis

M.J. van Weijsten, K.R. Venrooij K. Bonger

In Rheumatoid Arthritis (RA), B-cells mistakenly recognize autoantigens and produce anti-citrullinated antibodies. [1] Current therapies supress the entire immune system, increasing the risk of infection. [2] Our lab aims to optimize the specific elimination of autoreactive B-cells by targeting their B-cell receptor with an autoantigen construct. Valency has a large effect on the physicochemical and biological properties of an antigen. [3] In this study, we investigated how antigen valency affects BCR targeting in a cell model of RA.

We have synthesized a monomer, dimer, tetramer, and octamer of the same autoantigen, CCP4. Binding studies showed that the dimer, tetramer, and octamer have a significantly higher affinity to the BCR than the monomer. Furthermore, the dimer, tetramer and octamer internalised after 5-15 min. Finally, we show that the dimer has less competition with free-floating antibodies than the tetramer and octamer. In conclusion, the CCP4 dimer is sufficient to enhance binding, activate the B-cells and internalize into the lysosomes. We are currently working on strategies for selective elimination of autoreactive B-cells in RA using our CCP4 constructs.



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O-07 Abstract Lunteren 2023

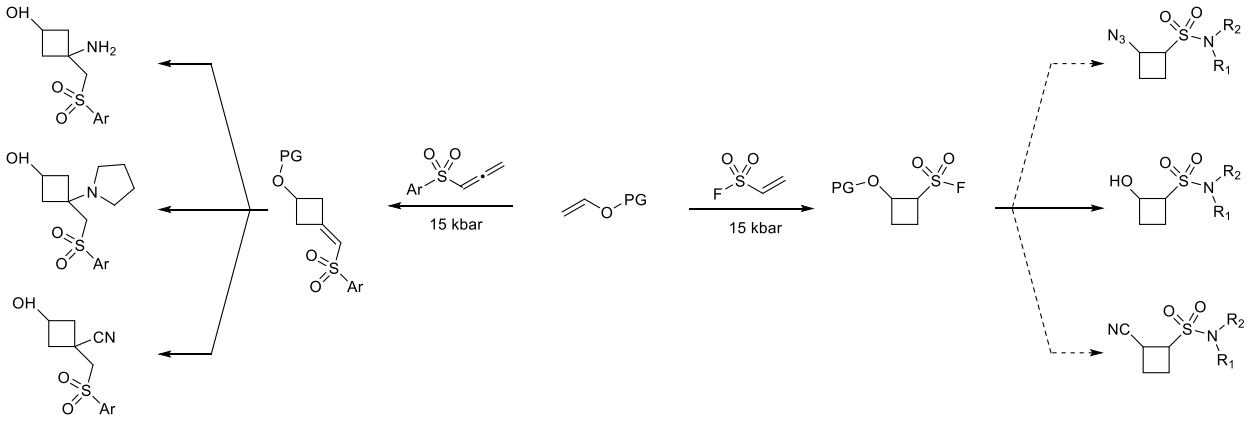
Authors details
Mathilde Janssen
Radboud University Nijmegen
Under supervision of Prof. Floris Rutjes and Dr. Daniel Blanco-Ania

Title
Synthesis of Cyclobutanes for Fragment-Based Drug Discovery

Abstract

Cyclobutanes offer unique opportunities in medicinal chemistry, because of their distinctive puckered structure [1]. Fragment-based drug discovery (FBDD) has become a well-established approach in medicinal chemistry to generate lead compounds. In current libraries, 3D small-ring fragments, such as cyclobutanes, are underrepresented because of the limited number of ways to synthesize them[2]. Therefore, we set out to synthesize novel FBDD-libraries containing cyclobutane fragments. Previously, various synthesis routes towards substituted cyclobutanes using [2+2] cycloadditions have been described [3]. However, in most cases alkenes with bulky and flat aromatic groups are required for the successful synthesis. As a result, molecules are generated that are not appropriate for FBDD, because of their size (>300 Da) and non-versatile substituents for further library preparation. Non-standard methods, like high pressure (10–15 kbar) and photoflow chemistry provide a unique opportunity to synthesize novel cyclobutane scaffolds using [2+2] cycloadditions. We used various alkenes and allenes with a variety of functional handles to afford 1,2- and 1,3-substituted cyclobutanes. For example, ethenesulfonyl fluoride (ESF) was used to form cyclobutanesulfonyl fluorides, which can be further modified using SUFFEX chemistry [4]. Subsequently, the synthesized scaffolds will be transformed into focused fragment libraries and screened for target binding.

Relevant keywords
Cyclobutanes, [2+2] cycloaddition, fragment-based drug discovery.



O-08 Divergent Total Synthesis Of Meroterpenoids From Ganoderma Mushrooms

Daan Bunt

Ganoderma mushrooms have been used in Asian traditional medicine for over 2,000 years. Consumption of these medicinal mushrooms is said to promote longevity and vitality, and its preparations are used therapeutically to treat various chronic diseases. Over 900 unique natural products have been isolated from Ganoderma mushrooms, many of which display interesting bioactivities. The most recently discovered class of compounds are the meroterpenoids, which have a characteristic conjugated structure consisting of a hydroquinone ring with an unsaturated γ-ketoacid. The meroterpenoids fornicin A, fornicin D, and ganodercin D, found in mushrooms of the Ganoderma genus, have been prepared in a concise and divergent synthesis route starting from two readily accessible building blocks. THP-protection of a phenolic hydroxyl group under basic conditions was developed, a protocol that adds to the versatility of this protecting group.

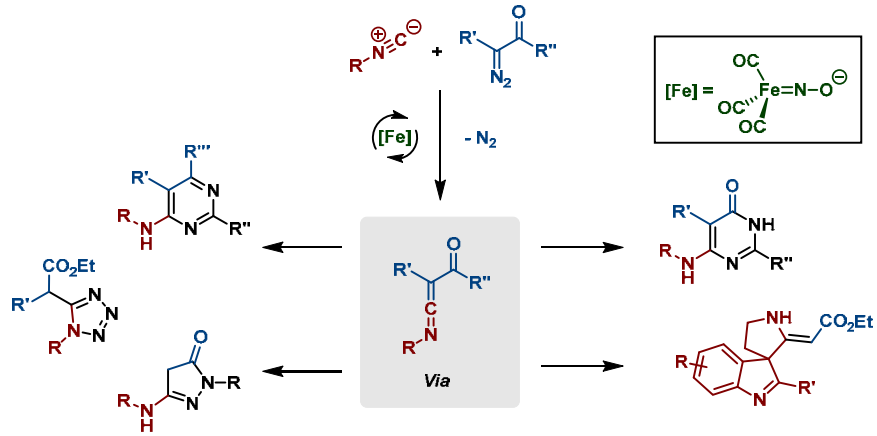
O-09

Iron-catalyzed carbene transfer to isocyanide

Application in the synthesis of heterocycles

Thomas R. Roose,[a] H. Daniel Preschel,[a] Helena Mayo Tejedor,[a] Jasper C. Roozee,[a] Trevor A. Hamlin,*[a] Bert U.W. Maes,*[b] Eelco Ruijter*[a] and Romano V.A. Orru*[a,c]

[a] Department of Chemistry & Pharmaceutical Science Vrije Universiteit Amsterdam
[b] Department of Chemistry, University of Antwerp
[c] Department of Organic Chemistry, Maastricht University



Isocyanides display unique reactivity as is evident by their use in cascade chemistry, multicomponent reactions, and transition metal catalysis. In the latter field, isocyanides have predominantly been used as inputs for Pd-catalyzed imidoylative cross-coupling reactions.[1] A new, less explored reactivity involves carbene transfer reactions, via *in situ* generated transition metal-carbenes. The coupling of carbenes and isocyanides leads to ketenimines, which have proven to be versatile synthetic intermediates.[2] To date, only a handful of cascade processes based on transition metal-catalysed transfer of carbenes to isocyanides has been reported.[2] Unfortunately, these methods often use rare and precious noble metals such as Pd or Rh, while base metal-catalysed processes remain scarce. We now report the use of the electron rich ferrate complex $[Fe(CO)_3NO]N(n\text{-}Bu)_4$[3] in the carbene transfer reaction of α-diazo esters to isocyanides to form ketenimine intermediates, which can be transformed *in situ*. For example, addition of amidines as 1,3-bisnucleophiles results in medicinally relevant 4-aminopyrimid-6-ones.[4]. In addition, we applied this methodology in the formal total synthesis of (±)-aspidospermidine, (±)-aspidofractinine and (±)-limaspermidine, using tryptamine derived isocyanides as input.

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O-10

Brain-inspired Chemical Reaction Networks

Dr. Albert S. Y. Wong

University of Twente, Faculty of Science and Technology,

Department of Molecules and Materials

Abstract: In this talk, I will discuss a crucial experimental stepping stone to gear current design efforts in chemical reaction networks (CRNs)—interconnected webs of chemical reactions—into the direction of neuromorphic systems. Artificial neural networks can perform intelligent tasks and in some cases outperform the human brain. The advances in Machine Learning and particularly its integration in our everyday life, however useful, mark the end of an era: Our current demands in computing using semiconductor-based hardware simply requires too much energy and is unsustainable. Alternative technologies that mimic the dynamical character of the human brain are urgently needed. Here, I will show our recent progress in creating CRNs that are capable of history-dependent functions (giving rise to behaviors such as synchronization, resonance and adaptation). My design uses a microfluidic platform to couple simple bistable reaction networks into inter- and randomly connected CRNs. The simple means employed to create networks with tunable and scalable interactions will open the door to explore how connectivity among structurally similar CRNs can provide functions for the merits of in-memory processing capacity. It will be significantly different from any reported work on chemical computing, as it will use chemical feedback loops as the minimal computing units to develop a general method which allows 'artificial' chemical reactions to become 'intelligent'.

Selected publication(s):

1. Kriukov, D. V.; Koyuncu, A. H.; **Wong, A. S. Y.*** "History dependence in a chemical reaction network enables dynamic switching" *Small* **2022**, 2107523.
2. Semenov, S. N.[#] & **Wong, A. S. Y.**[#] *et al.* "Rational Design of Functional and Tunable Oscillating Enzymatic Networks" *Nat. Chem.* **2015**. ([#]authors with equal contributions)
3. **Wong, A. S. Y.*** & Huck, W. T. S.* "Grip on Complexity in Chemical Reaction Networks" *Beilstein J. Org. Chem.***2017**.

