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Medicinal Chemistry, Talk **280**

Potent and selective, orally active GPBAR1 agonists as chemical biology probes

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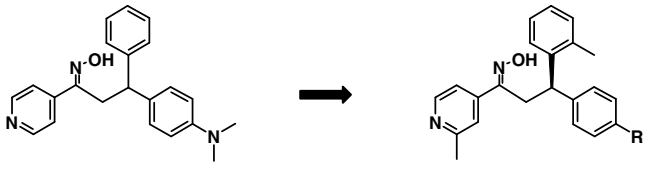
The G-protein coupled bile acid receptor 1 (GPBAR1) has emerged in recent years as a key component of the bile acid signalling network. GPBAR1 agonism has been proposed as a new mode of intervention for metabolic and inflammatory diseases [1].



1 2

Oxime **1** was found as low-nM full GPBAR1 agonist in a high-throughput screening campaign. However, compound **1** was not useful for in vivo studies due to poor physicochemical and metabolic properties. Optimisation work led to compounds of general structure **2**, which showed meaningful antidiabetic and antiinflammatory effects in rodents.

[1] T. W. H. Pols, L. G. Noriega, M. Nomura, J. Auwerx, K. Schoonjans, *J. Hepatol.* **2011**, *54*, 1263.

Medicinal Chemistry, Talk **281**

Pyridomycin As Lead For New Anti-Tuberculosis Agents

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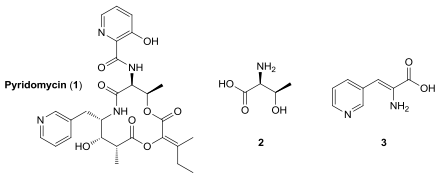
Pyridomycin (**1**) is a bacterial natural product that was first isolated from the S*treptomyces* strain no. 6706 in 1953 and was shown to exhibit significant *in vitro* anti-tubercular activity and low systemic toxicity in mice.[1,2]



In light of the pressing need for the development of new drugs against tuberculosis, we have started to explore the biology and medicinal chemistry of pyridomycin with a focus on the *de-novo* synthesis of analogs of the natural product lead. In this context we have identified structurally conserved analogs of **1** that retain almost full activity against *M. tuberculosis*. The synthesis of these compounds was based on a modular approach, which involved L-Thr (**2**) and dehydroamino acid **3** as two of the basic starting materials. Appropriate modifications of intermediates also led to two simplified acyclic analogs.
This contribution will discuss the structures and stereoselective synthesis of new pyridomycin analogs together with their biological activity.

[1] Maeda K. *et al*., *J. Antibiot. 6A*, **1953**, 140.
[2] Cole S. T., **2011**, personal communication.

Medicinal Chemistry, Talk **282**

Identification of NVP-BYL719, a potent and selective PI3Kα inhibitor

Giorgio Caravatti, Vito Guagnano, Robin Fairhurst, Patricia Imbach, Ian Bruce, Mark Knapp, Pascal Furet, Christine Fritsch, Alain De Pover, Francesca Blasco, Joachim Blanz, Doriano Fabbro, Frank Seiler, Marc Lang

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PI3Ks are lipid kinases that control signaling pathways involved in cell proliferation, motility, cell death and cell invasion. Class I PI3K contains four isoforms, p110α, p110β, p110δ and p110γ which carry out non redundant signaling functions. The α and β isoforms are ubiquitously expressed, whereas the δ and γ isoforms are expressed primarily in lymphocytes and engaged in the regulation of immune responses.

A gain of function in PI3K signaling is common to many types of human cancer, specifically, mutations in PIK3CA are found in more than 30% of various solid tumor types, including, breast, endometrium, bladder, colorectal as well as lung cancers.

As these mutations constitutively activate the lipid kinase activity of the protein, the cancer-specific mutants of p110α appear to be ideal therapeutic targets for anticancer drug development. p110α isoform specific inhibitors could be efficacious against tumors harboring p110α mutations and provide an improved safety profile compared to current pan-PI3K modulators.

Due to the high sequence homology around the catalytic site development of an isoform-selective inhibitor seemed difficult. To achieve this selectivity we tried to target a set of non-conserved amino acids located at the solvent exposed area of the ATP binding site. The 2-aminothiazole scaffold proved to be an excellent starting point for the development of potent PI3K inhibitors. Modification of key substituents and further optimization of the drug-like and PK properties have led to the identification of NVP-BYL719, a potent and selective PI3Kalpha inhibitor with a promising biological activity. SAR and the structural basis for the isoform selectivity will be discussed.

Medicinal Chemistry, Talk **283**

Multivalent Glycopeptide Dendrimers as *Pseudomonas aeruginosa* Biofilm Inhibitors

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The spread of antibiotic resistant bacteria is one of the most pressing problems in human health today. Antibiotic resistance occurs whenever an antibiotic exerts its effects by directly interfering with a key step in the life cycle of the bacterium, because selection pressure for survival automatically leads to the occurrence of resistance. In the case of the opportunistic pathogen *Pseudomonas aeruginosa* causing lethal airways infections in cystic fibrosis and immunocompromised patients, the formation of biofilms plays an important role in antibiotic resistance and disease progression. Biofilm formation is mediated in part by the galactose-specific lectin LecA (PA-IL) and the fucose-specific lectin LecB (PA-IIL). Capitalizing on the well-known cluster effect observed on binding of multivalent carbohydrates to lectins, we have reported the first cases of *P. aeruginosa* biofilm inhibition with multivalent lectin inhibitors, including the fucosylated glycopeptide dendrimer **FD2** (cFuc-KPL)$_4$(*K*FKI)$_2$*K*HI-NH$_2$ targeting LecB,[1] and the related galactosylated glycopeptide dendrimer **GalAG2** (βGal-KPL)$_4$(*K*FKI)$_2$ *K*HI-NH$_2$ targeting LecA.[2] Herein we report the synthesis, lectin binding and biofilm inhibition of higher generation dendrimer analogs of **GalAG2** prepared using a convergent thioether (ClAc) ligation[3], leading to nanomolar affinities towards LecA and improved biofilm inhibition.

