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Discovery of novel and highly selective allosteric inhibitors of PAK1

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Protein kinases mediate a variety of intracellular pathways and their aberrant activity is often associated with tumor initiation and progression. Many kinase inhibitors have been shown to be very powerful cancer therapeutics, with Glivec being the most prominent example used for the treatment of chronic myelogenous leukemia (CML). Most kinase inhibitors discovered to date block the ATP binding site which is highly conserved among different kinases and, as a result, such compounds very often suffer from lack of kinase selectivity. Discovery of inhibitors targeting novel allosteric kinase sites however is still considered very challenging.

Here we would like to disclose an example of allosteric inhibitor targeting PAK1 kinase. We will describe our strategy towards hit finding including the biochemical and biophysical approaches. We would like to disclose the first X-ray structure of an allosteric inhibitor bound to the PAK1 kinase. Hit optimization yielded very potent inhibitors with single-digit nanomolar PAK1 IC50s without making use of interactions with the hinge. Furthermore, the allosteric inhibitors modulated PAK1 at the cellular level. Compounds presented may be used as valuable research tools to study biological functions of the PAK1 kinase.

From Synthesis in Flow to Integrated Dose-Response Screening in Flow

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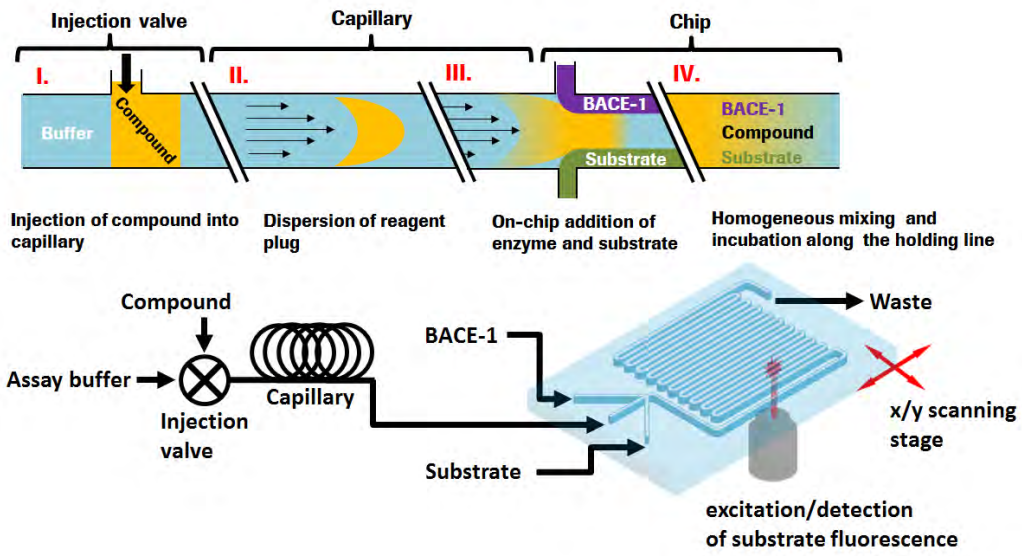
The identification of a lead compound through iterative generation of structure-activity relationship (SAR) data is at the core of early-stage drug discovery. A complete SAR cycle is composed of organic synthesis, compound purification, chemical structure confirmation, biological evaluation and data analysis. The workflow for generation of SAR data is usually distributed across highly specialized facilities and biological data on a new chemical structure is rarely available prior to one week after its synthesis. Parallelization of chemical synthesis and bioassaying has been the most common solution but remains largely cost-intensive due to lack of real-time feedback and consequential generation of irrelevant chemical examples. Thus, there is an imminent unmet need for merging chemical, analytical and biological procedures into a single continuous process that minimizes spatio-temporal barriers and fosters a cost-efficient lead discovery process. In this talk we demonstrate the seamless integration of a flow-compatible beta-secretase inhibition assay into a fully automated chemical flow synthesis and analysis platform that allows the generation of complete SAR cycles within 60 min from injection of the starting materials to generation of IC50 values.