O-11 Immobilisation of oleate hydratase on solid supports

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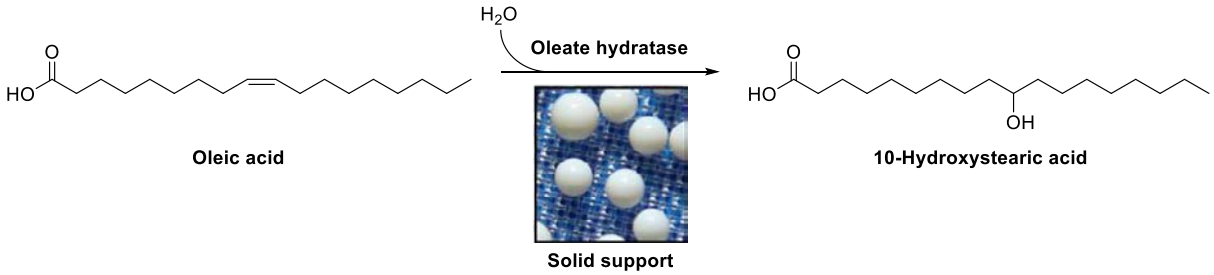
Oleate hydratase (Ohy) is an FAD dependent enzyme that catalyzes the hydration of unsaturated fatty acids forming hydroxy-fatty acids. This catalytic activity makes this enzyme a potential catalyst for valorization of biorenewable fatty acids into products for the chemical and polymer industry. However, the solubility of fatty acids in aqueous media is strongly limited and high amounts of co-solvents are necessary for solubilization, which are reported to deactivate the enzyme.

In this regard, we studied the immobilisation of the Ohy from *Rhodococcus erythropolis* on commercially available solid supports. Immobilisation is a powerful technique to improve the performance of enzymes in biotechnological processes. The carrier binding separates the enzyme from the reaction medium and prevents protein aggregation, thus, often leading to higher stability. We used a screening kit to test carriers (spherical polymeric beads) with different interaction types: a) covalent, b) adsorption, c) cationic, d) anionic and e) His-Ni^{2+}. The immobilisation process was evaluated by determination of the protein concentration in the supernatant before and after immobilisation as well as with activity measurements. 18 different carriers (Immobeads) from ChiralVision were screened. In general, high binding efficiencies of the enzyme to the carrier were observed. While the enzyme was inactivated when immobilized to most carrier types, the anionic carriers IB-ANI-3 and IB-ANI-4 (quaternary ammonium functionalized polystyrene) exhibited the highest residual activity amongst all carriers.

The activity recovery for these immobilized enzymes was approximately 30 % compared to the free enzyme, which is a good value taking into account that enzymes are often (partly) deactivated during the immobilization process. For all other tested supports, the activity recovery was below 5 %. This suggests that a strong binding of the enzyme to a support causes a (partly) deactivation of the enzyme possibly related to partly unfolding and to slower substrate diffusion into the active site. Subsequently, we studied the stability of the enzyme against different co-solvents and higher temperature. Leaching of the immobilized enzyme into the supernatant and storage stability were investigated as well. Lastly, we conducted recycling experiments with the immobilized enzyme. In conclusion, we report the first successful immobilisation of Ohy on solid carriers by ionic interaction.



O-12 Chemoenzymatic Synthesis of 13C Enriched Sialic Acids

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Sialic acid or N-acetylneuraminic acid (Neu5Ac) is a ubiquitous sugar residue found in the gut mucus layer. It is commonly found at the terminal location of sugar chains, and its prior removal is necessary for gut microbiota to gain access to the rich underlying sugar residues.

Metabolism of glycans by gut bacteria leading to the production of short chain fatty acids (SCFAs) is of great interest because of their known health benefits to human hosts. Through Stable Isotope Probing (SIP), 13C labelling of Neu5Ac can identify gut microbiota able to metabolise Neu5Ac and enable clear distinction of metabolites generated in the Neu5Ac metabolism pathway in the presence of other sugars.

To obtain these 13C enriched sugars, we have developed a facile chemoenzymatic synthesis route from the cheap and commercially available [U-13C]glucose. Chemical synthesis yielded the key intermediate, peracetylated N-acetyl mannosamine ([13C6]Ac4ManNAc) on a gram scale at 21% yield. Subsequently, enzymatic condensation of [13C6]ManNAc with [2-13C]pyruvate gave asymmetrically labelled [13C7]Neu5Ac, which can be used to prepare 3'-SL and 6'-SL through a facile one-pot enzymatic reaction using CMP-sialic acid synthetase and sialyltransferase. Synthesis of other forms of sialic acids are also possible as demonstrated by the synthesis of 2,7-anhydro Neu5Ac.

O-13

Amenamevir by Ugi-4CR

Xin Li

University of Groningen, Supervisor: Alexander Dömling

Amenamevir was first introduced to the Japanese market in 2017 for the treatment of herpes zoster (HZ) infection.[1] Up to now, 1,240,000 patients with HZ have been treated in Japan.[2] As a helicase-primase inhibitor (HPI), Amenamevir has a novel action mechanism from previously reported synthetic nucleoside compounds for the treatment of HZ, including acyclovir, and valacyclovir.[3] In contrast to acyclovir, the non-nucleoside Amenamevir inhibits helicase-primase, thereby suppressing the replication fork progression that separates double DNA strands into two single strands during DNA synthesis. Amenamevir showed superior antiviral activity compared to acyclovir during the DNA synthesis stage when it was used to treat herpes simplex virus (HSV) and varicella-zoster virus (VZV) related diseases,[4,5] Unlike acyclovir, its anti-VZV and anti-HSV activities were not attenuated by viral DNA synthesis in the infected cells. Among four available HPIs, Amenamevir has both anti-HSV and anti-VZV activity, while T157602, pritelivir and BILS 22 BS only have anti-HSV activity.[6, 7] Amenamevir is N-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-N-(2,6-dimethylphenyl)tetrahydro-2H-thiopyran-4-carboxamide-1,1-dioxide. It consists of α-aminoacyl-amide backbone with a C-terminal thiopyrane dioxide, an N-terminal p-1,2,4-oxadiazol-3-yl phenyl, and a 2,6-dimethylphenyl anilid sub-structure.

Herein we report a novel synthesis of Amenamevir exploiting the Ugi-4CR with carboxylic acid **1**, 2,6-dimethylaniline **2**, paraformaldehyde **3**, and 4-(1,2,4-oxadiazol-3-yl)-phenyl isocyanide **4** (Figure 1).

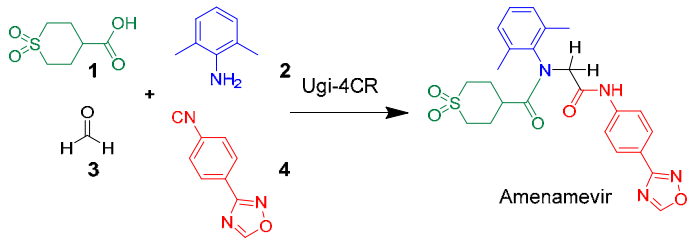

Figure 1. Fast constraction of Amenamevie by Ugi-4CR.

To demonstrate the green chemistry merits of our synthetic approach over the existing ones, we quantified and compared various reaction parameters such as the total yield, reaction time (h), amount of inorganic and organic solvents (mL), number of steps, process mass intensity (PMI), the E-factor and atom economy (AE) (Figure 2). Compared with the Kontani and Xumeng routes,[8,9] our current method not only gives a comparable yield (56%, including the isocyanide synthesis) to Xumeng route (63%, optimized from Kontani route), But outperforms both methods in other categories, such as the reaction time, amount of solvents (organic and inorganic), number of steps, the E-factor and AE, which will result in significant time and cost savings for industrial production. In addition, both Kontani and Xumeng's method require the use of HCl and chlorinated solvents (see ESI†), which does not meet the requirement of green chemistry and produces lots of inorganic waste. Last but not least, both competitor routes are more time and solvent amount consuming, hence less sustainable.

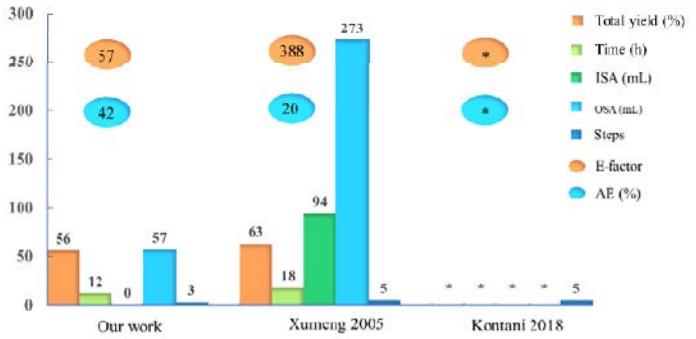

Figure. 2 Bar chart comparison between two representative procedures and our work (including the isocyanide synthesis) for the preparation of **Amenemevir**, including the total yield, reaction time, inorganice and organic waste, numbers of steps, the E-factor and atom economy (AE). *Not reported. The total yield of Kontani method was not reported in the original patent, and total yield of Xumeng method was calculated from the five steps together, the total yield of our method was calculated from three steps including the isocyanide synthesis.

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O-14

PHD LECTURE

TOTAL SYNTHESIS OF COMPLEX INDOLE ALKALOIDS BY A NITROARYL TRANSFER CASCADE REACTION

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Amsterdam Institute of Molecular and Life Sciences,
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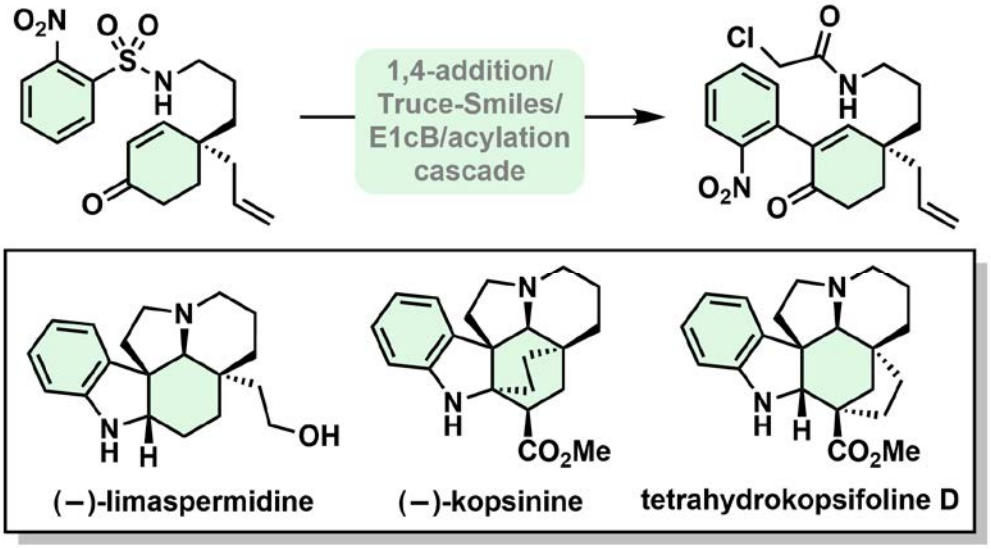
The medicinally relevant alkaloids of the *Aspidosperma* and *Kopsia* genera of flowering plants show high structural complexity, thus forming a challenging target for synthetic chemists.[1] Most syntheses rely on an indole starting material, necessitating the use of protecting groups. An alternative approach involves a late-stage Fischer indole synthesis, which may, however, result in low yields due to poor regioselectivity. In this work, we present a solution to both problems by making use of cascade chemistry.[2] This allows the combination of multiple elementary reaction steps in a single process, and thus inherently contributes to enhanced synthetic efficiency.



