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SCS Foundation

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ALFRED WERNER FUND, MASTER'S STUDENT SCHOLARSHIPS

The Alfred Werner Fund of the SCS Foundation, established in 2013, supports Master degree studies for excellent students from foreign countries in Chemistry or Biochemistry at a Swiss University or at a Federal Institute of Technology. The Foundation offers scholarships of CHF 30'000 each year for students nominated by the partner universities (see box with partner universities).

The program continues the initiatives and projects of the former foundation 'Stiftung für Stipendien auf dem Gebiete der Chemie', also known as the 'Alfred Werner Stiftung'. The scholarship program is supported by the Swiss chemical and pharmaceutical industry (see box with supporting companies) and a number of private donors.

So far, sixty scholarships have been granted to students from over 30 countries, most of them continuing their career in Switzerland. To learn more about the Alfred Werner Scholars, please visit the Gallery of alumni at https://foundation.scg.ch/scholarships/scholar-gallery

Partner Universities / Federal Institutes of Technology

EPFL · ETH zürich · University of Basel · UNIVERSITÄT BERN · UNIVERSITÉ DE FRIBOURG UNIVERSITÄT FREIBURG · UNIVERSITÉ DE GENÈVE · UNIVERSITÉ DE NEUCHÂTEL · University of Zurich

Supporting Companies

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Alfred Werner Master's Scholarships 2021–2023

For this period, the Committee of the Werner Fund had approved scholarships to the following students:

Seyed Mohamad Javad Chabok, EPFL Lausanne
Sharif University of Technology, Tehran, Iran
Jana Lukić, EPFL Lausanne
University of Belgrade, Serbia
Marina Teixeira Chagas, ETH Zurich
Universidade Federal do Rio de Janeiro, Brasil
Konstantin Weber, ETH Zurich
TU Wien, Austria
Uroš Stojiljković, University of Basel
University of Belgrade, Serbia
Bratislav Dačević, University of Basel
University of Belgrade, Serbia
Anamarija Nikoletić, University of Basel
University of Belgrade, Serbia
Eibhlin Meade, University of Basel
University College, Dublin, Republic of Ireland
Liliana Galvez Vazquez, University of Bern
Universidad Autonoma de Puebla, Mexico
Giorgi Meshvildishvili, University of Geneva
San Diego State University (Georgia Campus), Tbilisi, Georgia
Tomás Rodríguez, University of Geneva
University of Seville, Spain
Claire Grigglestone, University of Zurich
Trinity College, Hartford (CT), USA

Summary of the Master Theses from Students of the Term 2019–2021

Mahdi Assari
Nationality: *Iran*
Bachelor at: *Sharif University of Technology, Iran*
Master at: University of Geneva and EPFL (NCCR Chemical Biology Master's program)
Master thesis supervisor: *Prof. Christian Heinis, Laboratory of Therapeutic Proteins and Peptides (LPPT), EPFL*

Development of HTS Assays for Tissue Kallikrein 5 and 7 and Screening of 24,320 Macrocyclic Compounds

Netherton Syndrome is a rare inherited skin disease characterized by chronic skin inflammation and severe dehydration.[1] The disorder is associated with mutations in the SPINK5 gene, which encodes the serine protease inhibitor lympho-epithelial Kazal-type-related inhibitor (LEKTI). Loss of the inhibitor's function leads to the uncontrolled activity of the skin proteases tissue kallikrein 5 (KLK5) and tissue kallikrein 7 (KLK7), which are thought to cause the disease (Fig. 1).[2] The goal of my master project was to develop macrocycle-based KLK5 and KLK7 inhibitors, using a recently developed technology to synthesize and screen large combinatorial libraries of macrocyclic compounds.[3-4]

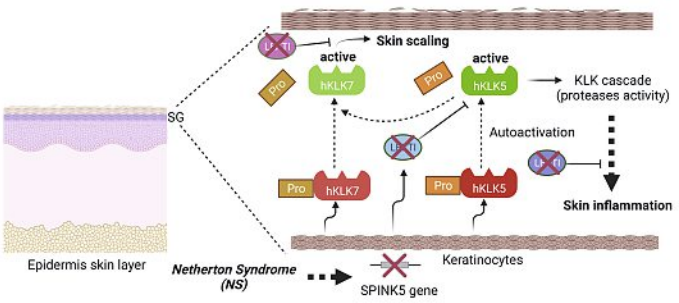

Fig. 1. Molecular events in skin of Netherton Syndrome (NS) patients. In epidermis layer of skin, the serine proteases KLK5 and KLK7 are secreted as inactive pro-enzymes and activated by KLK5. Hyperactivity of these proteases in the absence of their endogenous inhibitor (LEKTI) lead to skin inflammation in patients with NS.2 SG: stratum granulosum; LEKTI: lympho-epithelial Kazal-type-related inhibitor

In the first part of my project, I expressed and purified KLK7 as well as established high-throughput screening assays for KLK5 and KLK7. In a second step, I generated a library of 24,320 macrocyclic compounds by combinatorially cyclizing short peptides by diverse chemical linkers using acoustic droplet ejection technology, and I screened the library (Fig. 2).

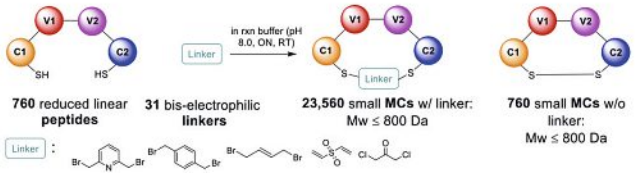

Fig. 2. Outline showing the combinatorial synthesis of 24,320 peptide-based macrocycles. 760 short linear peptides containing two thiol groups, synthesized on solid phase, were combinatorially cyclized with 31 bis-electrophilic linkers in wells of mictrotiter plates (only five linkers are shown as examples). The reagents were transferred in nanoliter volumes using acoustic dispensing, and the reactions were performed at a nanomole scale. V1 & V2: Variable building blocks (*e.g.* amino acids). C1 & C2: Constant building block cysteamine (C1) and mercapto propionic acid (C2).