M. Werner, C. Kuratli, R. E. Martin, R. Hochstrasser, D. Wechsler, T. Enderle, A. I. Alanine, H. Vogel, *Angew. Chem.* **2014**, *126*, 1730-1735; *Angew. Chem. Int. Ed.* **2014**, *53*, 1704-1708.

KGF-SCS Senior Industrial Investigator Award Lecture 2014: Challenges Rewards in Medicinal Chemistry Targeting Cardiovascular Metabolic Diseases

Werner Neidhart[1]

[1]F. Hoffmann-La Roche AG

Medicinal chemistry drug discovery programs in cardiovascular and metabolic diseases will be highlighted: Development of endothelin antagonists to address endothelial dysfunction (e.g. Tracleer, Avosentan), 11-beta hydroxysteroid dehydrogenase (11b-HSD1) inhibitors for dysregulated cellular glucocorticoid tonus (T2D Metabolic Syndrome) and non-covalent hormone sensitive lipase (HSL) inhibitors to study scope of direct inhibition of lipolysis in the conceptual frame of lipotoxicity diabetes. Translation of early clinical findings into improved follow-up molecules.

KGF-SCS Industrial Investigator Award Lecture 2014: «Contributions of biomolecular NMR to drug discovery»

Wolfgang Jahnke[1]

[1]Novartis Institutes for Biomedical Research

Drug discovery is an interdisciplinary effort. Biomolecular NMR spectroscopy is one of the technologies which can greatly aid drug discovery. NMR is a very sensitive and robust technique to detect and quantify molecular interactions. It can therefore be used for fragment-based screening and as an orthogonal validation tool for hits from other techniques (1). Furthermore, NMR gives structural information, and can thus be used to characterize binding sites or determine the structures of protein-ligand complexes.

The versatility of NMR as a biophysical tool in drug discovery will be illustrated using case studies such as the discovery of allosteric inhibitors of the kinase Bcr-Abl (2), or of farnesyl pyrophosphate synthase (3), the molecular target of bisphosphonates.

Above all, drug discovery is an interdisciplinary team effort. I wish to thank the many colleagues who share this effort: colleagues from structural biophysics, protein production, medicinal chemistry, biochemistry, biology, and other functions. It is a pleasure to work with them as a team, to advance drug discovery.

[1] W. Jahnke, H. Widmer. ”Protein NMR in biomedical research”. *Cell. Mol. Life Sci*. 61(5), 580-599 (2004)
[2] W. Jahnke, R.M. Grotzfeld, X. Pellé, A. Strauss, G. Fendrich, S.W. Cowan-Jacob, S. Cotesta, D. Fabbro, P. Furet, J. Mestan, A. Marzinzik. “Binding or bending: Distinction of allosteric Abl kinase agonists from antagonists by an NMR-based conformational assay”, *J. Am. Chem. Soc.* 132, 7043-7048 (2010)
[3] W. Jahnke, J.-M. Rondeau, S. Cotesta, A. Marzinzik, X. Pellé, M. Geiser, A. Strauss, M. Götte, F. Bitsch, R. Hemmig, C. Henry, S. Lehmann, J.F. Glickman, T.P. Roddy, S.J Stout, J. R. Green “Allosteric non-bisphosphonate FPPS inhibitors identified by fragment-based discovery”. *Nature Chemical Biology 6*, 660-666 (2010)

Engineering of high affinity probes for the visualization and analysis of bivalent epigenetic marks in living cells

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[1]EPFL Lausanne

Bivalent chromatin domains have significant roles in maintaining the pluripotency of embryonic stem cells (ES) as well as in cancer development. They are marked with a combination of repressive (H3 lysine 27 methylation, H3K27me3) and activating (H3 lysine 4 methylation, H3K4me3) post-translational modifications (PTMs) of histones. Bivalent domains have thus far mostly been studied by methods involving fixed, non-living cells or requiring lysis of large number of cells and by employing specific antibodies. Our aim is to develop a genetically encoded probe that binds specifically to bivalent nucleosomes to reveal the co-existence of H3K4me3 and H3K27me3 at the level of single live cells. This probe is designed to weakly interact with singly modified nucleosomes but it strongly binds to nucleosomes having both H3K4me3 and H3K27me3 marks, allowing for the detection of bivalent nucleosomes in various cell types and cellular processes.