We report an intramolecular conjugate addition/Truce-Smiles/E1cB cascade of 2-nitrobenzenesulfonamide-functionalized cyclohexenones as a new entry to the core scaffold of monoterpene indole alkaloids. The method was applied to the asymmetric total synthesis of (−)-limaspermidine, (−)-kopsinilam, and (−)-kopsinine, as well as the framework of the kopsifoline alkaloids. Furthermore, we show that the cascade tolerates various substituents on the nitroarene, opening the way to other natural products as well as non-natural analogues.

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O-15

Redox-controlled shunts in a synthetic chemical reaction cycle

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Abstract

Shunts, alternative pathways in chemical reaction networks, are ubiquitous in Nature, enabling adaptability to external and internal stimuli. We introduce a chemical reaction network (CRN) in which the recovery of a Michael-accepting species is driven by oxidation chemistry. Using weak oxidants can enable access to two shunts within this CRN with different kinetics and a reduced number of side reactions compared to the main cycle that is driven by strong oxidants. Further, we introduce a strategy to recycle one of the main products under flow conditions to partially reverse the CRN and control product speciation throughout time. These findings introduce new levels of control over artificial CRNs, driven by redox chemistry, narrowing the gap between synthetic and natural systems.

O-16 VUF26026: a second-generation photoswitchable ligand for histamine H_3 receptor photopharmacology

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*=co-shared

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Photopharmacology uses photoswitchable ligands as pharmacological tool compounds to yield spatiotemporal control of protein activity with light. Photopharmacology in the G protein-coupled receptor (GPCR) field has been emerging in recent years[1]. Histamine receptors are GPCRs which are key mediators in many pathophysiological processes ranging from inflammation and itching to obesity. The family of histamine receptors consists of four receptors, of which the histamine H_3 receptor (H_3R) is highly expressed in the central nervous system. Moreover, it has been identified as a potential target in diseases such as obesity, narcolepsy, Alzheimer's, and ADHD. Previously, our group published the first generation of photoswitchable H_3R antagonists[2]. Of these, VUF14862 showed interesting photopharmacological properties (>10-fold binding affinity upon illumination) and has proven to be a versatile tool compound. However, the ligand left room for improvement in terms of, e.g., illumination wavelengths, photostationary state and pharmacological properties. In this research, we aimed to improve several key properties by introducing an arylazopyrazole photoswitch. We show that key compound VUF26026 has improved photochemical and pharmacological features compared to our first-generation tool compound.

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[2] Hauwert *et al*. *J. Am. Chem*. Soc., **2018**, 140, *12*, 4232

O-17 Abstract title: **Lightening up NETosis**

Author details: **Ramos Cáceres, E. (Enebie); Bonger, K.M. (Kimberly); E.A.J. Reits (Eric); F.P.T.J. (Floris)**

Abstract:

Neutrophils form the first line of defense of our innate immune system against invading pathogens and inflammation. They kill their targets through a variety of mechanisms, including neutrophil extracellular traps (NETs). NETs are ‘’spiderweb-like’’ structures composed of decondensed chromatin decorated with antimicrobial agents. They form in response to specific stimuli through a peculiar form of cell death called ‘’NETosis’’. During NETosis, the nuclear envelop disintegrates and chromatin is decondensed. In the cytoplasm, decondensed chromatin mixes with the antimicrobial agents, eventually resulting in cell membrane rupture and NET ejection.[1,2]

Although a great deal of the molecular mechanisms of NETosis remain elusive, the antimicrobial functions of NETs are heavily dependent on the activity of myeloperoxidase (MPO). MPO is a heme-containing peroxidase whose main function is to catalyze the conversion of hydrogen peroxide into hypochlorous acid.[2]

In an effort to study neutrophil activity and the process of NET formation *in vitro* and *in vivo*, we have developed an activity-based probe (ABP) specifically targeted against MPO. This ABP is based on a mechanism-based 2-thioxanthine warhead published in literature and is equipped with the environment-sensitive fluorophore 4-N,N-dimethylamino-1,8-napthalimide (4-DMN).[3] This fluorophore becomes fluorescent only in the more hydrophobic environments of the enzymatic surface and has a very low fluorescence intensity in water. These characteristics confer the ABP a ‘’turn-on’’ character that greatly reduces background signal in applications such as live-cell microscopy (Fig. 1). This ABP will allow us to investigate MPO activity in living cells and visualize the process of NETosis in wash-free real time conditions.

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Keywords: **neutrophil, activity-based probe, myeloperoxidase**

Figure:

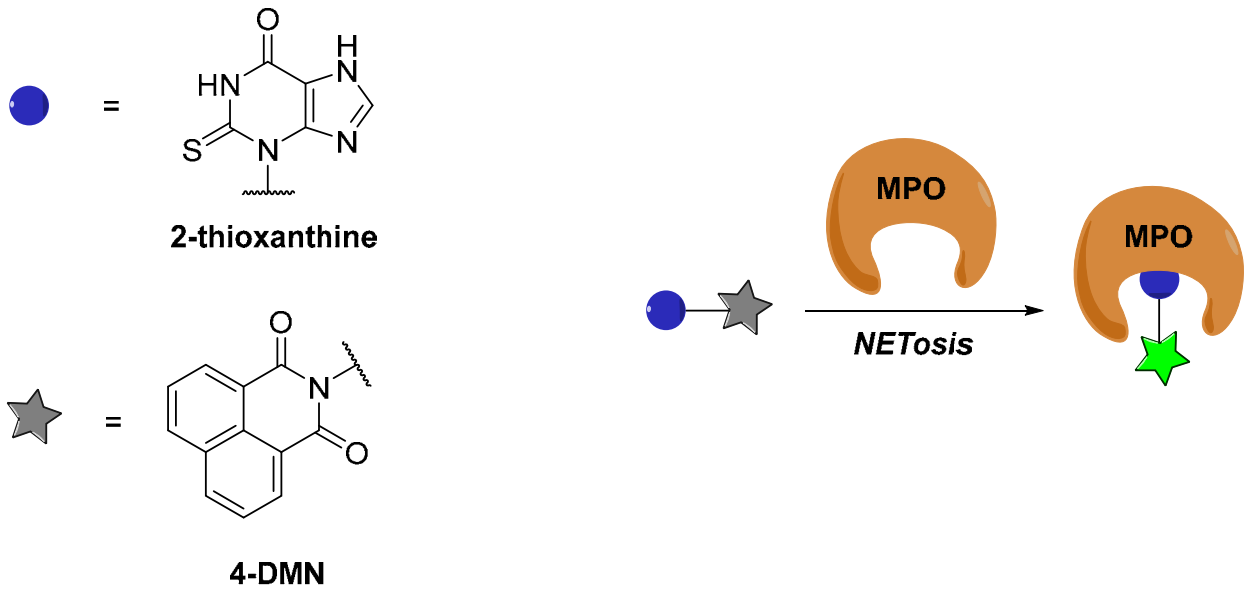

Figure 1. General concept of the environment-sensitive fluorescent ABP design. The environment-sensitive 4-DMN group contained in the activity-based probe ''turns on'' only when MPO is active and able to be inhibited by the 2-thioxanthine warhead.

O-18

Modular design for proteins assembling into antifouling coatings: case of gold surfaces

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Abstract:

Rendering surfaces antifouling is a crucial challenge whenever man made solid materials need to be interfaced with biological fluids, living cells or tissues. Physical or chemical properties of solid surfaces can readily be tuned by via thin molecular layers physically or chemically attached to them. Previously, we have proposed a modular design for a protein assembling into antifouling coatings.[1] We have demonstrated its efficacy for silica and plastic surfaces, here we demonstrate its application to gold surfaces. We believe the design can have important applications in streamlining the molecular assembly of biosensor surfaces.

[1]. Nicolò Alvisi, Chuanbao Zheng, Meike Lokker, Victor Boekestein, Robbert de Haas, Bauke Albada, and Renko de Vries "Design of Polypeptides Self-Assembling into Antifouling Coatings: Exploiting Multivalency." Biomacromolecules 23.9 (2022): 3507-3516.

O-19

Asymmetric Total Synthesis and Structure Revision of Di-*O*-acyl Trehalose DAT_2, an Antigenic Glycolipid from *M. tuberculosis*

Zonghao Lin[1], Jeya Prathap Kaniraj[1], Mira Holzheimer[1], Martine Gilleron[2], Johan Hekelaar[1], Adriaan J. Minnaard[1]*

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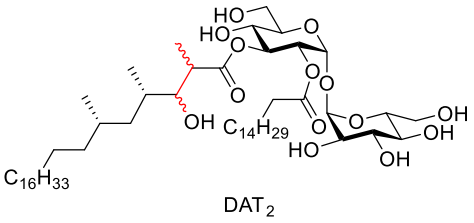
2. Institute of Pharmacology and Structural Biology (IPBS), Toulouse, France

DAT_2, a glycolipid located on the outer part of the mycobacterial cell wall, exhibits Mincle-activating properties[1, 2]. Our previous research demonstrated that HPLC-MS data of the putative structure assigned to natural DAT_2 did not match with natural samples[3].



DAT_2

Herein we disclose the asymmetric total synthesis of DAT_2 and three of its diastereomers, and the determination of its correct structure. Our synthesis uses highly stereoselective aldol reactions and crotylations for the formation of the α-methyl and β-hydroxyl units, and a late-stage Shiina esterification of the acyl chains to the trehalose core. The diastereomers of mycolipanolic acid and DAT_2 were analyzed by ^{1}H NMR, HPLC-MS/MS and GC-MS and compared with the authentic natural product. The study culminated in a revised structure of mycolipanolic acid and DAT_2. All four diastereomers of DAT_2 activate the human and mouse pattern recognition receptor Mincle but the natural DAT_2 diastereomer is most potent.