The screen identified many hits that showed strong inhibition of KLK7 and weaker hits for KLK5 inhibition. An analysis of the hits from the KLK7 screen revealed that the best activities were based on side products in the reactions such as disulfide-linked peptide dimers, pointing to problems in the macrocycle library synthesis procedures. The best three macrocyclic KLK7 inhibitors found showed rather weak activities in the micromolar range (K_is = 1.8 ± 0.2 µM, 14 ± 23 µM, 19 ± 9 µM). The identification of the problems with the combinatorial macrocycle synthesis in this thesis has allowed us to solve the problems in a follow-up project.

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[3] S. S. Kale, M. Bergeron-Brlek, Y. Wu, M. G. Kumar, M. V. Pham, J. Bortoli, J. Vesin, X.-D. Kong, J. F. Machado, K. Deyle, P. Gonschorek, G. Turcatti, L. Cendron, A. Angelini, C. Heinis, *Sci. Adv.* **2019**, *5*, eaaw2851, https://doi.org/10.1126/sciadv.aaw2851.
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Future Plans

After this project, I joined the laboratory of Electrophiles and Genome Operation of Prof. Yimon Aye at EPFL and performed series of projects related to genetic code expansion technology. Starting in September 2021, I joined the University of Chicago in the United States to continue my studies in the field of chemical biology as a PhD student. I wish to work in the exciting field of epitranscriptomics and RNA editing. I already miss many things about Switzerland and will stay grateful to the generous funding from the SCS Foundation without which this unique opportunity could not have happened. I would like to thank Prof. Christian Heinis and my lab assistant in this project, Mischa Schüttel, and all my friends and family who supported me during this period.

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Master at: *University of Geneva*
Master thesis supervisor: *Prof. Stefan Matile and Prof. Thierry Soldati*

Applications and Engineering of Mechanosensitive Flipper Probes: From Monitoring Membrane Tension at the Mycobacteria-containing Vacuole to the Development of Photocleavable Probes

Tuberculosis is the world's deadliest disease caused by a single infection agent, and Mycobacterium tuberculosis is its etiological agent. This pathogen can escape the phagosomal compartment of host macrophages by damaging their cellular membranes. Membrane damage is a key aspect of mycobacteria infection that dictates its success and dissemination. In this project, membrane damage is directly monitored at the membrane level during mycobacteria infection using mechanosensitive fluorescent flipper probes developed in Prof. Matile's group at the University of Geneva. A novel flipper probe was also synthesized which allows selective targeting of the probe in living cells to the intracellular compartments of interest and its subsequent release, with high spaciotemporal control.

Dictyostelium discoideum and murine microglial cells are host model systems to study bacterial infection with *Mycobacterium marinum*, a close relative to *Mycobacterium tuberculosis*.[1,2] Following phagocytic uptake, these pathogens block the maturation of the phagosome and reside in a replication-permissive niche, the mycobacterium-containing vacuole (MCV), where they can induce membrane damage and escape to the cytosol of the host. Membrane damage is one of the key steps during mycobacteria infection and directly correlates with the virulence of the pathogen. Although the consequences of membrane damage can be detected as the host tries to contain the damage by recruiting membrane repair machineries,[3] there is no method to detect damage directly at the membrane level in live infected cells. It has been previously shown that mechanosensitive fluorescent 'flipper' probes, developed at the University of Geneva, can report a decrease in membrane tension upon treatment of cells with the lysosomal membrane-damaging agent, LLOMe.[4] Flipper probes are planarizable push-pull fluorophores, consisting of two large lipophilic dithienothiophene paddles, one electron-rich and the other electron-poor, and a targeting headgroup. Outside membranes, in a free form, the paddles are out of co-planarity because of the steric hindrance from the two methyl units (Fig 1A).[5] However, inside membranes, due to the increased lateral pres-

sure, they planarize, increasing the electron transfer in the push-pull system, resulting in a red shift in the excitation maximum of the fluorophore and an increase in the fluorescence lifetime (Fig. 1A).[6] Thus, the fluorescence lifetime of the probe can be imaged in living cells by fluorescence lifetime imaging microscopy (FLIM), reporting lipid packing changes, which depends on the combination of membrane tension and lipid composition.[7] In homogenous lipid bilayer membranes, an increase in membrane tension is associated with a decrease in flipper fluorescence lifetime due to lower lipid packing and flipper deplanarization (Fig. 1B). In contrast, in physiological and heterogeneous lipid bilayer membranes, an increase in membrane tension is associated with an increase in flipper fluorescence lifetime due to membrane-tension-dependent lipid phase separation and a dominant response from planarized flippers in highly ordered microdomains (Fig. 1C).[6,7]