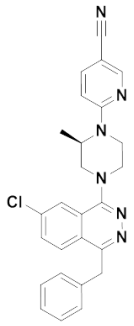
We designed, expressed and optimized a genetically encoded multivalent protein probe consisting of the rapidly maturating version of YFP, Venus, inserted between two binding domains, a PHD zinc finger and a Chromodomain, which cooperatively detect the bivalent marks. In order to validate and further optimize our probe for *in-vitro* and *in-vivo* applications, we used Expressed Protein Ligation (EPL) to synthesize two H3 histones carrying H3K4me3 and H3K27me3 modifications respectively, which were assembled with H2A, H2B, H4 and DNA to form bivalent nucleosomes. Quantitative measures of binding of the probe to these designer nucleosomes serves as an *in vitro* validation model. Expression and subsequent observation by fluorescence confocal microscopy allows the analysis of bivalent chromatin in stem cells and cancer cells. The advantage of genetically encoded probes is the possibility to study the functions and dynamics of bivalent chromatin in real time during cell differentiation and reprogramming which so far has not been possible by using current methods.

Sphingosine-1-Phosphate Lyase Inhibitors as an Alternative Therapeutic Strategy to S1P-Receptor Agonists for the Treatment of Multiple Sclerosis

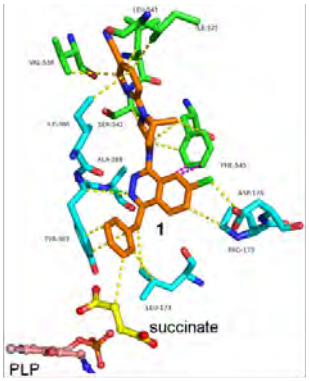
Berndt Oberhauser[1], Sven Weiler[1], Nadine Braendlin[1], Honnappa Srinivas[1], Andreas Billich[1]

[1]Novartis Pharma AG

The sphingosine-1-phosphate receptor ($S1P_1$) agonists Fingolimod (FTY720) has recently been approved for the treatment of multiple sclerosis (MS). After metabolic activation by phosphorylation, FTY720 acts as a functional antagonist by inducing internalization of $S1P_1$ receptors from the surface of T-cells. This blocks the egress of pathogenic T-cells from the lymph nodes by making them unable to respond to the physiological sphingosine-1-phosphate (S1P) gradient between the lymphatic system and the circulation. This gradient is retained by continuous degradation of S1P in lymphatic organs by the intracellular enzyme S1P-lyase. Inhibiting this enzyme would therefore provide an alternative opportunity to increase intracellular S1P levels and consequently block T-cells egress from lymphoid organs. Up to now no active site directed inhibitors of the S1P-lyase have been described.



S1P-lyase inhibitor **1**
IC_{50} = 210 ± 40 nM



co-crystal structure of inhibitor **1**
in the active site of S1P-lyase

The medicinal chemistry approach was initiated with a HTS campaign for inhibitors using a soluble form of the human enzyme. The chemical optimization program identified key structural features, the absolutely essential methyl-substitution on the piperazine ring and the correct electronic properties of the substituents on the pyridine and the phthalazine rings. With inhibitors approaching low nM IC_{50}s, co-crystallizations attempts with truncated human enzyme were successful and the first X-ray co-crystal structure of human S1P-lyase could be obtained. It shows the inhibitor bound in the substrate binding site about 5 Å distal to the catalytic center at the branching point of a Y-shaped channel which links the buried active site to the exterior efficiently blocking access of the substrate.

Inhibitors were characterized in cellular assays, where they dose-dependently increased intracellular S1P-levels. For further profiling we selected inhibitor 1 which showed sufficient oral bioavailability in rats . When we applied a single oral dose of 50 mg/kg a 90% reduction of CD4+ T-cells in the peripheral blood was observed which returned back to normal within three days. This encouraged us to test the compound in the experimental autoimmune encephalomyelitis (EAE) model in rats at the relatively low oral dose of 2 mg/kg b.i.d. and we observed a near-complete protection from disease symptoms. While our studies focused on MS as potential indication, other autoimmune diseases might also benefit from pharmacological inhibition of S1P-lyase. Our discovery of the first potent class of oral S1P-lyase inhibitors will enable further assessment of these options in preclinical models.