[1] E. M. V. Johansson et al., *Chem. Biol.* **2008**, *15*, 1249
[2] R. Kadam, M. Bergmann, et al., *Angew Chem Int Ed Engl.* **2011**, *50*, 10631
[3] N. Uhlich et al., *Org Biomol Chem* **2011**, *9*, 7071

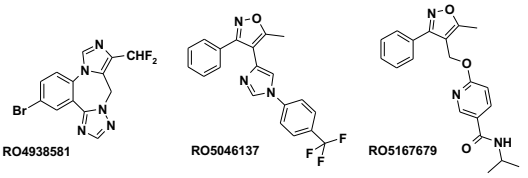
Medicinal Chemistry, Talk **284**

Novel Potent and Selective NAM's of the $GABA_A$ α5 Receptor Subtype

T. Ballard, B. Buettelmann, N. Clemann, H. Fischer, B. Han, M.-C. Hernandez, R. Gasser, R. Jakob-Roetne, S. Kirchner, F. Knoflach, H. Knust, M. Lucas, R. Moog, M. Nettekoven, E. Prinssen, H. Stadler, A. W. Thomas, G. Trube, P. Waldmeier

F. Hoffmann-La Roche AG
pRED, Pharmaceutical Research & Early Development, Basel, Switzerland

Extensive detailed pharmacological evidence exists in both rodents and humans suggesting non-selective inverse agonists at the benzodiazepine site of the $GABA_A$ receptor enhance cognitive functions. However, non-selective inverse agonists induce anxiogenic and pro-convulsive effects. Through the greater understanding of the complex pharmacology of the $GABA_A$ α5 receptor sub-types it is now strongly believed that the cognitive effects are mediated through negative allosteric modulation of the $GABA_A$ α5 receptor sub-type. [1]



We have identified a number of novel series' of potent and selective $GABA_A$ α5 receptor negative allosteric modulators. The talk will describe the discovery of these classes culminating in the full profile of key compounds.

[1] U. Rudolf, F. Knoflach, *Nature Reviews Drug Discovery* **2011**, *10*, 685.

Medicinal Chemistry, Talk **285**

Ligand-based virtual screening and *de novo* design as tools in hit and lead structure identification: success stories

Tiago Rodrigues, Jens Kunze, Birgit Zonsics, Michael R. Reutlinger, Anna M. Perna, Jan A. Hiss, Petra Schneider, Gisbert Schneider

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Computer-assisted drug design plays a growing role in early-stage medicinal chemistry programs. Virtual screening is widely used in hit- and lead discovery to feed medicinal chemists with potential entry points for a specific target.[1] In addition, *de novo* design is seeing new interest, particularly for the task of scaffold hopping.[2] Here, we report success stories using these techniques. We have successfully screened a virtual combinatorial library of 1,4-dihydropyrimidines by use of self-organizing maps. The synthesized molecule inhibited cyclin-dependent kinase 2 (CDK2).[3] We also have interest in exploring *de novo* design as a tool to tackle challenging drug targets. Hence, we extensively use our in-house software DOGS.[4] It requires a known bioactive compound as template to grow new molecules, placing emphasis on the synthesizability of suggested compounds.[4-6] As examples, new constructs representing significant scaffold-hops from amprenavir (HIV protease inhibitor) and VX680 (Aurora A kinase inhibitor), as well as their activities, will be presented. Overall, we show expeditious uses of *de novo* design, and its potential to become mainstay in hit discovery.

[1] Schneider, G. *Nat. Rev. Drug Discov.* **2010**, *9*, 273-276.
[2] Schneider, G. *J. Comput. Aided Mol. Des.* **2012**, *26*, 115-120.
[3] Schneider, P.; Stutz, K.; Kasper, L. *et al*. *Pharmaceuticals* **2011**, *4*, 1236-1247.
[4] Hartenfeller, M.; Zettl, H.; Walter, M. *et al*. *PloS Comput. Biol.* **2012**, *8*, e1002380.
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Medicinal Chemistry, Talk **286**

P53-MDM2 Interaction Inhibition by Tetrasubstituted Imidazoles

Guido Bold, Andrea Vaupel, Alain De Pover, Jörg Kallen, Keiichi Masuya, Joanna Hergovich Lisztwan and Pascal Furet

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The p53 tumor suppressor protein plays a key role in the control of cellular integrity. Alteration by loss of function of the p53 gene by mutations or deletions is observed in almost 50 % of all human cancer tissues. In other cancer tissues, still expressing the wild-type form, the normal function of p53 is altered by overexpression or amplification of MDM2, the main negative regulator of the tumor suppressor. In this setting, MDM2 mainly functions as a p53 specific ubiquitin ligase which, by binding to the N-terminal transactivation domain of p53, triggers its proteasomal degradation. Cancerous cells having elevated MDM2 levels are thus protected against p53 dependent apoptosis and cell cycle arrest mechanisms.

To restore normal p53 function in such tumor cells, one can envisage to disrupt the p53-MDM2 interaction by small molecules having high affinity for the p53 binding pocket of MDM2.[1] Some molecules exerting an antiproliferative activity by this mechanism have entered clinical evaluation.[2]

Structural information from the interaction of an octapeptidic inhibitor with MDM2[3] led us to the discovery of a new class of nonpeptide inhibitors of the p53-MDM2 interaction.[4] We report here the design of a second structural type of inhibitors, based on a tetrasubstituted imidazole motif.