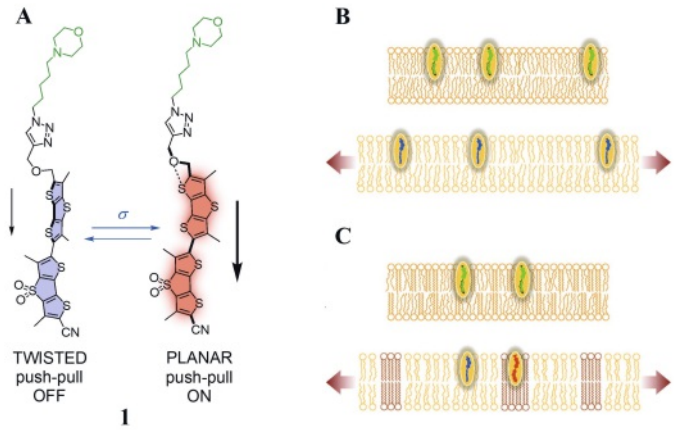

Fig. 1. A) LysoFlipper **1** in both twisted and planar forms. B) Decreasing fluorescence lifetimes with increasing tension applied to homogeneous membranes.[6] C. Increasing lifetimes with increasing tension applied to heterogeneous membranes.[6]

In the first part of the project, LysoFlipper **1**, which is designed to target acidic compartments, was shown to label lysosomes in the two host model systems used for infection. Fluorescence lifetime measurements following hyperosmotic shock, and upon membrane damage by LLOMe, showed that LysoFlipper **1** is mechanosensitive in murine microglial cells (Fig. 2A). Interestingly, LysoFlipper **1** can label the MCV during infection with *M. marinum* (Fig. 2C). In addition, monitoring membrane tension with LysoFlipper **1** at the MCV of murine microglial cells during infection with *M. marinum* revealed a decrease in membrane tension compared to lysosomes (Fig. 1B). Preliminary data indicate that there are differences in membrane tension at the MCV between cells infected with wild type *M. marinum* and cells infected with attenuated *M. marinum* strains (Fig. 1B).

In the second part of the project, a newly designed photocleavable HaloFlipper **2** was synthesized. Apart from the flipper backbone, this probe is designed to contain a photocleavable linker and a chloroalkane headgroup that covalently binds to the self-labeling enzyme, HaloTag (Fig. 3A).[8] This design allows the selective targeting of the photocleavable HaloFlipper **2** to the membrane of interest, and the spatiotemporal controlled quick release of the Flipper-TR **3**, which is membrane-impermeant and has high membrane partitioning (Fig. 3A).[8] Different experiments have demonstrated that the photocleavable HaloFlipper is cell permeant, selective to HaloTag, and can be released inside living cells (Fig. 3B).[8] More information will soon be available in a scientific publication.

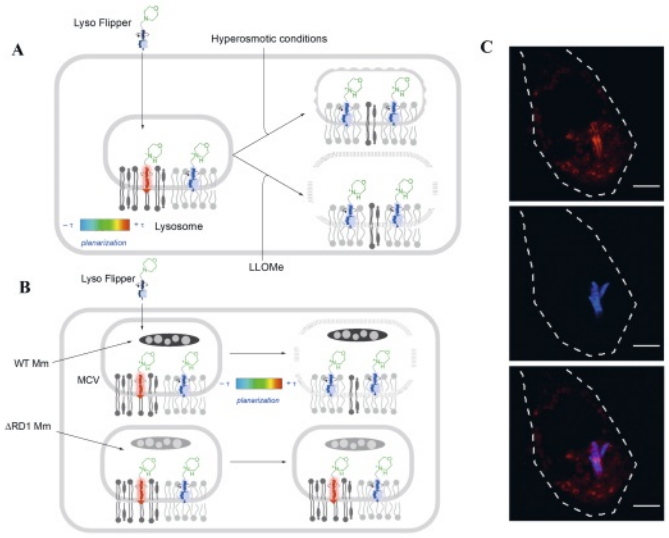

Fig. 2. A) Design of mechanosensitivity experiments by hyperosmotic shock and membrane damage in host model systems. B) Design of membrane tension monitoring experiments during mycobacteria infection. C) Localization of LysoFlipper 1 in BV2 cells infected with *M. marinum* at 16 hours post infection. Red: LysoFlipper, blue: *M. marinum*. Scalebar = 5 µm.

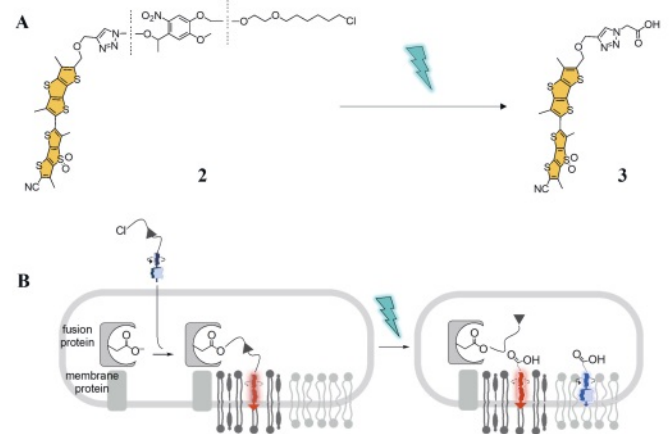

Fig. 3. A) The design of the novel photocleavable HaloFlipper **2** and its photocleavage, yielding Flipper-TR **3**. B) Mode of action of the photocleavable HaloFlipper.

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Future Plans

After completing my MSc thesis, I continued to work on the photocleavable HaloFlipper project to finalize the experiments needed for the submission of the scientific publication. Currently, I am working in Prof. Soldati's group to optimize the selective delivery of Flipper probes to the MCV and to study membrane damage caused by different strains of M. marinum. As I have a deep interest in this interdisciplinary subject, I plan on pursuing a PhD.