Disulfide-based prodrugs for improving the oral bioavailability of poorly water soluble drugs

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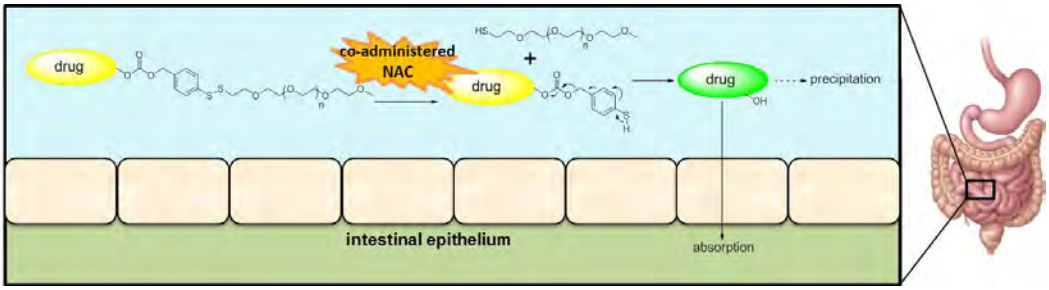
[1]ETH Zurich/Department of Chemistry and Applied Biosciences/Institute of Pharmaceutical Sciences, Vladimir-Prelog-Weg 1-5/10, 8093 Zurich

The delivery of poorly water-soluble drugs represents a considerable challenge in pharmaceutical sciences. Several approaches, such as solubilizing adjuvants (*i.e.*, co-solvents, surfactants, complexing agents) or molecular dispersion, have been developed to overcome the solubility issue. Most of the strategies are based on the physical interactions between drugs and excipients, which are not so stable neither controllable, especially when *in vivo*. Stimuli-responsive prodrug approach, linking the drug and solubilizing groups *via* covalent bonds, is regarded as a favorable choice in managing the *in vivo* drug delivery in a controllable way. Among drug-delivery routes, oral administration is the preferred modality because of convenience and better patient compliance. Surprisingly, only few prodrug approaches have been proposed for the oral delivery of poorly soluble drugs. [1]



Here, we report an oral prodrug strategy based on a redox-sensitive self-immolating platform (Scheme 1). A solubilizing group is conjugated to the drug *via* a disulfide bond in order to obtain a soluble prodrug. The reconversion of the prodrug takes place in the gut lumen by the action of a co-administered reducing agent, *N*-acetylcysteine (NAC), a safe dietary supplement. The disulfide bond cleavage generates an intermediate, which goes through a self-immolated process to release the free hydrophobic drug, which can then be absorbed. By controlling the amount of co-administered NAC, we can modulate the reconversion drug-release kinetic and location of the prodrug in the gastro-intestinal tract. Three prodrugs were successfully prepared with phenytoin, SN-38 and mitomycin C as the drug models. The reconversion kinetic was studied in pH 4.5/6.8 buffers, as well as in simulated gastric fluid (SGF)/simulated intestinal fluid (SIF). The drug-release was relatively slow in SGF but much faster in SIF, serving well with the fact that the main drug-absorbance location is in the small intestinal. This work was supported by a Novartis Fellowship to Dr. Tao Sun.

[1] Jarkko Rautio, Hanna Kumpulainen, Tycho Heimbach, Reza Oliyai, Dooman Oh, Tomi Järvinen, Jouko Savolainen, *Nat. Rev. Drug Discov.* **2008**, 7, 255–270.