[1] a) Millard, M.; Pathania, D.; Grande, F.; Xu, S; Neamati, N. *Curr. Pharm. Des.* **2011**, *17*, 536. (b) Brown, C. J.; Cheok, C. F.; Verma, C. S.; Lane, D. P. *Trends Pharmacol. Sci.* **2011**, *32*, 53.

[2] Cheok, C. .F.; Verma, C. S.; Baselga, J.; Lane, D. P. *Nat. Rev. Clin. Oncol*. **2011**, *8*, 25.
[3] García-Echeverría, C.; Chène, P.; Blommers, M. J. J.; Furet, P. *J. Med. Chem*. **2000**, *43*, 3205.

[4] published online: http://dx.doi.org/10.1016/j.bmcl.2012.03.083

Medicinal Chemistry, Talk **287**

Click-Peptides: Novel 1,2,3-Triazole Backbone-Modified Peptides for Tumor Targeting

Ibai E. Valverde[1], Andreas Bauman[1], Christiane Kluba[1], Alba Mascarin[1], Sandra Vomstein[1], Martin Walter[2], Thomas. L. Mindt[1]

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[2]Universitätsklinik für Nuklearmedizin, Inselspital, 3010 Bern, Switzerland

Regulatory peptides (e.g., somatostatin, bombesin) have been shown to be suitable vectors for the specific delivery of radioactivity to tumors for diagnostic and therapeutic applications in nuclear oncology.[1] However, due to their inherent instability *in vivo*, new strategies are needed for the stabilisation of radiopeptides towards proteases in order to improve their bioavailability and increase their accumulation in the targeted tissues. 1,2,3-triazoles, readily obtained by CuAAC, could be suitable amide bond surrogates which are resistant to proteolysis.[2] In the present study, we report the synthesis and pharmacological evaluation of radiolabelled, triazole-containing analogues of the gastrin releasing peptide receptor (GRPR) targeting peptide bombesin (BBN).

We have synthesized a series of analogues of [Nle^{14}]BBN(7-14), in which each amide bond is individually replaced by a 1,4-disubstituted 1,2,3-triazole. After radiolabelling of the peptidomimetics, their binding affinity, internalization kinetics and metabolic stability have been determined. First preclinical data on the *in vivo* evaluation will be presented.

To the best of our knowledge, this is the first report of the systematic replacement of amide bonds with 1,2,3-triazoles within the binding sequence of linear, high affinity peptides. The methodology holds great potential for the development of novel, stabilized peptide-based radiopharmaceuticals.

[1] V. Ambrosini, M. Fani, S. Fanti, F. Forrer, H.R. Maecke, *J. Nucl. Med.* **2011**, 52, 42S.
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Medicinal Chemistry, Talk **288**

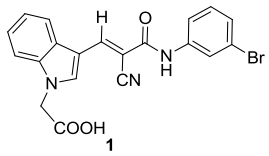
From HTS to the discovery of ACT-129968, a potent, selective and oral CRTH2 receptor antagonist for the treatment of allergic diseases

Anja Valdenaire, Julien Pothier, Kurt Hilpert, Carmela Gnerre, Patrick Hess, Luca Piali, Sylvie Froidevaux, Oliver Peter, Xavier Leroy, Markus A. Riederer, Heinz Fretz

Actelion Pharmaceuticals Ltd, Gewerbestrasse 16, CH-4123 Allschwil, Switzerland

More effective and safer treatment modalities are needed to treat patients suffering from allergic diseases. Recent approaches target the receptors of the lipid mediator prostaglandin D2 (PGD2). PGD2 is involved in allergic responses, for example, released PGD2 activates the G-protein coupled receptor CRTH2 (also known as DP2) and triggers pro-inflammatory signaling in Th2 cells, eosinophils and basophils.

In this presentation we report the SAR leading to the discovery and development of ACT-129968 (setipiprant), a novel CRTH2 receptor antagonist, originating from screening hit **1**. ACT-129968 was selected for clinical development based on its potency and selectivity for CRTH2, good pharmacokinetic properties and a favorable safety profile. ACT-129968 inhibits *in vitro* key mechanisms of allergic responses, such as PGD2-induced eosinophil activation and migration, as well as cytokine secretion by Th2 cells. Furthermore, ACT-129968 interferes with PGD2-induced lung eosinophilia in rats.



1

FLIPR (Ca^{2+} flux) hCRTH2 IC_{50}= 0.6 μM
Binding hCRTH2 IC_{50}= 0.5 μM

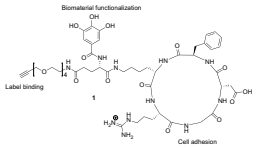
Medicinal Chemistry, Talk **289**

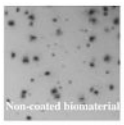
Chemical functionalization of biomaterials for the enhancement of endothelial cells adhesion

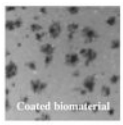
[1] Françoise Borcard, [1] Davide Staedler, [1] Horacio Comas, [2] Franziska Krauss Juillerat, [2] Urs T. Gonzenbach, [3] Lucienne Juillerat-Jeanneret and [1] Sandrine Gerber-Lemaire[1]

[1] ISIC, BCH, EPFL, CH-1015 Lausanne, Switzerland, [2] Department of Materials, ETH-Zürich, Zürich, Switzerland, [3] University Institute of Pathology, CHUV, Lausanne, Switzerland

Tissue engineering of permanent implants is a promising approach for the treatment of large bone defects. To achieve this goal, biomaterials must be seeded before implantation with histocompatible human bone-derived cells and a functional vascular system must be developed that together are expected to promote bone reconstruction. This project aims at the synthesis of multifunctional linkers designed to covalently link both particle-stabilized ceramic foams with defined pore structures [1] and human cells. A chemical linker containing specific entities for cell surface functionalization, and able to promote the attachment of human fetal osteoblasts to the biomaterials has already been developed and evaluated [2-3]. Here we present, the synthesis of a specific linker **1** and its conjugation to three different biomaterials. The evaluation of endothelial cells adhesion to these scaffolds is presented, as well as their ability to further evolve as a functional vascular system [4].