Leon Gabriel Feld
Nationality: *Germany*
Bachelor at: *ETH Zurich*
Master at: *ETH Zurich*
Master thesis supervisor: *Dr. Ivan Infante (Italian Institute of Technology, Genoa), Prof. Maksym V. Kovalenko*

Atomistic Simulations of Perovskite Quantum Dots at the Timescales of Excited State Lifetimes

Colloidal quantum dots (QDs) of cesium lead halide perovskites have attracted broad interest for their highly efficient, narrowband and spectrally tunable photoluminescence (PL).[1] Their prospective applications in classical and quantum light technologies require concerted efforts to understand and control the effects of structure and structure dynamics on PL characteristics. Towards these goals highly instrumental are ab initio calculations as they offer both atomistic and electronic insight and hence help to delineate the structure-property relationships.[2] However, excited state processes, paramount for understanding PL characteristics, usually occur in a timescale that cannot be readily captured by ab initio simulations. On the other hand, low-cost simulations with classical force fields (FFs), which can easily reach the emission lifetime scale, reveal no electronic structure information and thus provide limited insight into PL characteristics. We propose a workflow to accelerate molecular dynamics (MD) simulations of QDs by combining classical FFs with machine learned structure-property relations to access electronic structure information in $CsPbBr_3$ QDs at the nanosecond timescale.

For colloidal QDs, most analytical methods (NMR, XRD, …) can only provide restricted insight into the atomic structure of nanoscale systems. Yet, a precise understanding of the relationships between atomic structure or dynamics and PL characteristics is necessary to improve the optical properties of this material class. Thus, atomistic simulations play an important role in complementing experimental studies of PL in QDs. Currently, resource-demanding *ab initio* simulations cannot access timescales of most excited state processes (nanoseconds) and are hence limited to predictions in the short-time limit (few picoseconds). MD simulations based on classical FFs, on the other hand, can access much longer timescales, up to microseconds or even longer, but do not offer electronic structure information, which is needed to study PL processes. In recent years, many groups employed machine learning (ML) models in various areas of chemistry to achieve *ab initio* accuracy at reduced computational effort. A ML model, which was trained on a set of reference data at *ab initio* level, can accurately predict a quantum mechanical property for unknown structures.

In this project, we combined classical FFs and ML to access MD simulations with insight into electronic properties at nanosecond timescales. We employ classical FFs, whose parameters were obtained by fitting radial distribution functions (RDFs) of an *ab initio* MD trajectory of a 2.4 nm $CsPbBr_3$ QD (Fig. 1, left).[3] MD simulations based on these FFs accurately recover the RDFs (Fig. 1, right) and angular distribution functions of the reference MD simulation.

From a 1 nanosecond MD simulation based on the classical FFs, we sampled 1000 training structures employing a farthest-point sampling algorithm and performed density functional theory (DFT) calculations. Employing SOAP descriptors and kernel ridge regressions.[4] electronic properties such as total electronic energy (Fig. 2, left) or bandgap could be accurately learned.

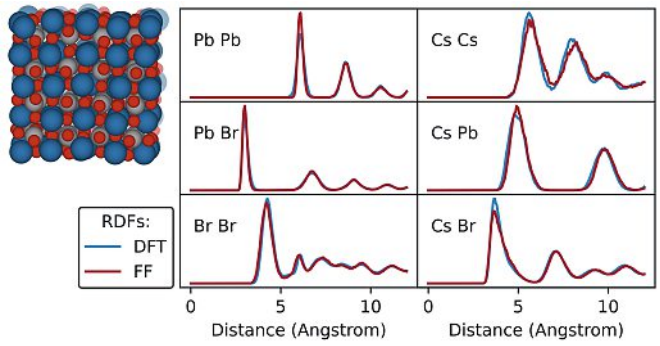

Fig. 1. MD simulations of a 2.4 nm CsPbBr3 QD (top left; Cs blue, Pb grey, Br red) employing classical FFs fitted to *ab initio* MD data. RDFs of different atom pairs from classical FF MD simulations agree well with the *ab initio* MD data (right).

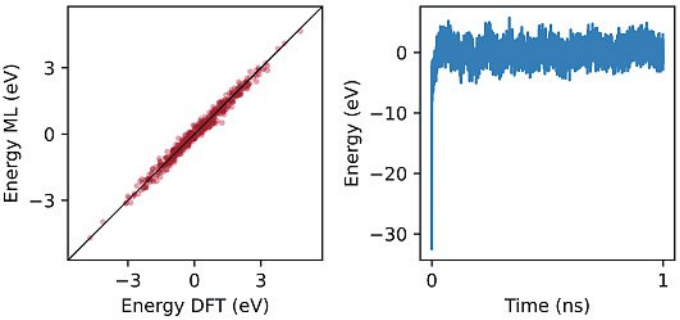

Fig. 2. Machine learning DFT energies for a 2.4 nm CsPbBr3 QD based on farthest-point sampling and SOAP kernel ridge regression. Left: Total energies calculated with DFT can be accurately predicted for randomly sampled test structures (dots). Right: Total energies predicted by ML for the nanosecond long classical MD trajectory starting from a 0 K structure and equilibrating to 300 K.

The low computation cost of ML predictions and the fast and accurate MD simulations based on our classical FFs enable us to access information on the electronic structure of QDs at the timescale of excited state lifetimes (Fig. 2, right). In future studies, this workflow will allow us to further understand the optical properties of perovskite QDs and complement experimental studies.

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Future Plans

After finishing my thesis at the Italian Institute of Technology, I returned to ETH Zurich to start my doctoral studies with Prof. Kovalenko earlier this year. In this project, which is part of the NCCR Catalysis (a consortium of the Swiss National Science Foundation), we study perovskite quantum dots by means of single-particle optical spectroscopy. Atomistic simulations of these materials remain an important tool to understand the processes governing the optical properties of single quantum dots.