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O-20

The isocyanide S_N2 reaction

Pravin Patil[#], Qiang Zheng[#], Alexander Dömling*

ABSTRACT

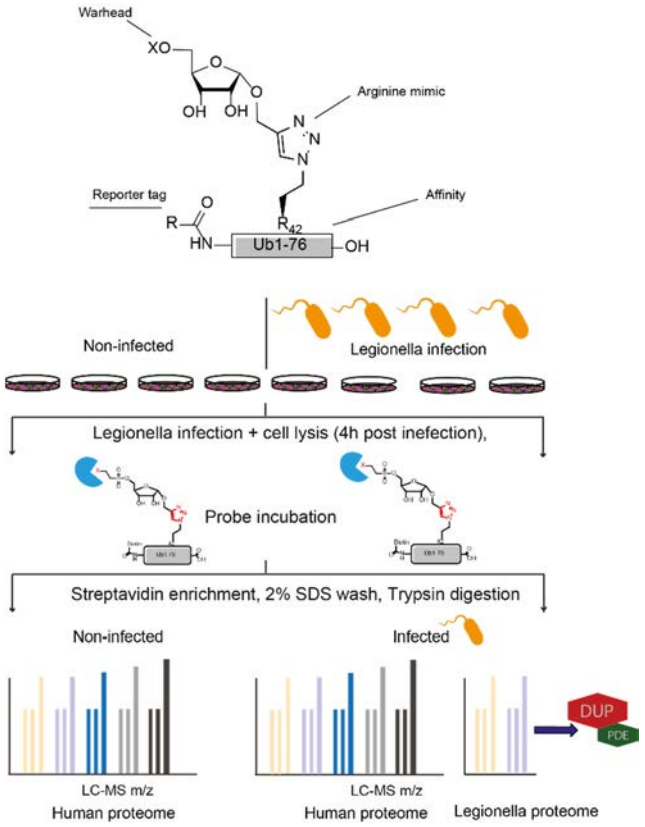
The nucleophilic substitution reaction (S_N2) is one of the oldest, yet very useful organic transformations and has found widespread applications for the synthesis of drugs and natural products. Typically, cyanide, oxygen, nitrogen, sulfur, or phosphorous nucleophiles replace a halogen or sulfonyl ester leaving group to form a new bond between the nucleophile and the electrophile. Isocyanides display an unusual versatile chemistry based on their C-centered lone pair and the C-centered frontier orbitals leading to radical, and multicomponent reactions. Surprisingly, the nucleophilic character of isocyanides has never been explored in S_N2 reactions. We discovered that isocyanides react as versatile nucleophiles in S_N2 reactions with alkyl halides in a general manner to afford highly substituted secondary amides by *in situ* hydrolysis of the intermediate nitrilium ion. The novel 3-component reaction has a broad scope regarding the structures of the isocyanide and electrophile components, functional group compatibility, scalability, use for late-stage modification of a drug and synthesis of highly complex compounds otherwise not easily accessible from simple precursors. Significantly, the isocyanide nucleophile comprises an unusual Umpolung amide carbanion synthon R-NHC(-)=O, useful as an alternative to the classical amide coupling.

O-21

Authors: Max S. Kloet, Gerbrand J. van der Heden van Noort

Keywords: Ubiquitin, Activity-based-probes, pathogenic enzymes

Activity-based profiling of legionella effectors



Work-flow of a pulldown utilizing ubiquitin-phosphoribose mimicking probes to capture *Legionella pneumophila* effector enzymes. The probes were tested in two groups, HEK cells infected with Legionella or non-infected cells and analyzed using proteomics.

Ubiquitination is the attachment of a 76 amino acid protein onto substrate proteins, a vital post translational modification (PTM) in eukaryotes. Upon infection of host cells the *Legionella pneumophila* bacterium releases effector enzymes that hijack the host-ubiquitination pathways, amongst which is the SidE-family. In the presence of NAD^+ The mono-adenosine-di-phosphate-ribose transferase (mART) domain of these multidomain proteins first modifies ubiquitin on Arg42 to form a reactive ubiquitin adenosine-diphosphate-ribose (Ub-ADPr) intermediate.[1] Ub-ADPr is then transferred to the phosphodiesterase (PDE) domain and reacts with the serine residue of host substrate proteins to form a serine-phosphoribosyl (Ser-PR) linkage between the targeted protein and ubiquitin. Ubiquitination in this non-canonical way results in the recruitment of ER-remodeling proteins and the formation of a Legionella containing vacuole which is crucial in the onset of legionnaires disease. This process is regulated by Legionella itself via DupA, another effector that cleaves the PR-linkage in order to maintain a proper cellular homeostasis.[2] In the process of performing the cleavage DupA forms a covalent intermediate using His67 of its active site. We aim to target DupA using this histidine and generate an activity-based probe to profile the activity of bacterial

enzymes during legionella infection. Synthesis of the probes combines furanose chemistry and peptide chemistry and the bond between ribose and ubiquitin is generated using click-chemistry. Warheads were effectively installed on the 5'-OH of ribose and ubiquitin was equipped with reporter molecules such as biotin or rhodamine. We developed and tested ubiquitin-based probes equipped with a reactive warhead on recombinant protein and verified reactivity of our probes in lysate of HEK cells infected with Legionella. Our data shows that we were able to pulldown DupA and DupB, which opens the opportunity to profile other pathogens and investigate whether these prokaryotes utilize a similar mechanism of infection.

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2) D. Shin *et al*., Mol Cell **77**, 164–179 (2020)

O-22

Well-defined Heparin Mimetics can Inhibit Binding of Trimeric Receptor Binding Domains of SARS-CoV-2 in a Length Dependent Manner

Lifeng Sun, Pradeep Chopra, Ilhan Tomris, Roosmarijn van der Woude, Lin Liu, Robert P. de Vries, and Geert-Jan Boons*

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ABSTRACT: The emergence of new SARS-CoV-2 variants and the dangers of long-covid necessitates the development of broad acting therapeutics that can reduce viral burden. SARS-CoV-2 employs heparan sulfate (HS) as an initial cellular attachment factor, and therefore there is interest to develop heparin as a therapeutic for SARS-CoV-2. Its use is, however, complicated by structural heterogeneity and the risk of causing bleeding and thrombocytopenia. Here, we describe the preparation of well-defined heparin mimetics by controlled head-to-tail assembly of HS-oligosaccharides having an alkyne or azide moiety by copper-catalyzed azide-alkyne cycloaddition (CuAAC). Alkyne and azide-containing sulfated oligosaccharides were prepared from a common precursor by modifying an anomeric linker with 4-pentynoic acid and by enzymatic extension with an *N*-acetyl-glucosamine having an azide moiety at C-6 ($GlcNAc6N_3$), respectively followed by CuAAC. The process of enzymatic extension with $GlcNAc6N_3$ followed by CuAAC with desired alkyne containing oligosaccharides could be repeated to give compounds composed of twenty and twenty-seven monosaccharides, respectively. The heparin mimetics could inhibit the binding of SARS-CoV-2 spike or RBD to immobilized heparin or to Vero E6 cells. The inhibitory potency increased with increasing chain length and a compound composed of four sulfated hexasaccharides linked by triazoles had a similar potency as unfractionated heparin. Sequence analysis and HS microarray binding studies with a wide range of RBDs of variants of concern indicate they have maintained HS binding capabilities and selectivities. The heparin mimetics exhibit no- or reduced binding to antithrombin III and platelet factor 4, respectively which are associated with side effects.

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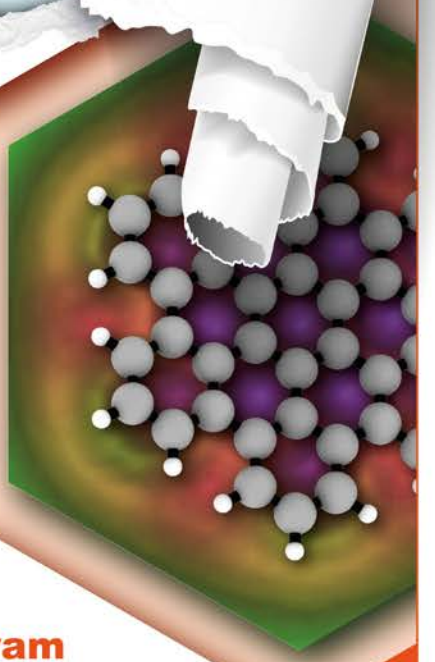

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POSTER PRESENTATIONS

P-01 Reformatting improved CXCR4 nanobodies for biophysical detection methods

Keywords: phage display panning, proximity detection probes, click chemistry

Stephanie Anbuhl

Co-Authors: Nick Bergkamp, Simon Mobach, Claudia Perez, Marco Siderius, Martine Smit, Raimond Heukers

The chemokine receptor CXCR4 and its chemokine ligand CXCL12 play an important role in immune cell migration, hematopoiesis, and cardiovascular development. Furthermore, CXCR4 is overexpressed on a wide variety of cancer cells. CXCR4 was the first GPCR targeted by camelid-derived variable domains of heavy chain-only antibodies (single-domain antibodies, also known as VHH or nanobodies). Although these are valuable tools to detect and antagonize the receptor, all of them bind to the extracellular side of CXCR4 and displace CXCL12. In this study, we aimed to identify new nanobodies with higher affinities and potencies, against previously untargeted epitopes of CXCR4 and/or with new functionalities. We performed DNA immunizations followed by single or multiple phage-display panning rounds under variable selection pressure using excess of CXCL12 or existing nanobody VUN400, followed by screening and next generation sequencing. Additionally, higher order multivalent nanobody-formats were generated to maximize ligand displacement potencies. The generated nanobodies and formats displayed improved affinities, modulated CXCR4 clustering, antagonized CXCL12-induced signaling with picomolar potencies and showed differing preferences for particular small molecule-bound receptor conformations. Binders were developed into new probes for detecting endogenous CXCR4 clusters using either nanobody-based time-resolved fluorescence- or bioluminescence resonance energy transfer (TR-FRET and BRET) with luciferase-fused and fluorescently labeled nanobodies and proximity ligation assay (PLA) using oligo-conjugated nanobodies. Taken together, a broad panel of new CXCR4 targeting molecules and formats with picomolar affinities and new modes of action were identified. Some of these were further developed to accommodate different technologies for the investigation of endogenous CXCR4 clusters with high sensitivity and resolution. This new toolbox can provide new insights in CXCR4 and its oligomerization partners in cancer.

P-02 VUF26026: a second-generation photoswitchable ligand for histamine H_3 receptor photopharmacology

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Photopharmacology uses photoswitchable ligands as pharmacological tool compounds to yield spatiotemporal control of protein activity with light. Photopharmacology in the G protein-coupled receptor (GPCR) field has been emerging in recent years[1]. Histamine receptors are GPCRs which are key mediators in many pathophysiological processes ranging from inflammation and itching to obesity. The family of histamine receptors consists of four receptors, of which the histamine H_3 receptor (H_3R) is highly expressed in the central nervous system. Moreover, it has been identified as a potential target in diseases such as obesity, narcolepsy, Alzheimer's, and ADHD. Previously, our group published the first generation of photoswitchable H_3R antagonists[2]. Of these, VUF14862 showed interesting photopharmacological properties (>10-fold binding affinity upon illumination) and has proven to be a versatile tool compound. However, the ligand left room for improvement in terms of, e.g., illumination wavelengths, photostationary state and pharmacological properties. In this research, we aimed to improve several key properties by introducing an arylazopyrazole photoswitch. We show that key compound VUF26026 has improved photochemical and pharmacological features compared to our first-generation tool compound.