[1] Krauss Juillerat, F. and al. *Mat. Lett* . **2010**, 64, 1468-1470. [2] Comas, H. and al., S. *Appl. Mater. Interface*, **2012**, 4, 573-576. [3] Borcard, F. and al. *J. Bioconjugate Chem.,* **2011**, *22*, 1422-14. [4] Borcard, F. and al. *J. Med. Chem.*, **2012**, *submitted.*

Medicinal Chemistry, Talk **290**

First-in-class, Non-covalent and Competitive Spiropiperidine Hormone Sensitive Lipase Inhibitors

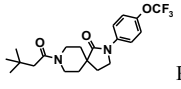
W. Neidhart, J. Ackermann, A. Conte, D. Hunziker M. Nettekoven, H. Fischer, T. Schulz-Gasch, S. Wertheimer, K.-S. Huang & K. Conde-Knappe.

F. Hoffmann-La Roche Ltd, CH-4070 Basel, Switzerland.

Hormone sensitive lipase (HSL) is an intracellular neutral serine lipase/esterase highly expressed in adipose tissue where it controls release of free fatty acids from triglycerides upon hormonal stimulus. As such, it is a regulator of adipocyte lipolysis and it has been shown that type II diabetic individuals exhibit enhanced lipolytic activity due to up-regulation of HSL. There is evidence that this chronic increase of plasma levels of free fatty acids further exacerbates insulin resistance. This is likely driven by ectopic accumulation of triglycerides in liver, pancreas and muscle causing pathological damage.

Thus, it was rationalized that pharmacological inhibition of HSL may restore exaggerated plasma free fatty acid and triglyceride levels and be of therapeutic value for the treatment of type II diabetes.

In the effort towards non-covalent and competitive HSL inhibitors, a potent and selective lead series of spiropipiperidene lactams was generated from a HTS hit cluster through molecular design and homology modeling (e.g. RO5448303). Competitive, non-covalent binding kinetics to the enzyme were confirmed for key compounds. The spiropiperidines are a first-in-class, novel chemotype of inhibitors due to the fact that the HSL inhibitors published so far are metal electrophiles or reactive acylators which modify the enzyme active site in a time-dependent manner what can raise safety concerns. Conclusion: A novel class of potent & selective HSL inhibitors was developed. Key compounds show high enzyme and cell potencies in the low nanomolar range and have favorable PK/PD properties enabling to study the effect of inhibition of HSL in animal models of obesity & type II diabetes.



RO5448303

Medicinal Chemistry, Talk **291**

Scoring multipole electrostatics in atomistic simulations to better understand binding-affinity energetics of fluoroaromatic inhibitors to carbonic anhydrase

Tristan Bereau, Fabien W. Monnard, Thomas R. Ward, and Markus Meuwly*

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The incorporation of fluorine in pharmaceutical products has enjoyed growing interests due to its ability to improve protein-ligand binding, metabolic stability, and modulate physicochemical properties, e.g., lipophilicity, basicity. While the effects of fluorine are relatively well understood [1], an accurate determination of the energetics of specific protein-ligand interactions still call for quantitative studies. In this regard, a computational approach provides both atomistic resolution and a decomposition of the interactions at hand.

In this work, we study the effects of degrees and patterns of fluorination on the binding affinity of various inhibitors with carbonic anhydrase II. The method is validated by comparing free-energy calculations with experimentally determined binding affinities—similar to a previous study of non-fluorinated ligands [2].

While the computational power at hand limits these simulations to a point-charge (PC) representation of the electrostatics, we evaluate the effects of multipole (MTP) interactions on the ligand by scoring PC-sampled conformations with a MTP energy function. The results provide a detailed decomposition of the multipolar interactions that drive protein-ligand binding.

[1] K. Müller, C. Faeh, and F. Diederich, *Science* **2007**, *317*, 1881.
[2] M. Schmid, E. S. Nogueira, F. W. Monnard, T. R. Ward, and M. Meuwly, *Chem. Sci* **2011**, *3*, 690-700.

Medicinal Chemistry, Talk **292**

SOM230: A new therapeutic modality for Cushing's disease

Ian Lewis[1], Janos Pless, Rainer Kneuer, Daniel Hoyer, Antonio P. Silva, Gisbert Weckbecker, Christian Bruns and Herbert A. Schmid

Global Discovery Chemistry, Global Imaging, Autoimmune, Neuroscience and Oncology Research Departments,

[1]Novartis Institutes of Biomedical Research, CH-4002 Basel, Switzerland.

SOM230 has recently shown promise as the first effective pituitary directed medical treatment for Cushing's disease. Indeed, the multiple high affinity binding of SOM230 to somatostatin receptor subtypes enables much more effective inhibition of ACTH release in-vitro and in-vivo. Recent Phase III clinical studies involving treatment of Cushing's disease with SOM230 have demonstrated that SOM230 produced a rapid and sustained reduction in urinary free cortisol (UFC) levels in the majority of patients with significant improvements in signs and symptoms of Cushing's disease[1].

[1]. Colao, Annamaria; Petersenn, Stephan; Newell-Price, John; Findling, James W.; Gu, Feng; Maldonado, Mario; Schoenherr, Ulrike; Mills, David; Salgado, Luiz Roberto; Biller, Beverly M. K., A 12-month phase 3 study of pasireotide in Cushing's disease, New England Journal of Medicine, Vol. 366, 914-924, 2012.

Medicinal Chemistry, Talk **293**

Synthesis and biological evaluation of ^{18}F labeled fluoroethoxy and fluoropropyl tryptophan analogs as potential PET tumor imaging agents.