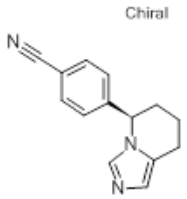
Selective Aldosterone Synthase Inhibitors (ASI) - Design of an Orally Active Proof of Concept Compound

Johannes Aebi[1], Benoit Hornsperger[1], Hans-Jakob Krebs[1], Bernd Kuhn[1], Hans Peter Märki[1], Alexander Mayweg[1], Kurt Amrein[1] *

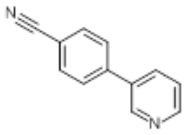
[1]F. Hoffmann-La Roche AG

Aldosterone is a steroid hormone (mineralocorticoid family) produced mainly by the zona glomerulosa of the adrenal cortex. The last biosynthetic step is mediated by aldosterone synthase (CYP11B2) an enzyme exclusively involved in the synthesis of aldosterone making it a premier target for inhibitors to lower aldosterone levels in circulation. CYP11B2 in humans is nearly identical (~93 % sequence identity [(2)]) to CYP11B1 an enzyme that is critical for cortisol synthesis. Despite this difficulty, several animal models were established to proof, compare and deepen knowledge about aldosterone synthase inhibition. All studies thus far were performed with the non-selective inhibitor fadrozol FAD286. FAD286 was shown to improve kidney function and morphology.

Therefore, there is an urgent need for selective CYP11B2 inhibitors. Unfortunately, the low homology of CYP11B2 between mouse and humans makes it difficult to find compounds which can be used in human and rodents, the preferred species for proof of concept experiments.



Fadrozole (FAD286)
CYP11B2 IC50 (*h*): **6 nM**; Select. (*h*) **12**
CYP11B2 IC50 (*m*): **190 nM**



Pyridine Hit
CYP11B2 IC50 (*h*): **40 nM**; Select. (*h*) **8**

An aryl pyridine hit compound derived from a focused screen has been optimized into potent and selective CYP11B2 inhibitors with good activity against both the human and non-human primate enzyme and against the enzyme in rodents. They have proven highly useful in animal models across species.

[1] Pitt, B.; Zannad, F.; Remme, W. J.; Cody, R.; Castaigne, A.; Perez, A.; Palensky, J.; Wittes, J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized aldactone evaluation study investigators. N. Engl. J. Med. 1999, 341, 709−717.
[2] Pitt Cerny, M. A. Progress Towards Clinically Useful Aldosterone Synthase Inhibitors. Current Topics in Medicinal Chemistry, 2013, 13, 1385-1401.

Ru(II) Complexes and Photodynamic Therapy: a Win-Win Combination

Cristina Mari[1], Vanessa Pierroz[1], Riccardo Rubbiani[1], Malay Patra[1], Stefano Ferrari[1], Gilles Gasser[1] *

[1]University of Zurich

The power to trigger the toxicity of a biologically active species with spatial and temporal control is a strongly chased achievement in the anticancer field. This possibility can reduce dramatically the side effects associated with traditional chemotherapy, together with the arising resistance. The synergistic action of a non-toxic compound (e.g. photosensitizer, PS), molecular oxygen and light is exploited by mankind since centuries and recently it was applied as a medical technique, known as Photodynamic Therapy, for the treatment of skin related disease and also cancer.[1] However, only two of the approved PSs (mainly based on a porphyrin skeleton) contain a metal ion, which is absolutely surprising considering that nowadays around 50% of traditional chemotherapy relies on the uses of platinum-containing compounds. The introduction of a metal ion can strongly improve the activity of porphyrins as PSs and, furthermore, the application of a non-porphyrin based metal complex as PS can solve some of the drawbacks associated to the approved systems such as non trivial synthesis, poor bioavailability, systemic accumulation and general light sensitivity. In this context, we explored the potential of six Ru(II) polypyridyl complexes as optimized PSs (Fig. 1). These substitutionally inert complexes are easily synthesized and are stable in human blood plasma. They exhibit an impressive molecular oxygen sensitization, together with the absence of toxicity in the dark on both healthy and non cancerogenic cell lines. Furthermore, **1** and **2** displayed a strong phototoxicity when irradiated at 420 nm with low light doses (9.27 $J \cdot cm^2$), with phototoxic indexes (dark to light toxicity ratio) of more than 150 and 40 respectively. Further studies to elucidate the mode of phototoxic action suggested that the mechanism is involving the genetic material, as supported by the strong binding affinity of the complexes for DNA, the nuclear localization and the ability to cleave DNA upon light irradiation.[2]