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P-03

Computational binding analysis of H_3 photoswitchable antagonists VUF14738 and VUF14862

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The histamine H_3 receptor (H_3R) is a class A G protein-coupled receptor predominantly expressed in the central nervous system where it plays an important role in cognitive processes.[1] However, several aspects of H_3R signalling and function in diseases remain elusive. In this context, photoswitchable ligands that can dynamically isomerize between their *trans* and *cis* configuration upon illumination can help investigate these mechanisms.[2] Two successful examples are the photoswitchable H_3 antagonists VUF14738 and VUF14862 which show high affinity differences between their *trans* and *cis* isomers and can thus dynamically modulate H_3 receptor signalling.[3] Here, we present a computational study on VUF14738 and VUF14862, which aims to explain the H_3 affinity difference between isomers. Using the recently published H_3 X-ray structure[4] in combination with molecular docking and molecular dynamics simulations, we provide insights into the binding mode of these antagonists. We explain the 12-fold higher affinity of *cis*-VUF14738 compared to its *trans* isomer by predicting its key interaction with $Y94^{2.64}$ and its stability during simulation, whilst the interactions with $Y194^{ECL2}$ and $F398^{7.39}$ of *trans*-VUF14862 explain its 11-fold higher affinity compared to its *cis* isomer. Lastly, the predicted binding poses corroborate with site-directed mutagenesis data of Y91, Y94, and Y394. Our findings give insights into the binding of photoswitchable H_3 antagonists on a molecular level which can be used to further optimize these ligands to enhance photopharmacological properties.

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P-04 *A cheminformatics workflow for 3D fragment library design*

Tom Dekker[1], Mathilde A.C.H. Janssen[2], Rene W.M. Aben[2], Hans W. Scheeren[2], Daniel Blanco-Ania[2], Floris P.J.T. Rutjes[2], Maikel Wijtmans[1] and Iwan J.P. de Esch[1]

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Fragment-based drug discovery (FBDD) has grown into a well-established drug discovery approach, as is evident from the six FDA-approved drugs and various clinical candidates it has produced up to January 2022. Compared to high-throughput screening, smaller molecules are screened which allows for the use of smaller libraries to sample the same degree of chemical space. Like most screening libraries, FBDD libraries are dominated by flat molecules and this has resulted in a growing interest in 3D fragments. Effective library design is crucial for FBDD success, and we developed an automated workflow using the open-source KNIME software to facilitate this process. The workflow is focused on three-dimensional (3D) fragments, but also considers more conventional parameters such as diversity and novelty. It selects novel and diverse fragments with suitable physicochemical properties and 3D character (using metrics such as PMI) from virtual libraries that are generated within the workflow. The workflow can be used to generate large and diverse libraries or select a smaller set of unique screening compounds to complement existing fragment libraries.

P-05

Beyond Inverse Electron-Demand Diels-Alder Reaction: Tetrazine-Thiol Exchange (TeTEx) as a Novel Click Reaction

Katerina Gavriel, Dr. Kevin Neumann
Institute of Molecules and Materials, Radboud University

With the development of click chemistry, tetrazines were proven to be powerful chemical tools for ligations, drug delivery/activation and pre-targeted labelling of biomolecules. Tetrazines are predominately associated with their unique reactivity during the inverse electron-demand Diels-Alder (IEDDA) reaction.

Here, we report a new click reaction involving the displacement of a methyl thiol moiety from an asymmetric tetrazine by means of a substitution reaction, which we refer to as tetrazine-thiol exchange (TeTEx). Our studies reveal that TeTEx performs exceptionally well in buffered solutions, using stoichiometric amounts of thiol substrate, even under micromolar concentrations. We demonstrate that the reaction occurs highly chemoselectively and in the presence of reducing agents enabling the modification of biomolecules. Notably, TeTEx is reversed upon addition of excess of thiols.

We believe that TeTEx holds a great potential as a ligation tool and could open up new opportunities not only in the field of chemical biology but also in neighboring fields such as synthetic chemistry and material science.

P-06 Abstract Lunteren

Asad Halimi

Infections with multidrug-resistant bacteria, like methicillin-resistant *Staphylococcus aureus* (MRSA), are emerging as major threats to human health.[1] This is caused by the fact that present antibacterial therapies are becoming less and less effective against these pathogens. This rapid bacterial resistance development to the current antibiotics, which address a limited number of essential bacterial targets, urges the development of both novel antibiotics as well as innovative methods to discover novel druggable targets for antibiotics.[2]

The use of covalent inhibitors is a promising approach to antibacterial drug discovery as witnessed by the fast that more than 1/3 of all covalent inhibitors on the market are anti-infectives.[3] In our group, we develop covalent inhibitors and chemoproteomic technologies in order to map, which binding sites in bacteria are especially suitable for covalent inhibitor design.[4,5] In this project, we are specifically interested in reversibly covalent inhibitors[6] as they can retain the advantages of irreversible inhibitors, like the chance for increased binding affinity and selectivity, while reducing potential stability and toxicity challenges. We have evaluated a commercial library of reversibly covalent cyanoacrylamide[5,6] fragments for antibacterial activity in MRSA and synthesized a focused library to explore the structure-activity relationships of the hits. For cyanoacrylamides with minimal inhibitory concentrations (MICs) against MRSA of less than 50 μM, a profile of potential toxicity (MTT assay in a human cell line, hemolysis assay) was obtained and their general thiol activity will be evaluated to filter out toxic and extremely reactive compounds. The most promising compounds will form the basis for identifying druggable cysteines in the bacterial proteome of MRSA. Target elucidation of the fragments will be performed using our competitive residue-specific proteomics isoDTB-ABPP method.[4,5] Using this approach, cysteines in essential proteins of MRSA that are especially suitable for covalent liganding will be identified fostering the development of antibiotics with novel modes-of-action.

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P-07

SuFEx-based Sequence-Defined (Chiral) Oligomers

Yu Han, Fedor Miloserdov, Han Zuilhof

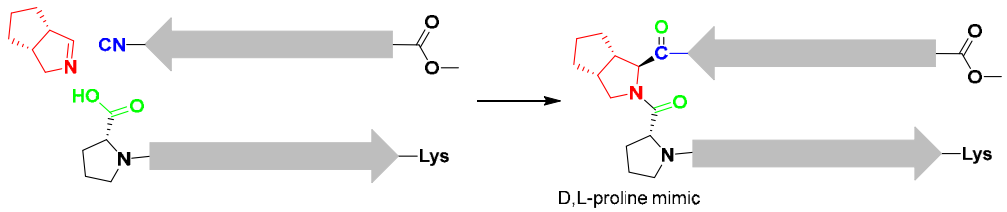
Sulfur–fluoride exchange reaction (SuFEx) is a click reaction reported by Sharpless in 2014. Here we will present our results on the synthesis of chiral SuFEx-based sequence-defined oligomers. Several synthetic routes towards diverse SuFEx-based oligomers will be discussed. Furthermore, particular attention will be given toward the control of the chirality during the synthesis of sequence-defined oligomers, as a method to further increase the information density stored in these molecules.

P-08 MULTICOMPONENT SYNTHESIS OF BETA-TURN MIMETICS

Jay Hanssens

Abstract

The secondary structure of peptides and proteins is highly important for their functioning. In that respect, a well-studied structural feature of proteins/peptides are turn motifs. Such turns allow the structure of a peptide chain to fold back on itself, thus facilitating the formation of globular proteins. One such turn, the β-turn, is well known and is present in a great variety of peptides and proteins. It also stabilizes the formation of β-sheets. A template that has extensively been used for the nucleation of such sheets is D-Pro-L-Pro to provide antiparallel β-sheets.[1] Here we propose a novel method for the synthesis of such D,L-proline based β-turns to facilitate the formation of β-sheets. The Ugi multi-component reaction is an ideal method for the synthesis of a D-proline-L-proline mimic in a single step. By employment of a chiral imine, a selective Ugi reaction should successfully result in the respective β-turn.[2] The multicomponent approach greatly diminishes the difficulty of attaining this structural motif and could result in much higher yields compared to conventional methods. Moreover, this method allows the possibility of ligating two peptide segments together. In that respect, this methodology is suitable for the synthesis of the previously reported β-catenine protein-protein-interaction (PPI) inhibitor as model substrate.[3]



Scheme 1. *General reaction scheme of multicomponent D,L-Proline mimic synthesis.*

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P-09

Synthesis of Affinity-Based Probe for Elucidation of Branched ADPr Signalling Pathway

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ADP-ribosylation is a reversible post-translational modification crucial for signalling in multiple cellular processes such as DNA repair, mitosis and apoptosis. These signalling pathways are influenced by the different existing structures of ADP-ribosylation: mono-ADP-ribosylation, linear poly-ADP-ribosylation, and branched-ADP-ribosylation. The latter form remains the least studied due to its low natural abundance and complex molecular structure. These difficulties can be overcome by using synthetic, structurally well-defined chemical tools. In this study, an affinity-based probe for the elucidation of the branched ADPr signalling pathway was synthesized. The structure of this probe is based on a branched ADPr-trimer with an attached biotin tag, making it suitable for exploring new branched ADPr readers in a proteomic screening. A complementary liquid- and solid-phase approach was used to synthesize the probe based on P(V)-P(III) chemistry. This form of chemistry enabled the installation of the essential pyrophosphates present in all ADP-ribosylated molecules. Liquid-phase chemistry was used to create suitable P(V)- and P(III)-based building blocks. Solid-phase chemistry then enabled the coupling of these building blocks to yield an alkyne-containing branched ADPr-trimer. This alkyne-containing trimer was functionalized in the last step with a biotin tag to provide the novel affinity-based probe. This tool will be applied in the first-ever proteomic screening for branched ADPr readers and has the potential to form the foundation for elucidating the branched ADPr signalling pathway.

P-10

Discovery of an ENaC Inhibitor for the Treatment of Cystic Fibrosis

Dr. Bart Herlé
Boehringer Ingelheim

No abstract available

P-11

Click ‘n CRISPR:
Genetic modification via Cell Penetrating Peptide assisted Cas9 delivery

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Abstract

The CRISPR-Cas9 system allows for the site-specific modification of genetic material. The method requires a Cas9 enzyme loaded with a single guide RNA (sgRNA), which can be introduced in the cell as DNA, RNA, or protein.[1] The latter has the advantage of being immediately active and showing less off-target effects.[2] However, the large size of Cas9 complicates transport over the cell membrane. To control Cas9 uptake, we have equipped the enzyme with a split, activatable cell penetrating peptide (CPP) and demonstrated successful cytosolic uptake upon CPP activation. Using our approach, we can, for the first time, selectively induce Cas9 uptake in specific cell types allowing precise genetic editing in those cells.

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P-12

The total synthesis of a constitutional isomer of (+) -2*R*,3*R*-corynomycolic acid from *Corynebacterium sp*.