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Master thesis supervisors: *Profs. Robbie Loewith, Nicolas Winssinger, and Anne-Claude Gavin*

Screening for Small-molecule Inhibitors of mTORC2-lipid Interactions

Protein-lipid interactions play a crucial role in the structure and function of membranes and signal transduction from the extracellular matrix into the cytosol. These interactions are precisely controlled events and their misregulation can affect essential signalling pathways in the cell.[1] *In this project, we focused on the mammalian target of rapamycin complex 2 (mTORC2), a major regulator of cellular growth and proliferation.*[2] *Since we lack a selective inhibitor of mTOR complex 2, the detailed interpretation of its regulation, translocation and activation remains unknown.*

Inhibiting the PI3K/mTORC2/Akt pathway on mTORC2 level could help overcome resistance to rapalogs in cancer treatment. Hence, understanding mTORC2 ultimately would bring an essential contribution to molecular and cell biology and, finally, translational medicine in general.

This project aimed to screen for selective small molecule inhibitors of mTORC2. We targeted mSin1, a distinct subunit of mTOR complex 2.[2b] mSin1 is a Pleckstrin homology domain (PH domain) containing protein responsible for mTORC2 recruitment to the membranes (Fig. 1).[3] The PH domain expresses its role through protein binding to the membrane compartments containing phosphatidylinositol-phosphates (PIPs).[4] Besides, mSin1 is necessary for mTORC2 capacity to phosphorylate Akt1.[2a]

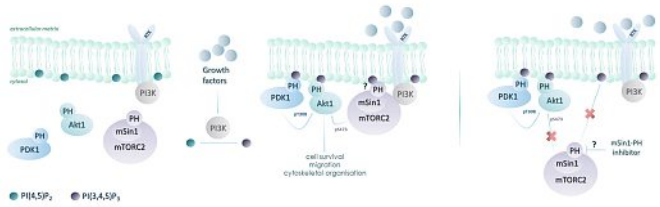

Fig. 1. Targeting the interaction of mTORC2 unique subunit mSin1 (using its Pleckstrin Homology domain-PH) with the plasma membrane as a strategy for developing selective mOTRC2 inhibitors.

We constructed a completely new library where the rational design aims to inhibit the interactions between PH domains and membranes. We built a 240 000 members fragment-based PNA-encoded chemical library to identify the best binders of the PH domain of mSin1. The fragment-based approach has disclosed relatively good binders of the targeted proteins, but with poor selectivity. The hit compounds discovered in this screening were assembled and combinatorially connected with five linkers bringing the 625-membered focused library (Fig. 2). The focused library revealed a set of small molecules that exhibited high affinity and significant selectivity for the PH domain of mSin1 over the Akt1.

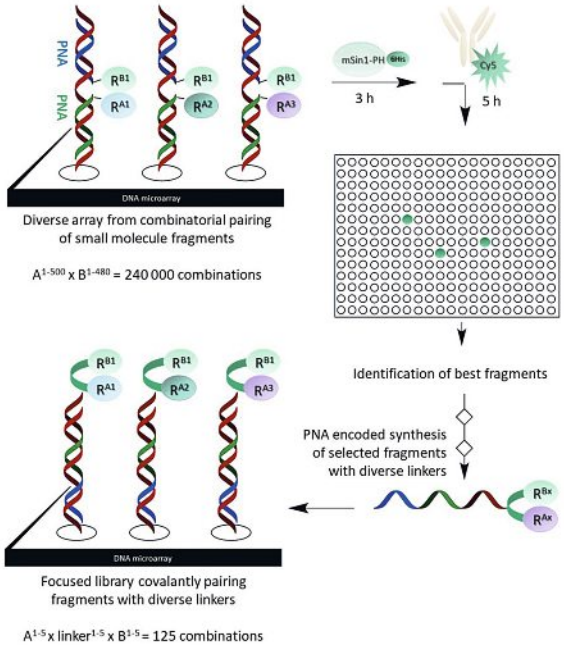

Fig. 2. General procedure of fragment-based screening; The pipeline of the screening process from the primary screening to the focused library.

Validation of the compounds disclosed that all hits successfully interact with the mSin1 PH domain in the affinity pulldown assay. Furthermore, most of the compounds inhibited mSin1–lipid interactions in flotation assay. Lastly, the compounds were tested for their potency to inhibit mTORC2 activity in a cell-based assay using MCF-7 breast cancer cell line. We measured the phosphorylation level of Akt1 and concluded that compounds revealed in the focused library had higher activity than the fragments selected in primary screening. The addition of the compounds decreased Akt1 phosphorylation 5-fold compared to the control.

Given the role of mTORC2 in cancer metastasis, it is essential to understand how it precisely interacts with the plasma membrane to guarantee the proper signal transduction from the extracellular matrix into the cytosol. Using flotation assay, we have identified phosphatidylinositol-3,4,5-trisphosphate and phosphatidylinositol-3,4-bisphosphate as the most prominent binders of the mSin1 PH domain in the plasma membrane and that the presence of calcium increases the strength of the interactions.

As part of this project, we have established a pipeline for discovering small-molecule inhibitors of mTORC2-lipid interactions.

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[4] E. Ingley, B. A. Hemmings, *J. Cell. Biochem.* **1994**, *56*, 436, https://doi.org/https://doi.org/10.1002/jcb.240560403.

Future Plans

I started my PhD project under the supervision of Profs. Robbie Loewith and Nicolas Winssinger at the University of Geneva. I will work in the domain of Chemical Biology using chemistry as a tool to improve the understanding of biological systems. I believe that it is crucial to think in an interdisciplinary manner deleting the line between chemistry and biology. My goal is to develop chemical probes, work on drug design and discovery and finally contribute to healthcare, on both, fundamental and applied level.