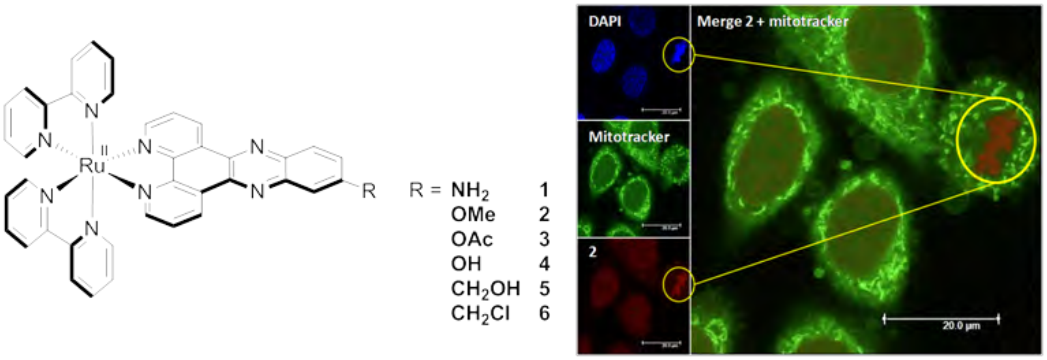


Fig. 1. Structures of Ru complexes and fluorescence microscopy image of HeLa cells incubated with complex **2**.

[1] Dolmans, D. *et al.*, *Nature Rev. Cancer* **2003**, 3, 380-387.
[2] Mari, C. *et al.*, **2014**, *submitted*.

Discovery of a potent $P2Y_{12}$ receptor antagonist with an improved efficacy/safety ratio

Eva Caroff[1], Francis Hubler[1], Emmanuel Meyer[1], Dorte Renneberg[1], Alexander Treiber[1], Markus Kramberg[1], Markus Rey[1], Patrick Hess[1], Kurt Hilpert[1], Markus A. Riederer[1], Beat Steiner[1] *

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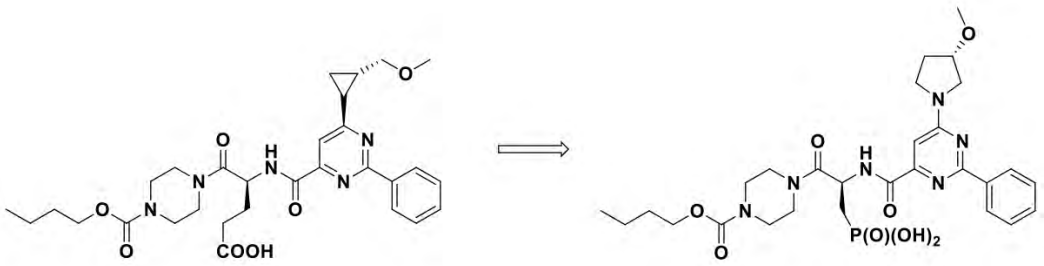
Acute coronary syndrome (ACS) is a clinical manifestation of coronary artery disease and is one of the leading causes of death worldwide. $P2Y_{12}$ antagonists represent an important anti-platelet therapy for patients with ACS and those undergoing percutaneous coronary intervention. Recent post-hoc analyses of several anti-platelet clinical trials emphasized the need for improved antiplatelet agents that are fully efficacious and have a reduced propensity to cause major bleeding. Herein we present the identification of 2-phenyl-pyrimidine-4-carboxamide analogs as $P2Y_{12}$ antagonists. A successful medicinal chemistry program delivered compounds that showed high potency in the disease-relevant platelet aggregation assay in human plasma. Further optimization efforts led to the discovery of ACT-475 showing efficacy in the rat ferric chloride thrombosis model and an improved safety profile in the rat surgical blood loss model as compared to ACT-881.