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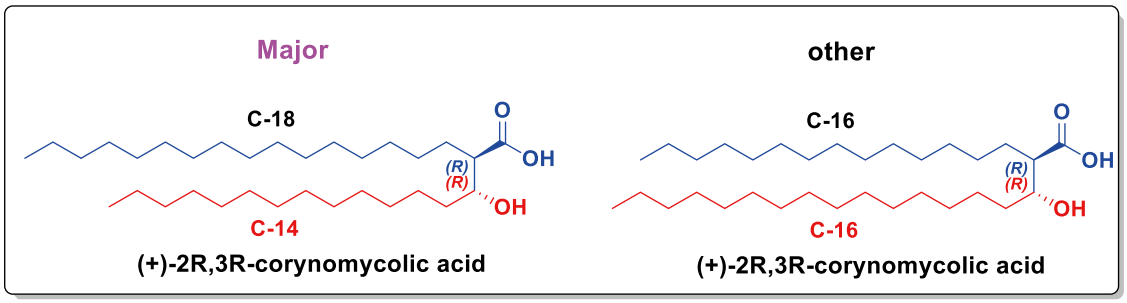
Introduction: Corynebacteria are an order within the actinobacteria that includes numerous human pathogens, such as the etiologic agents of tuberculosis, leprosy and diphtheria. Corynebacteria are characterized by an atypical envelope containing unique high molecular weight α-branched β- hydroxylated fatty acids (C30–90), called mycolic acids[1]. Mycolic acids (MA) from corynebacteria (termed corynomycolic acids) are shorter in length and simpler in structure[2] than mycobacterial mycolic acids, and constitute synthetically accessible targets whose relationships to the authentic mycobacterial materials is more readily appreciated. It has been shown that these mycolic acids play a critical role in the structure and function of the cell wall[2].



The structure of C32 mycolic acids (32 carbons in the chain), according to the literature are depicted above, However the major species of (18:0/14:0) C32 MA has not yet been synthesized and its properties are unknown[3]. Herein, we present the total synthesis of the major species (18:0/14:0) of the corynnomycolic acids (C-18+C-14 = C32) and their glycolipids via a Fráter-Seebach alkylation reaction; and both constitutional isomers are characterized well with all the physicochemical methods including collision induced dissociation (CID) mass spectrometry.

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P-13

Total synthesis of Acidobacterial tetraether lipid-*br*GDGT

Samarpita Mahapatra

Acidobacteria comprise one of the globally distributed and highly diverse phyla of the domain *Bacteria*. Membranes of these bacteria contain characteristic lipids that are considered to have survived Deep time owing to their resistance to degradation. Hence, they are a good source to study the origin of life and its evolution. The lipid content of these microorganisms is mainly comprised of glycerol dialkyl glycerol tetraethers (GDGTs) that give strength for survival in extreme environmental conditions. The tetraether lipids present in these microorganisms have a structure that differs from the archaeal lipids. Whereas the hydrocarbon chains have an isoprenoid nature in case of archaea, in acidobacterial lipids the chains have a fatty acid origin. Still, these lipids also have methyl branches (and cyclopentane rings in some cases) but not as regular as in archaea. Therefore these lipids are called *br*GDGTs (*branched* GDGT).

Till date no syntheses of *br*GDGTs have been reported and also the stereochemistry of the methyl branches of these lipids is also undetermined. We aim to carry out the first total synthesis of these *br*GDGTs and along with that determine the stereochemistry by comparison with the natural samples.

P-14

Chemoenzymatic Synthesis of 13C Enriched Sialic Acids

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Sialic acid or N-acetylneuraminic acid (Neu5Ac) is a ubiquitous sugar residue found in the gut mucus layer. It is commonly found at the terminal location of sugar chains, and its prior removal is necessary for gut microbiota to gain access to the rich underlying sugar residues.

Metabolism of glycans by gut bacteria leading to the production of short chain fatty acids (SCFAs) is of great interest because of their known health benefits to human hosts. Through Stable Isotope Probing (SIP), 13C labelling of Neu5Ac can identify gut microbiota able to metabolise Neu5Ac and enable clear distinction of metabolites generated in the Neu5Ac metabolism pathway in the presence of other sugars.

To obtain these 13C enriched sugars, we have developed a facile chemoenzymatic synthesis route from the cheap and commercially available [U-13C]glucose. Chemical synthesis yielded the key intermediate, peracetylated N-acetyl mannosamine ([13C6]Ac4ManNAc) on a gram scale at 21% yield. Subsequently, enzymatic condensation of [13C6]ManNAc with [2-13C]pyruvate gave asymmetrically labelled [13C7]Neu5Ac, which can be used to prepare 3'-SL and 6'-SL through a facile one-pot enzymatic reaction using CMP-sialic acid synthetase and sialyltransferase. Synthesis of other forms of sialic acids are also possible as demonstrated by the synthesis of 2,7-anhydro Neu5Ac.

P-15

CONCISE AND MODULAR ONE-POT MULTICOMPONENT SYNTHESIS OF HIGHLY FUNCTIONALIZED ASSYMETRIC AZA-BODIPY FLUOROPHORES

H. Daniel Preschel, A. Kruithof, A. Chen, and S. Panday

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Within medicinal and bio-chemical scientific communities the development of novel fluorescent imaging techniques has consistently acquired significant research interest. The aza-BODIPY class of NIR fluorescent dyes have emerged as highly anticipated candidates for broad scope of *in-vivo* applications e.g *live cell imaging* and *image guided surgery*.[1] However, despite their promising potential: tunable photophysical properties, high molar absorption coefficient, excellent quantum yield and (photo)-stability, the limited synthetic access towards aza-BODIPYs has hampered their applications thus far.[2]

In particular, *in-vivo* monitoring of biologicals often requires the correct bio-distribution and intercellular compartmentalization of the fluorescent dye. A common strategy is the installment of a single bio-orthogonal functionality to facilitate (covalent) target-selective ligation of the bio-molecule under investigation.[3] With this in mind we developed a novel modular synthetic route towards asymmetric aza-BODIPY's highlighted by a one-pot microwave-assisted formal [4+1] cycloaddition between in situ-generated azadienes **1** and 9-fluorenyl isocyanide **2** as the key step. This concise and highly modular methodology allowed us to synthesize a variety of highly functionalized, water soluble aza-BODIPY's **3** aimed at target specific in-vivo fluorescent labeling by facile bio-orthogonal ligation methods, e.g. click chemistry and esterifications.

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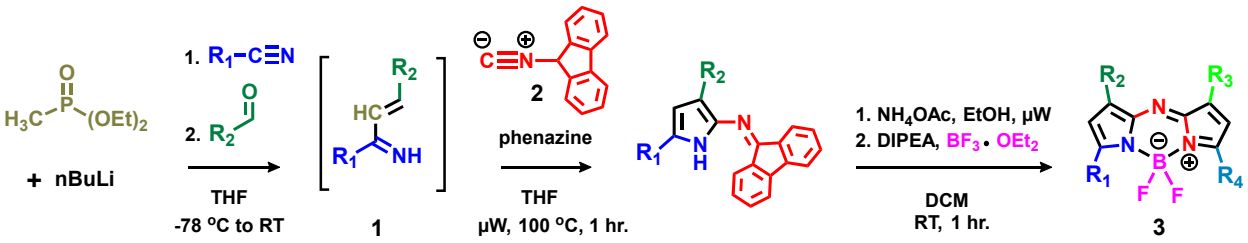

Keywords (max 5)

Live cell imaging – fluorescent labeling – fluorescence guided surgery – aza-BODIPYs, multicomponent synthesis – isocyanides – bio-orthogonal chemistry.

P-16

HIGHLY STEREOSELECTIVE CHEMOENZYMATIC MULTICOMPONENT SYNTHESIS OF THE SARS-COV-2-MAIN PROTEASE INHIBITOR NIRMATRELVIR

H. Daniel Preschel, R. Otte, B. Horst Ying Zhuo, Rebecca E. Ruscoe, Ashleigh J. Burke, Rachel Cowan, Brendan Horst, Sven Hennig, Elwin Janssen, Anthony Green, Nicholas J. Turner, Eelco Ruijter

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The Covid-19 pandemic has impacted global health, society, and economies in a way that is unprecedented in modern history. Although large-scale vaccination against SARS-CoV-2 has brought the pandemic under control, serious concerns over the rise of new virus variants potentially evading an immune response remain [1]. Consequently, rapid synthetic access towards efficacious small molecule drugs like Nirmatrelvir, the active ingredient in Pfizer's orally available Paxlovid™, is urgently required.

In contrary to the rather linear synthesis routes currently employed [2], we present a modular and operationally straight forward multicomponent strategy towards nanomolar mechanism-based protease inhibitors like Nirmatrelvir. The combination of a highly enantioselective bioenzymatic desymmetrization towards imine **2** [3], and a fully diastereoselective Ugi 3 component reaction with densely functionalized isocyanide **1** and trifluoro carboxylic acid **3**, directly affords this valuable API in an atom-efficient one-pot process absent of any intermediate purification steps. We anticipate this methodology provides a valuable tool in diversity orientated drug discovery efforts e.g the synthesis and screening of new active drug candidates.

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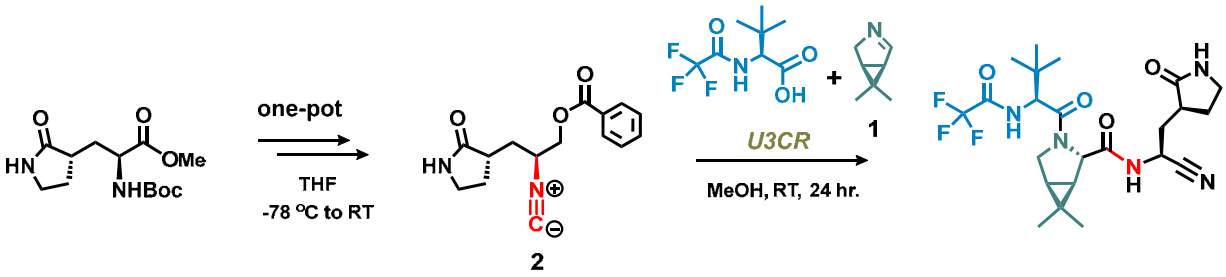

Keywords (max 5)

antivirals – biocatalysis – multicomponent reactions – nirmatrelvir – protease inhibitors

P-17 Abstract title: **Lightening up NETosis**

Author details: **Ramos Cáceres, E. (Enebie); Bonger, K.M. (Kimberly); E.A.J. Reits (Eric); F.P.T.J. (Floris)**

Abstract:

Neutrophils form the first line of defense of our innate immune system against invading pathogens and inflammation. They kill their targets through a variety of mechanisms, including neutrophil extracellular traps (NETs). NETs are ‘’spiderweb-like’’ structures composed of decondensed chromatin decorated with antimicrobial agents. They form in response to specific stimuli through a peculiar form of cell death called ‘’NETosis’’. During NETosis, the nuclear envelop disintegrates and chromatin is decondensed. In the cytoplasm, decondensed chromatin mixes with the antimicrobial agents, eventually resulting in cell membrane rupture and NET ejection.[1,2]

Although a great deal of the molecular mechanisms of NETosis remain elusive, the antimicrobial functions of NETs are heavily dependent on the activity of myeloperoxidase (MPO). MPO is a heme-containing peroxidase whose main function is to catalyze the conversion of hydrogen peroxide into hypochlorous acid.[2]

In an effort to study neutrophil activity and the process of NET formation *in vitro* and *in vivo*, we have developed an activity-based probe (ABP) specifically targeted against MPO. This ABP is based on a mechanism-based 2-thioxanthine warhead published in literature and is equipped with the environment-sensitive fluorophore 4-N,N-dimethylamino-1,8-napthalimide (4-DMN).[3] This fluorophore becomes fluorescent only in the more hydrophobic environments of the enzymatic surface and has a very low fluorescence intensity in water. These characteristics confer the ABP a ‘’turn-on’’ character that greatly reduces background signal in applications such as live-cell microscopy (Fig. 1). This ABP will allow us to investigate MPO activity in living cells and visualize the process of NETosis in wash-free real time conditions.