Valeriia Hutskalova
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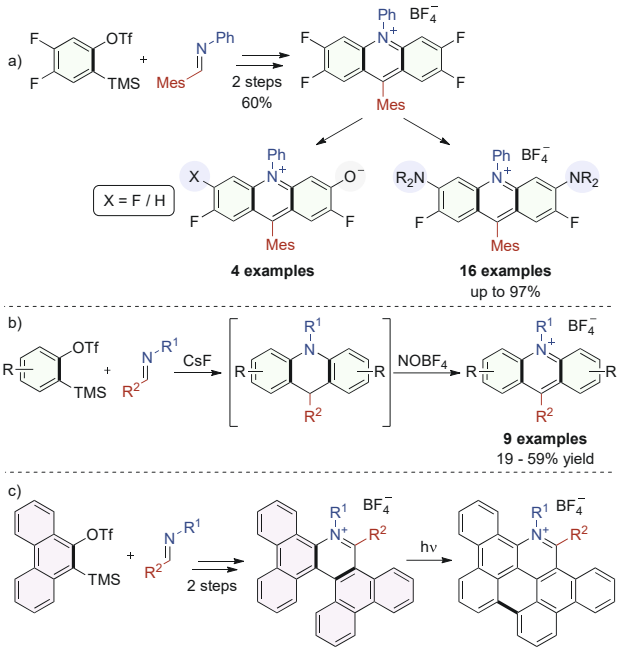
Master at: *University of Basel*
Master thesis supervisor: *Prof. Dr. Christof Sparr*

Development of New Synthetic Approaches Towards Acridinium Salts and Their Applications

In my Masters project, we developed a short two-step route to acridinium dyes involving an aryne-imine-aryne coupling combined with a subsequent oxidation. This divergent strategy was also applied for the preparation of a tetrafluorinated acridinium salt which served as a linchpin intermediate for the late-stage diversification by nucleophilic aromatic substitution yielding diverse aciridinium dyes including aza-rhodols, a novel class of the photocatalysts. Mild reaction conditions allowed synthesis of bifunctional catalysts to merge amine and photoredox catalysis, while favorable unique properties of aza-rhodols prompted their application for photoredox C–N cross-couplings.

Acridinium salts, introduced by Fukuzumi and refined by Nicewicz,[1,2] have emerged as valuable organic cationic photocatalysts due to their favorable photophysical features. To expand the scope of this photocatalysts class, our group earlier reported a new strategy towards acridinium salts utilizing the reaction between 1,5-bifunctional organometallic reagents and esters.[3] In my project, we aimed at the development of new synthetic approach towards acridinium photocatalysts which would involve a late-stage diversification to avoid multistep syntheses.[4]

We demonstrated that the tetrafluorinated acridinium derivative, prepared *via* an aryne-imine-aryne coupling followed by the subsequent acridane oxidation, could be efficiently used as a linchpin intermediate for late-stage derivatizations (Scheme 1a). In this approach, various substituents are introduced at the C3- and C6-positions of the acridinium core in the last step *via* nucleophilic aromatic substitution reaction under mild conditions. The methodology was applied for the synthesis of 20 new acridinium salts with high yields including novel aza-rhodol photocatalysts which were successfully used for photoredox catalytic C–N cross-coupling due to uniquely low $E_{1/2}$(PC/PC$^-$). Furthermore, the late-stage diversification strategy was also utilized for the preparation of the bifunctional amine/acridinium catalysts. Next, we questioned whether the synthetic route towards our linchpin tetrafluorinated intermediate could find application for the diverse acridinium salts preparation.



Scheme 1. Developed routes towards synthesis and diversification of acridinium salts.

We hence explored the two-step approach comprising an aryne-imine-aryne coupling followed by oxidation with different imines and arynes precursors and showed the generality of the strategy by the preparation of nine acridinium derivatives with good yields (Scheme 1b).[5] Interestingly, a unique reaction pathway in the aryne-imine-aryne coupling was later observed with phenanthryne as an aryne precursor (Scheme 1c). In particular, mesityl-phenyltetrabenzophenanthridinium tetrafluoroborate was formed upon oxidation instead of the expected acridinium derivative.[6] The obtained compound can be assigned as 7-aza[5] helicenium derivative which shows the tendency to undergo light-promoted cyclodehydrogenation yielding a planar product.

In summary, we have developed novel strategies towards acridinium salts via the aryne-imine-aryne coupling followed by oxidation and late-stage diversifications. The unique reactivity of aryne precursors with an extended π-system was also discovered and investigated. Our ongoing studies are focused on the application of the acridinium salts that are accessible by our new synthetic routes.

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[6] V. Hutskalova, C. Sparr, *Helv. Chim. Acta* **2021**, https://doi.org/10.1002/hlca.202100182.

Future Plans

After completing my Masters project in October 2020, I started my PhD studies at the University of Basel under the supervision of Prof. Christof Sparr. My current research is focused on the application of our acridinium photocatalysts and the development of catalytic approaches to unique stereochemical systems.

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New Fidaxomicin Antibiotics: Combining Metabolic Engineering and Semisynthesis

Since the discovery of antibiotics, bacteria have evolved alongside modern medicine to defy the treatments used against them. This has resulted in the rise of antimicrobial resistance, sometimes referred to as a 'silent pandemic', which is increasing in significance to this day. The impact is estimated to be comparable to climate change, both in delay and severity.[1] One aspect that will contribute to solving this challenge is the discovery and development of new antibiotics. This work focused on the synthesis of new derivatives of the complex natural product fidaxomicin.