ACT-881
LTA IC_{50} = 31nM [1]
in human platelet-rich plasma

ACT-475
LTA IC_{50} = 6 nM
in human platelet-rich plasma

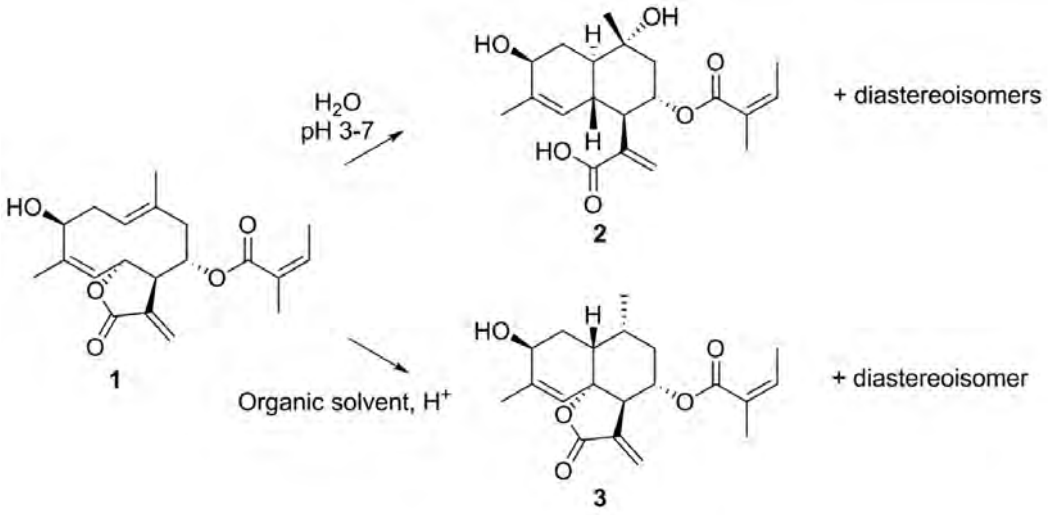
[1] Caroff, E.; Meyer, E.; Treiber, A.; Hilpert, K.; Riederer, M. A. *Bioorg. Med. Chem. Lett.* accepted.

Transannular cyclization of the sesquiterpene lactone nobilin into cadinane-type derivatives

Maria De Mieri[1], Ursula Thormann[2], Georgios Imanidis[2], Markus Neuburger[1], Marcel Kaiser[3], Reto Brun[3], Matthias Hamburger[1] *

[1]University of Basel, [2]University of Applied Sciences and Arts Northwestern Switzerland, FHNW, [3]Swiss Tropical and Public Health Insitute, Basel

Sesquiterpene lactones (SQLs) are an important class of secondary metabolites of the plant family Asteraceae that have shown a wide spectrum of biological activities including anti-inflammatory, anti-tumor, and antimicrobial properties. [1] Nobilin (**1)** is a major anti-inflammatory germacranolide in flowers of *Anthemis nobilis*, but the compound was found to be unstable when tested in the *in vitro* Caco-2 absorption model.



To gain a basic understanding of this chemical instability we undertook a preparative isolation of the degradation products of **1** in water, to simulate the physiological medium. Extensive spectroscopic and crystallographic studies allowed us to identify the main structures and to postulate a mechanism of degradation. All the degradation products (**2** and **3** are shown as examples) possess a cadinanolide scaffold generated by transannular cyclization. The acid catalyzed transannular cyclization of other natural cyclodecadiene-containing compounds is considered to be biomimetic and has been extensively studied to provide insights in their biosynthesis. [2] On the basis of these considerations, we performed a degradation study in organic media in presence of acids of different strength. The antitrypanosomal activity of some of the degradation products has been evaluated and compared to nobilin (**1)**.