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Keywords: **neutrophil, activity-based probe, myeloperoxidase**

Figure:

P-18

Iron-catalyzed carbene transfer to isocyanide

Application in the synthesis of heterocycles

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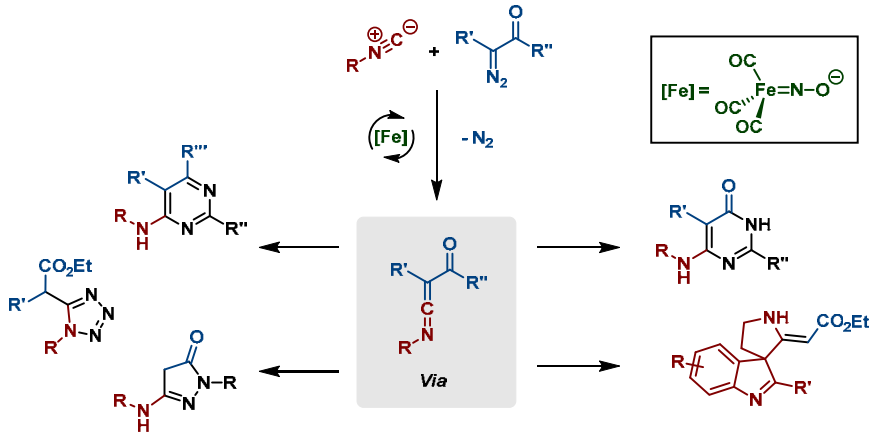

Isocyanides display unique reactivity as is evident by their use in cascade chemistry, multicomponent reactions, and transition metal catalysis. In the latter field, isocyanides have predominantly been used as inputs for Pd-catalyzed imidoylative cross-coupling reactions.[1] A new, less explored reactivity involves carbene transfer reactions, via *in situ* generated transition metal-carbenes. The coupling of carbenes and isocyanides leads to ketenimines, which have proven to be versatile synthetic intermediates.[2] To date, only a handful of cascade processes based on transition metal-catalysed transfer of carbenes to isocyanides has been reported.[2] Unfortunately, these methods often use rare and precious noble metals such as Pd or Rh, while base metal-catalysed processes remain scarce. We now report the use of the electron rich ferrate complex $[Fe(CO)_3NO]N(n\text{-}Bu)_4$[3] in the carbene transfer reaction of α-diazo esters to isocyanides to form ketenimine intermediates, which can be transformed *in situ*. For example, addition of amidines as 1,3-bisnucleophiles results in medicinally relevant 4-aminopyrimid-6-ones.[4]. In addition, we applied this methodology in the formal total synthesis of (±)-aspidospermidine, (±)-aspidofractinine and (±)-limaspermidine, using tryptamine derived isocyanides as input.

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P-19 Chemical Synthesis of Glycopeptide containing L-Arabinosylated Hydroxyproline and Sulfated Tyrosine

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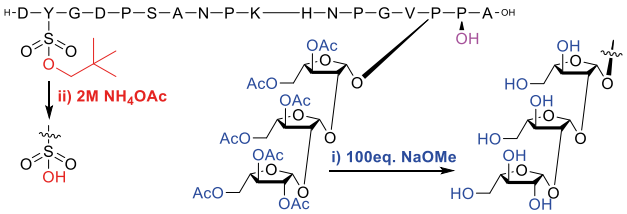

Post-translationally modified peptides are important regulating molecules for living organisms. Here we report the stereoselective total synthesis of β-1,2-linked L-arabinosylated Fmoc-protected hydroxyproline building blocks and their incorporation, together with sulfated tyrosine and hydroxyproline, into the plant peptide hormone PSY1. Clean glycopeptides were obtained by performing acetyl removal from the L-arabinose groups prior to deprotection of the neopentyl-protected sulfated tyrosine.

P-20 Profiling arginine residues in MRSA using novel electrophiles

Marnix Roseboom

Covalent inhibitors are making a comeback in medicinal chemistry and chemical biology due to the growing understanding of electrophilic reactivity towards nucleophilic residues. While traditional therapeutics reversibly bind to their biological target, covalent inhibitors form a strong covalent bond, enhancing the inhibiting effect. This mechanism is relevant in many antibiotics and is becoming increasingly important due to bacterial antibiotic resistance.

Of all residues, cysteine is mostly targeted for covalent inhibition for their high nucleophilicity. However, cysteine is relatively uncommon in many proteomes, meaning that many potential drug targets remain undiscovered. Arginine is a more common amino acid and displays a plethora of biologically relevant functions such as protein interactions, enzyme function and protein structure, making this an attractive drug target. However, targeting arginine is more challenging, which is why research is now focused on discovering novel electrophiles binding to this residue.

Recently, we used a phenylglyoxal (PhGO) probe for proteome-wide profiling, initiating the development towards arginine-selective warheads. In this project, chemical probes based on PhGO are synthesized and utilized in an activity-based protein profiling workflow on Methicillin-resistant *Staphylococcus aureus* lysate. With this, we aim to globally map arginine, outline residue reactivity and discover new potential drug targets to battle bacterial drug resistance.

P-21

Virtual screening of lead structures for $P2Y_{12}$ receptor PET tracer development

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The $P2Y_{12}$ receptor ($P2Y_{12}R$), a well-known drug target for antithrombotic agents, is also involved in microglia regulation during neuroinflammation. To get a detailed insight into $P2Y_{12}R$-mediated dynamics in the brain, positron emission tomography (PET) can be applied. However, so far no successful brain permeable $P2Y_{12}R$ PET tracer has been reported.[1] The aim of the present study is to find novel brain permeable lead structures, acting as $P2Y_{12}R$ antagonists by using a consensus virtual screening approach based on both ligand and structure-based modeling. To this end, complementary pharmacophore models were created by flexible alignment of six known $P2Y_{12}R$ antagonists and a high-throughput docking protocol was set up using a crystal structure of an antagonist-bound $P2Y_{12}R$.[2] After validation, the models were used in a screening of an in-house proprietary library (8427 drug-like compounds). The combined hit list from both approaches were processed (*e.g.,* CNS PET MPO scoring[3]) and a set of chemically diverse hit representatives were tested in an *in vitro* binding assay. Hits with > 80% displacement were further explored by testing structural analogs, which in the end resulted in three new structural leads (K_i of 1–2 μM) for further optimization. On-going work focusses on optimization of these found compounds.

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P-22

Well-defined Heparin Mimetics can Inhibit Binding of Trimeric Receptor Binding Domains of SARS-CoV-2 in a Length Dependent Manner

Lifeng Sun, Pradeep Chopra, Ilhan Tomris, Roosmarijn van der Woude, Lin Liu, Robert P. de Vries, and Geert-Jan Boons*

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ABSTRACT: The emergence of new SARS-CoV-2 variants and the dangers of long-covid necessitates the development of broad acting therapeutics that can reduce viral burden. SARS-CoV-2 employs heparan sulfate (HS) as an initial cellular attachment factor, and therefore there is interest to develop heparin as a therapeutic for SARS-CoV-2. Its use is, however, complicated by structural heterogeneity and the risk of causing bleeding and thrombocytopenia. Here, we describe the preparation of well-defined heparin mimetics by controlled head-to-tail assembly of HS-oligosaccharides having an alkyne or azide moiety by copper-catalyzed azide-alkyne cycloaddition (CuAAC). Alkyne and azide-containing sulfated oligosaccharides were prepared from a common precursor by modifying an anomeric linker with 4-pentynoic acid and by enzymatic extension with an *N*-acetyl-glucosamine having an azide moiety at C-6 ($GlcNAc6N_3$), respectively followed by CuAAC. The process of enzymatic extension with $GlcNAc6N_3$ followed by CuAAC with desired alkyne containing oligosaccharides could be repeated to give compounds composed of twenty and twenty-seven monosaccharides, respectively. The heparin mimetics could inhibit the binding of SARS-CoV-2 spike or RBD to immobilized heparin or to Vero E6 cells. The inhibitory potency increased with increasing chain length and a compound composed of four sulfated hexasaccharides linked by triazoles had a similar potency as unfractionated heparin. Sequence analysis and HS microarray binding studies with a wide range of RBDs of variants of concern indicate they have maintained HS binding capabilities and selectivities. The heparin mimetics exhibit no- or reduced binding to antithrombin III and platelet factor 4, respectively which are associated with side effects.

P-23 One CAAR T cell to rule them all

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Autoimmune diseases are on the rise globally. Yet, treatment is often complex and non-specific. For instance, in Rheumatoid Arthritis (RA) only a small percentage of autoreactive B cells sustain the disease, while current treatment often eliminates the entire B-cell population, leading to immune deficiency. Living drugs like Chimeric Autoantibody Receptor (CAAR) T cells are genetically encoded to produce autoantigens and lure autoreactive B cells. Upon successful recognition of the target, the T cells selectively kill these autoreactive B cells. However, many autoimmune diseases, including RA, involve autoantigens that contain non-natural elements, which the CAAR T cells cannot produce themselves.

We have designed a CAAR T platform where the engineered CAAR T cell receptor can be labelled to contain any non-natural antigen. The platform is based on a self-labeling enzyme, which we functionalized with a citrulline-containing autoantigens as well as a fluorophore allowing imaging of cell-cell interactions. We observed significant cell engagement and increase in early and late activation markers of the T cells. Our system is highly modular and allows for various chemistry on the T cell, allowing us to have full control over T cells targets and activation.

P-24

Authors: Halana C. Vlaming, Gerbrand J. van der Heden van Noort

Keywords: Ubiquitin, High-Throughput Screening, mART.

Towards new antibiotics; targeting Legionella enzymes.

Protein ubiquitination is a crucial post-translational modification in eukaryotic cells.[1,2] Conventional ubiquitination is executed by a three-enzyme system that requires ATP.[3,4] The pathogenic *Legionella pneumophila* bacterium uses a different class of enzymes, called the SidE family, that ubiquitinate host proteins in a unique fashion. Being independent of ATP, this family use NAD^+ to adenosine diphosphate (ADP)-ribosylate ubiquitin as initial step, using the mono-ADP-ribosyltransferase (mART) domain.[5] Next, the phosphodiesterase (PDE) domain of the SidE enzymes catalyze formation of a phosphoribosyl link between ubiquitin and a serine residue in the target substrate host protein. Legionella hereby hijacks the host's ubiquitination system and dampens the host's immune response towards the bacterial infection.[1,4] We here show our investigations on the mechanism of SidE mART activity, by synthesizing ubiquitin probes to explore covalent binding with the R-S-E motif of this mART domain.[3] In addition, a fluorescence-based assay will be presented where ε-NAD is used to obtain a fluorescent signal upon SidE activity. With this assay, High-Throughput Screening can be performed where drug-like libraries are screened, already resulting in a potent hit that shows an IC50 of 221 nM. Encouraged by these results, further screening of several libraries, ranging from drug-like- to covalent fragment-based libraries, are ongoing. The hits obtained from these efforts will be further validated and might lead to potential small molecule compounds for future drug-development.