Fidaxomicin (**1**) is marketed for the treatment of Clostridioides difficile infections in the gastrointestinal tract (GIT). It excels in the treatment of this disease, since fidaxomicin's insolubility in water restricts it to the gut. Fidaxomicin is also active in vitro against other high priority pathogens such as Staphylococcus aureus and Mycobacterium tuberculosis.[2] While low water solubility is an advantage for the treatment of GIT infections, it prevents uptake of the antibiotic into the bloodstream and therefore treatment of systemic infections.

To control the unfavourable pharmacokinetic properties of fidaxomicin, changes to its molecular structure are required that also maintain its potent antibiotic properties. We sought an approach that could replace parts of fidaxomicin, rather than directly adding substituents which would increase the molecular weight even further. In collaboration with the Müller group at the Helmholtz Institute for Pharmaceutical Research Saarland, a mutant fidaxomicin producer strain was engineered. This strain lacks the glycosyltransferase that normally installs the right-hand side of **1**, and cultivation led to the isolation of shunt metabolite **2**. It was tested against M. tuberculosis by our collaborators, the Sander group at the Institute of Medical Microbiology (University of Zurich), to reveal that antibiotic activity was lost almost entirely.

Using site-selective catalysis we were able to introduce a range of substituents at C18 (see Fig. 1) through direct modification of fidaxomicin. Guided by molecular modelling, new derivatives were designed to mimic the binding mode of the sugar and arene moieties of **1** to its target enzyme. Testing against M. tuberculosis revealed that several of these derivatives partially restore antibiotic activity, while drastically reducing structural complexity.

This work lays the groundwork for the design of improved fidaxomicin antibiotics. Further development will lead to candidates that expand the single agent fidaxomicin to its own class of antibiotics. Continued improvement of antibiotics will be a crucial part in the 'arms race' against the emergence of antimicrobial resistance.

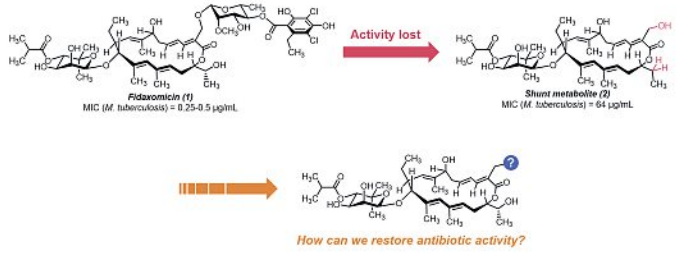

Fig. 1. Structures of fidaxomicin (**1**) and shunt metabolite (**2**) with their respective activities against *M. tuberculosis*. General strategy for the installation of substituents in the search of new fidaxomicin antibiotics.

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Future Plans and Acknowledgement

After completing the Specialized Master in Chemical and Molecular Sciences in March 2021, I stayed in the group of Prof. Dr. Karl Gademann to pursue a doctorate, carrying on the work on new anti-infectives.

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Novel Photoswitchable Protein Degrader Tools

In recent years, a novel approach that combines small molecules' properties and cell degradation machinery has emerged as a promising strategy to precisely control the expression levels of challenging protein targets. PROTACs[1] (Fig. 1) are heterobifunctional small molecules that catalytically induce protein degradation by forming a ternary complex between the protein of interest (POI), the heterobifunctional molecule, and an E3 ubiquitin ligase, which induces ubiquitination and subsequent protein degradation due to proximity induced interaction.[2]

The Carreira group has previously reported on photoswitchable PROTACs[3] (photoPROTACs) which offer optical control over protein degradation. In a continuation of this proof-of-concept work, the goal of this project was to expand this approach to other protein targets. In particular, we implemented a novel approach to access novel azotriazole photoswitches from azoacetylenes *via in situ* desilylative CuAAC (Copper-catalyzed

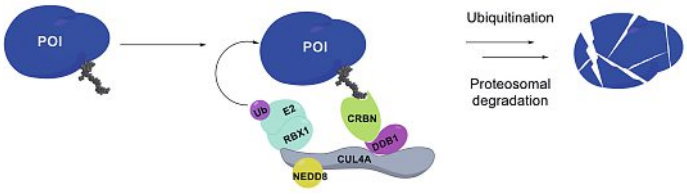

Fig. 1. General mechanism of action of PROTACs. In dark grey, an exemplary PROTAC molecule is depicted. CRBN, DDB1, CUL4A, NEDD8, RBX1, and E2 constitute the CRBN E3 ligase complex, Ub ubiquitin.

azide-alkyne cycloaddition).[4] Accordingly, we prepared 'clickable' protein recruiters **1** and **2** bearing azide or azoacetylene moieties (Fig. 2). This enabled efficient access to photoswitchable PROTAC candidate molecules displaying high bistability and high isomeric ratios in the respective photostationary states. At a later stage, this strategy allowed us to focus on the introduction of a variety of linker lengths in a modular sense.

Fig. 2. Assembly of photoswitchable PROTAC candidates from building blocks **1** and **2**.

[1] M. Toure, C. M. Crews, *Angew. Chem. Int. Ed.* **2016**, *55*, 1966, https://doi.org/10.1002/anie.201507978.
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[3] P. Pfaff, K. T. G. Samarasinghe, C. M. Crews, E. M. Carreira, *ACS Cent. Sci.* **2019**, *5*, 1682, https://doi.org/10.1021/acscentsci.9b00713.
[4] P. Pfaff, F. Anderl, M. Fink, M. Balkenhohl, E. M. Carreira, *J. Am. Chem. Soc.* **2021**, *143*, 14495, https://doi.org/10.1021/jacs.1c06014.

Future Plans

After my thesis, I did an internship at Roche in the Medicinal Chemistry department. Currently I am a visiting researcher at the Massachusetts Institute of Technology (MIT) in the group of Professor S. Buchwald, working on the implementation of Pd-mediated reactions for novel combinatorial library platforms. Upon my return to Switzerland, I will start working for a management consulting firm in Zurich.