Aristeidis Chiotellis[1], Linjing Mu[2], Svetlana Selivanova[1], Adrienne Müller[1], Holger Siebeneicher[3], Keith Graham[3], Stefanie D. Krämer[1], Roger Schibli[1,2], Simon M. Ametamey[1]

[1] Center for Radiopharmaceutical Sciences ETH-PSI-USZ, Institute of Pharmaceutical Sciences ETH, Zurich, Switzerland
[2] Center for Radiopharmaceutical Sciences ETH-PSI-USZ, Department of Nuclear Medicine, University Hospital Zurich, Zurich, Switzerland
[3] Bayer Healthcare Pharmaceuticals, Berlin, Germany

One interesting metabolic process, as a target for metabolic tumour imaging, is the increased protein metabolism in proliferating cancer cells. Avid uptake of amino acids is a distinct feature of uncontrollably growing cancer cells and in this respect, amino acids based tracers represent a promising class of radiopharmaceuticals for tumor imaging. We recently reported on 5-(2-[^{18}F]fluoroethoxy)tryptophan (5-[^{18}F]FEHTP) as a PET probe for tumor imaging and quantification of LAT1 (L amino acid transporter subtype 1) activity[1]. In this study, five novel ^{18}F-labeled tryptophan derivatives were synthesized and evaluated. Three of these compounds bear a fluoroethoxy substitution at the 4-, 6- or 7- position of the tryptophan ring. The remaining two are 3-fluoropropropyl derivatives where the fluoropropyl side chain is attached to either position 2- or 5- of the indole ring. Cold reference compounds and precursors were prepared by multi-step approaches. The [^{18}F]fluoroethoxytryptophans were synthesized by a rapid and efficient one step *O*-alkylation reaction of the corresponding hydroxyltryptophans with [^{18}F]-fluoroethyltosylate. The 3-[^{18}F]fluoropropyltryptophans were prepared by a two step reaction sequence involving nucleophilic fluorination of fully tert-butyl protected mesylate precursors and subsequent deprotection. All radiolabeled compounds were evaluated *in vitro* and *in vivo* using positron emission tomography and these results will also be presented.

[1] Stefanie Krämer et al., *J. Nucl. Med.* **2012**, *53*, 434

Medicinal Chemistry, Talk **294**

FimH Antagonists for the Treatment of Urinary Tract Infections

Lijuan Pang, Simon Kleeb, Katrin Lemme, Said Rabbani, Meike Scharenberg, Beat Ernst*

Institute of Molecular Pharmacy, University of Basel
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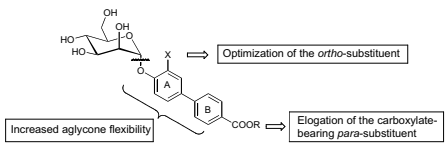
Urinary tract infections (UTIs), primarily caused by uropathogenic *Escherichia coli* (UPEC), affect millions of people and account for significant morbidity and high medical costs. UPEC strains encode filamentous surface adhesive organelles, the so-called type 1 pili. At the tips of these pili, FimH lectins are located. Blocking these lectins with soluble carbohydrates or analogs thereof prevents the bacterial adhesion to host cells and therefore offers a potential therapeutic approach for prevention and treatment of UTIs [1, 2]. Although numerous FimH antagonists have been developed so far, few of them have met the requirement for clinical applications due to poor pharmacokinetic properties. Here we describe modified biphenyl α-D-mannosides as FimH antagonists to improve their binding affinity, to explore their binding mode and to optimize their pharmacokinetic properties. As a result, a structure-activity relationship (SAR) and a structure-property relationship (SPR) were established for a series of biphenyl α-D-mannosides.



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Medicinal Chemistry **295**

Development of New Silicon-Based Building Blocks for a Direct ^{18}F-Labeling of Biomolecules for PET Imaging

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Prosthetic groups containing silicon as the labeling site have successfully been used for direct ^{18}F labeling of peptides for PET studies [1]. Major drawback of this kind of building blocks is their high lipophilicity contributed by the silicon substituents leading to a high uptake in the liver when tested *in vivo*. In the quest of developing a silicon building block with more hydrophilic properties several potential compounds were investigated. The two *tert*-butyl moieties that are directly attached to the silicon atom are retained since they are known to be crucial for the stability of the silicon-fluoride bond towards hydrolysis [2]. The hydrolytic stability of the silicon-fluoride bond of the compounds of interest was analyzed using DFT calculations. The building block with the highest predicted silicon-fluoride bond was synthesized in four steps and coupled to benzyl amine to form a simple model compound for a peptide. Direct fluorination with ^{19}F$^-$ did not lead to the desired reference compound but to decomposition. The reference compound was synthesized by an alternative route using a rhodium catalyst. NMR studies confirmed the instability of the compound in the presence of traces of water. These findings show that the silicon-methylene bond was destabilized by the electron withdrawing fluoride and the carbonyl group of the amide bond leading to its hydrolyis. Future investigations will not only focus on the stability of the silicon-fluoride bond but also on the stability of the other silicon-substituents bonds.

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Medicinal Chemistry **296**

Membrane disrupting antimicrobial peptide dendrimers with multiple amino termini

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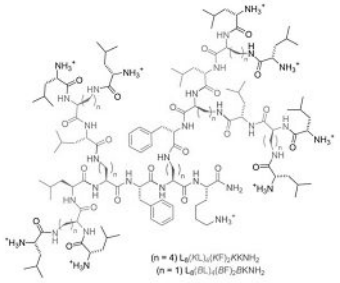
Many antimicrobial peptides (AMPs) act by disrupting microbial membranes.[1] The discovery of AMP dendrimers in which positive charges are provided by the multiple amino termini at the dendrimer periphery was carried out with a split-and-mix library approach.[2] This new type of AMPs acts as membrane disrupting agent and shows remarkably low haemolytic activity. These 3rd generation peptide dendrimers with hydrophobic amino acids in their branches and multiple free amino termini as the source of positive charges possess significant antimicrobial activities against Gram positive and Gram negative bacteria.[3]