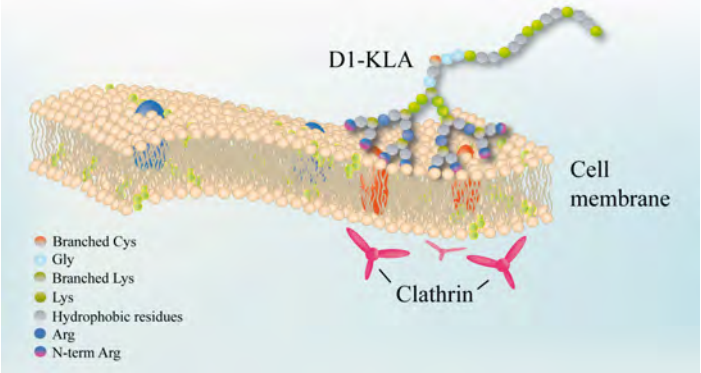
[1] S. Zimmermann, M. Kaiser, R. Brun, M. Hamburger, M. Adams, Planta Med. 2012, 78, 553-556.
[2] J.-L. Lòpez-Pérez, A.F. Barrero et al. Chem. Eur. J. 2013, 19, 6598-6612.

Designed Cell Penetrating Peptide Dendrimers Efficiently Internalize Cargo into Cells

Emilyne Blattes[1], Gabriela A. Eggimann[1], Stefanie Buschor[1], Rasomoy Biswas[1], Stephan M. Kammer[1], Tamis Darbre[1], Jean-Louis Reymond[1] *

[1]University of Berne

The cell membrane poses an impermeable barrier for a large number of compounds, in particular peptides, limiting their use as drugs. Nevertheless the discovery of the cell penetrating properties of the HIV-1 Tat protein led to the discovery of a variety of cell penetrating peptides (CPP) derived from naturally occurring sequences. CPP can serve as carriers for drug delivery. However they suffer from the typical metabolic instability of linear peptides and tend to be hemolytic and cytotoxic. We showed recently that peptide dendrimers containing very short mono- or dipeptide branches[1] are generally more resistant to proteolytic degradation compared to linear peptides. Moreover they show almost no cytotoxicity when used for DNA transfection[2] and very weak hemolysis when designed as antimicrobials[3], most likely a benefit of their globular conformation enforced by the dendritic topology. Herein, we report a broader survey of CPP redesigned in multi-branched topology leading to cell penetrating peptide dendrimers (CPPD)[4]. The cellular uptake was observed in most of the tested CPPDs and was favored with peptide dendrimers containing a balanced ratio of cationic and hydrophobic residues. Dendrimers **D1** inspired by the Tat peptide and **D11** inspired by pVEC efficiently localized in the cytoplasm and were used to deliver cytotoxic cargo into cells. The investigated CPPDs were not intrinsically cytotoxic and showed only moderate hemolysis.



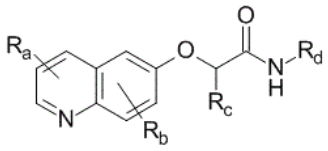
[1] J. L. Reymond and T. Darbre, *Org. Biomol. Chem.*, **2012**, 10, 1483-1492. [2] A. Kwok, G. A. Eggimann, J. L. Reymond, T. Darbre and F. Hollfelder, *ACS Nano*, **2013**, 7, 4668-4682. [3] M. Stach, N. Maillard, R. U. Kadam, D. Kalbermatter, M. Meury, M. G. P. Page, D. Fotiadis, T. Darbre and J.-L. Reymond, *Medchemcomm*, **2012**, 3, 86-8. [4] G.A. Eggimann, E. Blattes, S. Buschor, R. Biswas, S.M. Kammer, T. Darbre and J.-L. Reymond, *ChemComm*, **2014**, accepted

Synthesis and fungicidal activity of quinolin-6-yloxyacetamides, a novel class of tubulin polymerization inhibitors

Laura Quaranta[1], Renaud Beaudegnies[1], Raphael Dumeunier[1], Guillaume Berthon[1]

[1]Syngenta Crop Protection AG

Compounds of the type shown below are examples of a new chemical class of tubulin polymerization inhibitors with potent activity against a broad spectrum of agronomically relevant diseases, comparable to commercialised standards. Aspects of the discovery, synthesis, biology and structure-activity relationships together with design considerations will be presented.



[1] Clemens Lamberth et al., *Synlett*, 2014, 858.
[2] Clemens Lamberth et al., *Bioorg. Med. Chem. Lett*, **2014**, *submitted*