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Impact of Hybrid CO_2-CO Feeds on Methanol Synthesis over In_2O_3-based Catalysts

Thermocatalytic conversion of CO_2 and renewable H_2 to sustainably produce methanol is a promising approach to promote CO_2 utilization for which, In_2O_3-based catalysts have emerged as frontrunner systems.[1] However, in general, catalytic performance has so far been determined on single-pass conversion using purified CO_2 and H_2 streams which is unrealistic in an industrial setting; wherein, CO is invariably present as a feed component or a recycled byproduct (Fig. 1). For this scenario, a set of dedicated cycle experiments were devised, in which CO_2 in the hydrogenation feed is gradually replaced by CO and then reintroduced to evaluate the performance of In_2O_3 in bulk form, supported on m-ZrO_2 and other carriers, and promoted by palladium or nickel.[2]

Full cycle (FC), half-cycle (HC) and reverse half-cycle (rHC) experiments were performed to elucidate the sensitivity of catalytic systems to CO. The ratio of CO to total amount of carbon oxides in the feed stream (CO/CO_x = (CO_2+CO)) was defined as R, which was raised from 0 to 0.5 before returning to 0 at the same rate in the FC. The FC was split into two independent half-cycles to ascertain the impact of introducing CO and reintroducing CO_2 on the catalytic system.

An upper limit of R = 0.5, was selected for primarily two reasons. Firstly, R > 0.5 would represent a feed stream more similar to syngas as opposed to CO_2-rich feeds obtained via biomass gasification and secondly, AspenPlus-based simulations yield R = 0.2 as the thermodynamic equilibrium limit upon recycling. In fact, the absolute sustainability of a process for methanol synthesis using captured CO_2 was shown by a system engineering analysis based on planetary boundaries.[3]

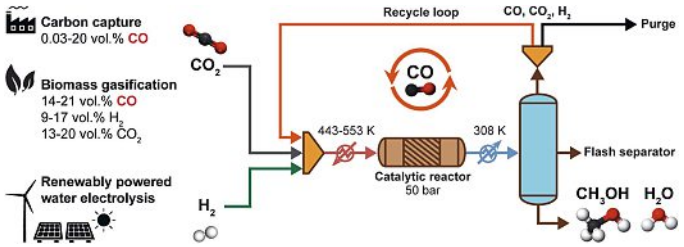

Fig. 1. Process concept for CO_2-based methanol synthesis utilizing practically relevant hybrid CO_2-CO feed streams.

Methanol productivity over In_2O_3/*monoclinic*-ZrO_2 increases 1.2-fold when CO_2 is replaced by CO in an amount corresponding to the thermodynamic equilibrium limit, owing to an augmented density of oxygen vacancies induced by co-fed CO and resistance to sintering which was corroborated by in-depth characterization of the catalysts. However, other In_2O_3-based catalysts deactivate due to an interplay of CO/H_2O-induced sintering and CO inhibition (ca. 20–40%) (Fig. 2).

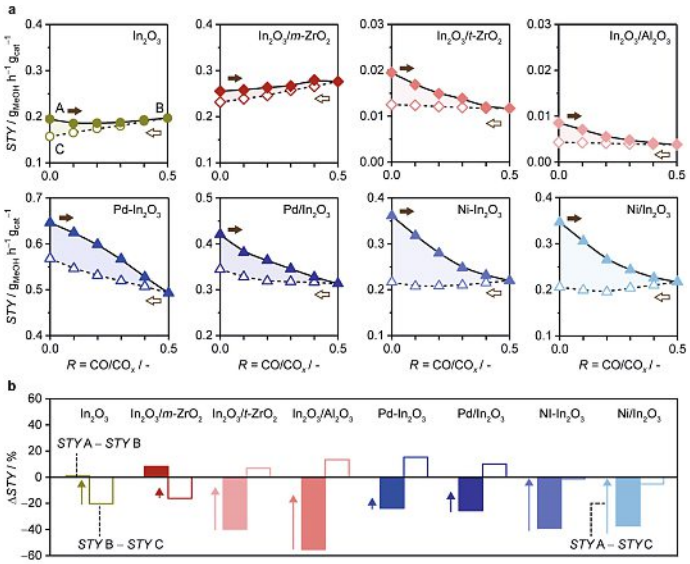

Fig. 2. (a) Methanol space-time yield (*STY*) during CO*x* hydrogenation over In_2O_3-based catalysts as a function of R (R = CO/ CO*x*) in a FC experiment. (b) Variation of methanol *STY* for In_2O_3-based catalysts along the forward and backward branches (bars), and in the whole FC (arrows). Reaction conditions: T = 553 K, P = 5 MPa, H_2/CO*x* = 4, and WHSV = 24,000 $cm^3\ h^{-1}\ gcat^{-1}$. Filled and empty arrows in (a) indicate the forward and backward direction of the cycle, respectively.

Based on the knowledge acquired from the cycle experiments, operation regimes for In_2O_3/m-ZrO_2 and Pd-In_2O_3 systems were effectively optimized to maximize their methanol productivity. Overall, the study uncovered the impact of hybrid CO_2-CO feeds on a relevant class of catalysts for CO_2-based methanol synthesis, offering a novel approach to assess performance under practically-relevant conditions, which serves as a stepping-stone to accelerate the development of industrially-viable catalytic technologies for this transformation and other CO_2-based conversions.

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Future Plans

Currently I am interning at Dow Chemical (Tarragona, Spain), and am extremely interested in the domain of process engineering, catalysis, and polymers.