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Medicinal Chemistry **297**

Dendritic Peptides for Cell Penetration

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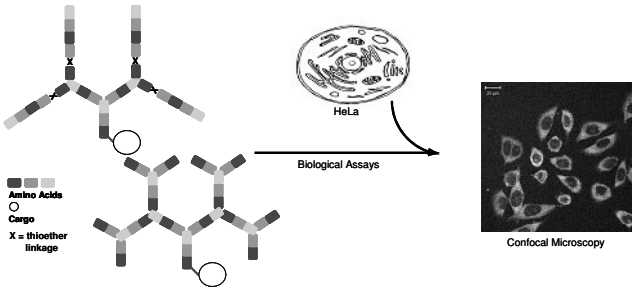
The delivery of therapeutic molecules into the human body is sometimes limited by solubility and uptake problems. One system to improve the cellular uptake of such therapeutic compounds are cell-penetrating peptides (CPPs).[1] It is known that the multivalency effect – the presentation of several copies of a CPP motif on a single molecule – can increase the cellular uptake.[2] Peptide dendrimers represent a group of tree-like, multivalent macromolecules, which are synthesized for different chemical and biological applications in our group.[3] By combining linear CPPs with peptide dendrimers we got well defined branched molecules with high cell uptake potency. We also designed new dendritic cell penetrating peptides with similar activities like linear CPPs. The results show that these peptides can transport efficiently a hydrophobic cargo into the cells with low cytotoxicity.



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Medicinal Chemistry **298**

Can we do Virtual Screening with Billions of Molecules?

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The high attrition rate of clinical compounds in pharmaceutical research is a big problem during the last decades. Therefore, the need to identify novel chemo types is an important objective for many drug discovery projects. The already publicly available small molecule database GDB-13[1] was already successful applied to ligand-based[2][3] and structure-based[4][5] virtual screening programs.

Here we report the extension of the approach up to 17 atoms with more than 160 billion molecules. Since the previously described GDB-13 algorithm was nearly at the technical limit of computation, we introduced an entirely new and much faster algorithm. We defined a set of restriction rules for functional groups and topology, based on statistical occurrence of structural elements in ZINC.

The database was classified by the Molecular Quantum Numbers[6] (MQN) to allow rapid browsing of thousands of small molecules similar to the already published GDB-13 Browser.[2] On 10 example drugs, we retrieved the 10,000 MQN-neighbours from GDB-17 and compared them to the parent drug in terms of shape similarity using ROCS. The MQN-neighbours have a high average shape similarity to the parent drug compared to randomly selected GDB-17 molecules.

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Medicinal Chemistry **299**

Chemical Space Analogs of α7 Nicotinic Receptor Agonists

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In the past, our group successfully demonstrated the use of the Chemical Universe Database GDB-11 in a fragment based approach to find new modulators of the nicotinic acetylcholine receptor (nAChR). [1]
The extended version of the database, GDB-13, includes 977 million organic molecules up to 13 atoms of C, N, O, Cl, S that are virtually possible, incorporating simple rules of chemical stability and synthetic practicability. GDB-13 was arranged to a specific subset to find analogs of nicotine by ligand-based virtual screening of 43.7 million molecules with the browser on our group webpage. [2,3] The hits were classified by city-block distance in the Molecular Quantum Number space (CB_{MQN}) combined with restrictions to exclude unwanted structural elements. The compounds were profiled by electrophysiology in *Xenopus oocytes* expressing human nAChR's.
In this work a similar approach is presented targeting new structural analogs of known α7 nicotinic receptor agonists.

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Medicinal Chemistry **300**

Dual-Targeting Conjugates Designed to Improve the Efficacy of Radiolabeled Peptides

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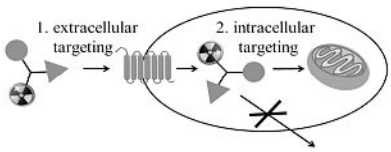
Radiopeptides, which target cell membrane receptors that are overexpressed by tumor cells, have been proven very useful for the diagnosis and therapy of cancerous diseases in nuclear medicine. However, after specific uptake into cancer cells, a rapid washout of the radioactivity is frequently observed. The combination with an additional entity directed against an intracellular target could result in a longer retention of the radioactivity in cancer cells and thus, improve the efficacy of the radiopharmaceutical.



Starting from readily available building blocks and applying click chemistry,[1] we assembled a trifunctional conjugate containing 1) the binding sequence of gastrin releasing peptide receptor (GRPr) targeting peptide bombesin (BBS), 2) a triphenylphosphonium (TPP) moiety specific for mitochondria, and 3) a tridentate chelating system for radiolabeling with the SPECT probe $[^{99m}Tc(CO)_3]^+$. The dual-targeting radiopeptide and a reference compound, lacking the TPP moiety, were evaluated side-by-side *in vitro* for stability, lipophilicity, receptor affinity, mitochondria binding, and cell internalization/externalization. Even though we were able to demonstrate individually the specificity of the conjugate to both extra- and intracellular targets, no difference in cellular retention of radioactivity could be observed. The described methodology used for the preparation of dual-targeting radioconjugates is modular and can be extended to different tumor-seeking vectors and intracellular targets.

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Medicinal Chemistry **301**

Effect of different spacers on Neurotensin-based radiotracers

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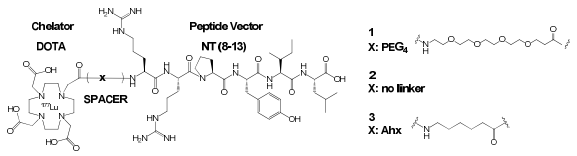
Neurotensin (NT) is a 13 amino acid regulatory peptide with nanomolar affinity towards NT receptors, which are overexpressed by human tumours e.g. colon cancer and small lung carcinoma.[1] Therefore, the minimum binding sequence NT(8-13) represents an interesting vector for the development of peptidic radiotracers for tumour imaging and therapy. The common design of such tracers includes a tumour-seeking peptide vector which is linked through a spacer to a chelator for complexation of a metallic radionuclide. The spacer can have a significant influence on the biological properties of such conjugates.[2] Surprisingly, the effect of different spacers has yet not been studied for radiopeptide conjugates based on NT(8-13).