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P-25

A covalent synthesis of [2]catenane – tackling the uncleavable ester.

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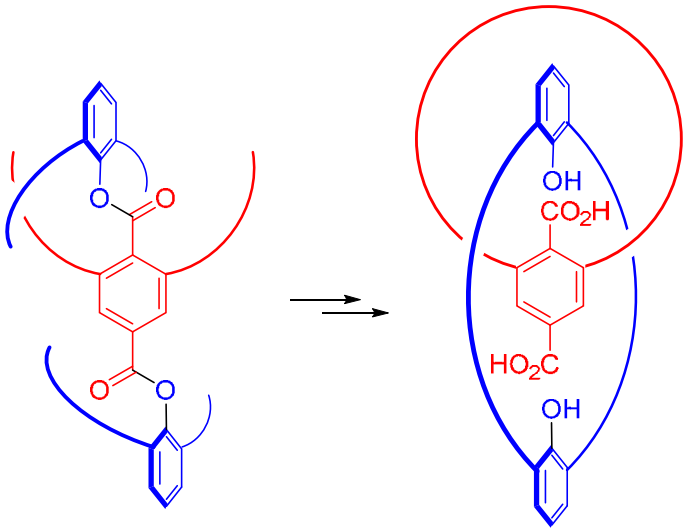

With the ultimate future aim to prepare the synthetically highly elusive natural lasso peptides, the UvA synthesis groups develops covalent methodology to make rotaxanes and catenanes. Because the phenyl moieties of aryl benzoates have a perpendicular conformation they have been found in our hands to be excellent templates for the synthesis mechanically interlocked molecules (see scheme). Mechanically interlocked molecules can exert unique steric effects known as the so called 'catenand effect'. Along these lines, previous attempts to liberate a [2]catenane by simple ester saponification from its precatenane precursor were unsuccessful. Also replacing installing a p-methoxy phenol ester allowing oxidative cleavage thus yielding the catenane with 1,4-benzoquinone moieties failed. In the end, several attempts towards the cleavage were performed and reduction with LAH is, so far, the only way to liberate the final [2]catenane from the phthaloyl diester in high overall yields.

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P-26

Modular design for proteins assembling into antifouling coatings: case of gold surfaces

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Abstract:

Rendering surfaces antifouling is a crucial challenge whenever man made solid materials need to be interfaced with biological fluids, living cells or tissues. Physical or chemical properties of solid surfaces can readily be tuned by via thin molecular layers physically or chemically attached to them. Previously, we have proposed a modular design for a protein assembling into antifouling coatings.[1] We have demonstrated its efficacy for silica and plastic surfaces, here we demonstrate its application to gold surfaces. We believe the design can have important applications in streamlining the molecular assembly of biosensor surfaces.

[1]. Nicolò Alvisi, Chuanbao Zheng, Meike Lokker, Victor Boekestein, Robbert de Haas, Bauke Albada, and Renko de Vries "Design of Polypeptides Self-Assembling into Antifouling Coatings: Exploiting Multivalency." Biomacromolecules 23.9 (2022): 3507-3516.

P-27

CYCLOALKYLAMINES AS POTENT INHIBITORS FOR THE HUMAN NOREPINEPHRINE TRANSPORTER

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The human norepinephrine transporter (hNET), encoded by the SLC6A2 gene, is one of the three monoamine transporters responsible for the reuptake of neurotransmitters from the synaptic cleft.[1] Because of the major involvement of these transporters in the central nervous system, reuptake inhibition of their endogenous substrates has been the main therapeutic strategy to treat disorders such as Parkinson's disease, depression and ADHD.[2] Current strategies encompass the selective inhibition of a single transporter or combined inhibition of two or three of the transporters.[3] Unfortunately, lack of efficacy as well as the risk of adverse side effects are common for these type of treatments.[3] Hence, there is a need for novel monoamine transporter inhibitors as well as a better understanding of their binding mechanism.
Recent in-house virtual screening efforts utilizing a proteochemometric model discovered **GIFT1147**, a cycloalkylamine, as a potent inhibitor for hNET (Figure 1A).[4] In this study we further optimized the cycloalkylamine scaffold (Figure 1B) and to establish a structure-activity relationship on the hNET.

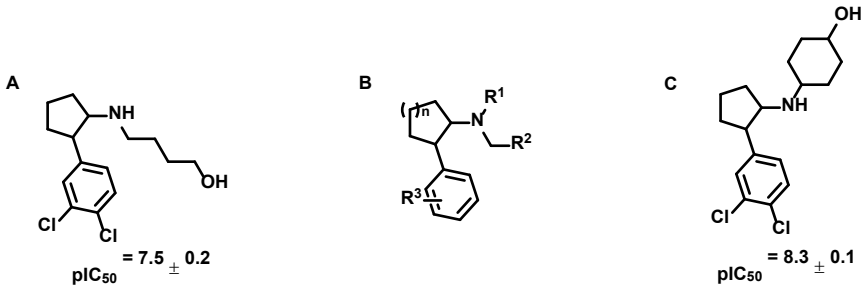

Figure 1. Molecular structures of GIFT1147 (A) and cycloalkylamine scaffold (B)

Twenty cycloalkylamine derivatives were designed and synthesized. All novel inhibitors were screened on their hNET inhibition using an impedance-based 'transporter activity through receptor activation' (TRACT) assay. Moreover, selectivity towards the other monoamine transporters (hDAT, hSERT) was determined with a fluorescent neurotransmitter uptake assay.

From the twenty novel cycloalkylamines it was discovered that variations on the R^3-position resulted in complete loss of hNET inhibition, indicating an essential role for the dichlorophenyl ring in inhibitor binding. Moreover, substituting the original butylalcohol on the R^2-position with a more rigid cyclohexanol resulted in the hit-compound **GIFT1215** (Figure 1C) with an inhibitory potency similar to the commonly used reference inhibitor nisoxetine (pIC_{50}: 8.3 ± 0.1 vs. 8.2 ± 0.1, respectively). In conclusion, these derivatives provide more insight into the chemical properties important to hNET inhibition and therefore new potential for monoamine transport-related treatments.

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P-28 Hybrid covalent/supramolecular synthesis of [3]rotaxanes as photoactive electron shuttles

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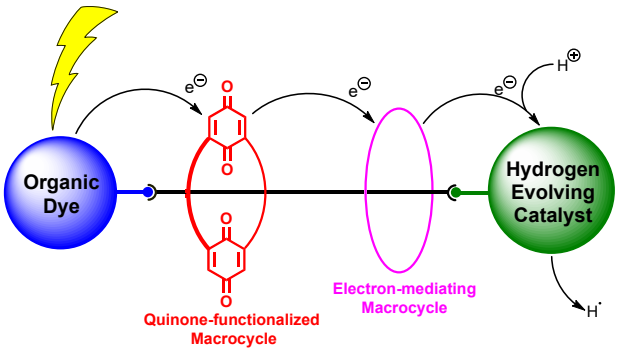
Recombination of the released electron from the organic dye is an unsolved problem in artificial photosynthetic devices. We want to solve this problem by incorporating redox mediators in the macrocycles of [3]rotaxanes as unidirectional electron transporters from the stoppering dye at one end to the stoppering hydrogen evolving catalyst at the other end. The first quinone-functionalized macrocycle synthesized by covalent templated methodology can cancel out the negative charge through the combination of protonation of the quinone radical anion. The second redox-active macrocycle with a lower reduction potential generated from supramolecular synthesis enables unidirectional electron transport thus preventing rapid recombination.



P-29 Harnessing mechanical chirality by enzymatic kinetic resolution

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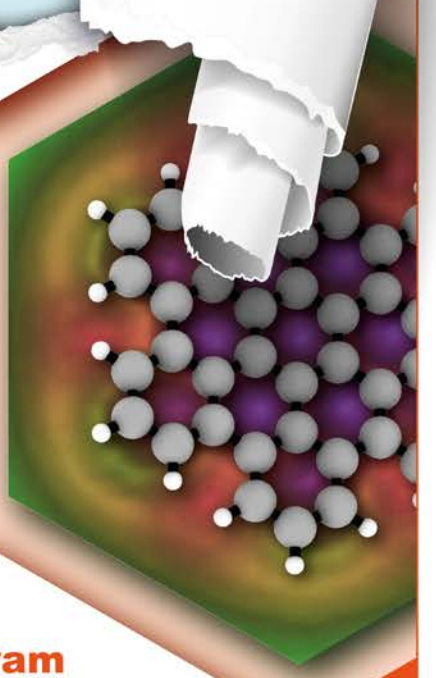
Rotaxanes can be described as a class of mechanically interlocked molecular architectures consisting of a macrocycle encircling a linear and end-stoppered thread component. If the stoppering thread end groups are sufficiently large, the ring and thread remain connected via a so called mechanical bond despite the absence of a covalent bond between the two components. In nature, especially in the realm of peptides, a plethora of mechanically interlocked molecules can be found. In case both the ring and thread contain directionality, the resulting rotaxanes display mechanical chirality, a fascinating molecular physical property that is also found in nature like lasso peptides. Now we are tackling with the mechanical chirality so that we can synthesize lasso peptides in the future.

KNCV

March 30th & 31st

LUNTEREN IS BACK!



2023 National Symposium

For students, academia and industry

Organic Chemistry Division

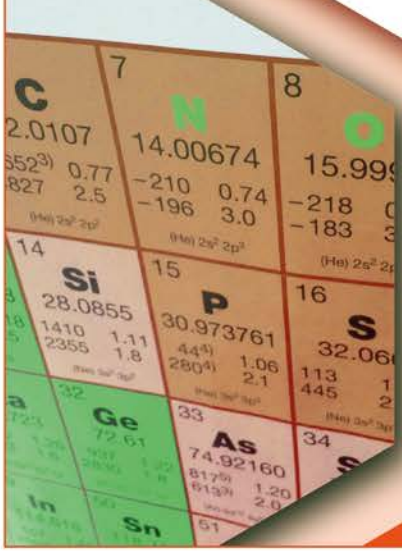
MCCB
Medicinal Chemistry & Chemical Biology

Program

Do you like making & studying molecules? Join our 2-day symposium at Lunteren and present your work in a presentation or poster. Meet your colleages, discuss, socialize and have fun.

We hope to see you there!

INCLUDING THE UNDERWORLD



Register & more info:
www.soc.kncv.nl