Three different DOTA-NT(8-13) conjugates were prepared, compound **1** with a hydrophilic spacer (PEG_4), derivative **2** without spacer, and conjugate **3** with an hydrophobic spacer (Ahx: aminohexanoic acid). The peptide conjugates were efficiently synthesized using solid phase synthesis and successfully labelled with ^{177}Lu in excellent radiochemical purity and yield (>99%). A systematic biological evaluation of the compounds was performed *in vitro,* including cell internalization, receptor binding affinity, hydrophilicity and blood serum stability. The complete data set will be presented.

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Medicinal Chemistry **302**

Insights into the Glycocode – Structural Analysis of Carbohydrates in Solution

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Because carbohydrates/lectin interactions are involved in many relevant biological processes like signal transduction, pathogen-host interaction, or inflammation, they are interesting therapeutic targets.[1] However, in contrast to proteins and nucleic acids, the three-dimensional (3D) structure of carbohydrates in solution is still not understood completely.

Classical NMR spectroscopy of oligosaccharides in their free state is not able to provide sufficient distance restraints to determine a well-defined structure. Due to the fast tumbling time of small molecules, the NOE built-up rates are slow in NOESY experiments and the ROESY technique has to be used instead. However, ROESY has the drawback of yielding smaller theoretical NOEs corresponding to a maximal distance of 4 Å.

To address this problem, we developed a toolbox approach, linking oligosaccharides chemically to a ^{13}C-/^{15}N-labeled protein, *i.e.* by turning a small oligosaccharide into a large "glycoprotein", we alter its tumbling properties. With the increase of tumbling time, the range to detect NOEs and to obtain structural information is improved substantially.[2] The potential of this new approach was successfully demonstarted on a model trisaccharide. When this structure was analyzed, an interresidual noncanonical H-bond was identified, that contributes importantly to the rigidity of the trisaccharide in solution.

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Medicinal Chemistry **303**

Distinct Binding Modes for Substituted Lewis Structures to DC-SIGN

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Dentritic cells (DCs) have the function of presenting antigens to other processing cells of the immune system, particularly T-cells. DC-SIGN (DC-specific ICAM-3-grabbing non-integrin) is one of the major receptors on DCs involved in the uptake of pathogens and has gained increasing interest over the last decade as it is crucially involved in infections caused by HIV-1, Ebola virus, *Mycobacterium tuberculosis* and various other pathogens. High-mannosylated *N*-glycans or L-fucose-containing trisaccharide motifs such as the Lewis blood group antigens $Lewis^a$ and $Lewis^x$, which are surface components of these microorganisms, mediate binding to DC-SIGN.[1, 2]

Crystallographic data for DC-SIGN in complex with a $Lewis^x$-containing pentasaccharide suggest that the terminal sugar residues, L-fucose and D-galactose, are predominantly involved in binding.[3]

We elucidated the interaction of $Lewis^a$ as well as $Lewis^x$ bearing two different aglycones with DC-SIGN. Binding assays together with STD NMR analysis revealed distinct, substitution-dependent binding modes. Eventually, molecular modelling and mutagenesis studies support the assumption of a switch of the binding mode when introducing hydrophobic residues at the reducing end of the Lewis trisaccharides. Based on this information a new series of potential high-affinity DC-SIGN antagonists can be designed.

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Medicinal Chemistry **304**

Design, Synthesis and Biological Evaluation of Mannosylated Diarylamines as FimH Antagonists

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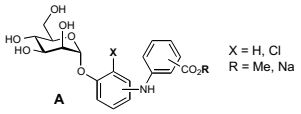
Uropathogenic strains of *Escherichia coli* (UPEC) are accounting for more than 70% of all urinary tract infections (UTIs). Particularly affected are women, who have a 40-50% risk to experience at least one symptomatic UTI episode at some time during their life [1]. These infections are initiated by the adhesion of the mannose-binding lectin FimH, located at the tips of bacterial type 1 pili, to oligomannosides of the glycoprotein uroplakin in the uroepithelium. Since bacterial resistance to antibiotics is a major problem of recurrent infections, blocking of bacterial adhesion with D-mannosides is a promising therapeutic approach to UTI.

Based on docking studies to the crystal structure of the FimH lectin domain [2], a library of low molecular weight mannosylated diarylamines **A** was synthesized and biologically evaluated as FimH antagonists in two different assays, a target-based binding assay [3] and a function-based FACS assay [4]. Furthermore, pharmacokinetic parameters of the FimH antagonists, which are critical for oral bioavailability (lipophilicity, solubility, and membrane permeation), were determined.



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Medicinal Chemistry **305**

Structural Evidence for an Induced Fit of E-selectin upon Small Molecule Ligand Binding

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The C-type lectin E-selectin is involved in a variety of inflammatory diseases. Lead optimization of glycomimetic antagonists for E-selectin has not been guided by X-ray crystallography to date.

In this study, E-selectin was co-crystallized in presence of sialyl Lewis^x (2.8 Å) and a mimic thereof (2.0 Å) with a 20-fold improved affinity, in which the D-Neu5Ac and the D-Glc*N*Ac moieties were replaced by (*S*)-cyclohexyl lactic acid and (1*R*,2*R*,3*S*)-3-methylcyclohexane-1,2-diol, respectively [1].

Co-crystallization with both ligands revealed an alternative protein conformation, in which the lectin- and EGF-like domains are separated, similar as for P-selectin co-crystallized with its glycoprotein ligand (PSGL-1) [2]. This conformational shift might be a result of an induced fit, which is not observed for a soaked E-selectin-sLe^x structure [2]. Three loop regions in the lectin domain are rearranged. The loop consisting of amino acids 80-90 is significantly shifted towards the ligand binding site, which no longer is a flat surface and forms a shallow pocket around the ligand. Most prominently, Arg84 is flipped towards the ligand, however, without any direct interaction. The overall binding mode of the sLe^x mimic is similar to that of sLe^x itself, *i.e.* the complexation of L-fucose to Ca^{2+} and the orientation of the D-galactose moiety. This confirms that (1*R*,2*R*,3*S*)-3-methylcyclohexane-1,2-diol is a suitable substituent of the D-Glc*N*Ac moiety by pre-organizing the relevant pharmacophores in the bioactive conformation.

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Medicinal Chemistry **306**

Alteration of adenylate energy charge in *Trypanosoma brucei*: Towards the understanding of growth inhibition induced by 4-[5-(4-phenoxyphenyl)-2*H*-pyrazol-3-yl]-morpholin.

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T. brucei rhodesiense and *T. brucei gambiense* are the causative agents of Human African Trypanosomiasis (HAT; African sleeping sickness). Current treatment options for HAT are scarce, toxic, no longer effective or very difficult to administer. Therefore, new drugs are required to treat this disease.

Our previous research activities found that 4-[5-(4-phenoxyphenyl)-2*H*-pyrazol-3-yl]-morpholine (compound 1) exhibits antitrypanosomal activity with an IC_{50} of 1 μM, and chemical proteomics identified *Trypanosoma brucei* adenosine kinase (TbAK) as the intracellular target. TbAK is an important enzyme involved in the purine salvage pathway of the parasite, and subsequent biochemical analyses found this compound to be a strong activator[1,2].

The intracellular purine levels of Trypanosomes incubated with compound 1 were analyzed using an ion-pair HPLC/UV method. The results revealed that the adenylate energy charge[3] as well as ADP/ATP and AMP/ATP ratios were altered upon incubation of the cells with the compound. Furthermore the ATP/AMP ratio varied as the square of the ADP/ATP ratio while the GTP/ATP balance remained unaffected. Taken together, we find that compound 1 interferes with adenine nucleotide levels, with AMP being the key regulatory molecule of the adenylate energy charge in the parasite.

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Medicinal Chemistry **307**

Allosteric Ligands for IspD

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A worldwide rising emergence of resistant pathogens and weeds underline the need of new drugs with novel mode of action. One promising target for the development of new antimalarials, antibiotics or herbicides is the non-mevalonate pathway for isoprenoid synthesis. This pathway occurs in many bacteria, some algae, plants, and in certain protozoa such as the malaria parasite *Plasmodium*, but is absent in humans.[1]
In a combined approach of high throughput screening and molecular modeling we obtained the first inhibitors for IspD (4-Diphosphocytidyl-2*C*-methyl-D-erythritol Synthase, EC 2.7.7.60), the third enzyme in the pathway.[2] We revealed an allosteric binding site in IspD from *Arabidopsis thaliana* and could prove the binding mode by three co-crystal structures in total. Lead optimization and distinct water replacement resulted in an improved IC_{50} value of 35 ± 7 nM and significant greenhouse activity.

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Medicinal Chemistry **308**

Rational Design, Synthesis and Biological Testing of Inhibitors Targeting the Substrate Binding Site of IspE

Michael Harder[1], Paolo Mombelli[1], Andri Schütz[1], Boris Illarionov[2], Markus Fischer[2], Adelbert Bacher[3], François Diederich

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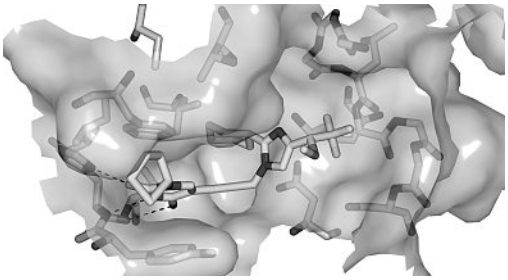
The kinase IspE is involved in the mevalonate-independent biosynthetic pathway of isoprenoid precursor (IPP, DMAPP) synthesis. The pathway is a promising target for the development of new drugs with a novel mode of action, since it is present in many pathogens, but absent in humans.
Our research group reported the development of active inhibitors against the enzyme from *Escherichia coli*.[1] A rational, structure-based design approach was employed for a new class of compounds as potential inhibitors for IspE. The synthesis and biological evaluation of the new ligands are presented.



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Medicinal Chemistry **309**

Structure-Based Design and Synthesis of Inhibitors of Arylsulfate Sulfotransferase (ASST); on a Quest for New Antimicrobial Compounds for Treatment of Urinary Tract Infections

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The PAPS-independent arylsulfate sulfotransferase (ASST) is an enzyme specific to uropathogenic *Escherichia coli* strains (UPEC) and is thus an attractive target for the development of drugs against urinary tract infections (UTI). The exact physiological role of ASST is still unknown, but functions such as e.g. detoxification of medically active compounds are likely. The recently solved X-ray structure of ASST, together with kinetic data revealed that ASST is a homodimer of 64 kDa subunits that catalyzes the exchange of sulfuryl groups between phenolic compounds in a ping-pong bi-bi mechanism in which the enzyme is transiently sulfurylated at a catalytic histidine residue[1]. We are trying to generate rationally designed ASST inhibitors targeting the single substrate binding site of the enzyme, and investigate inhibitor binding through crystallographic analysis of ASST-inhibitor complexes and enzyme kinetics.

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Medicinal Chemistry **310**

Water-soluble organometallic cages to transport and protect photodynamic therapy agents

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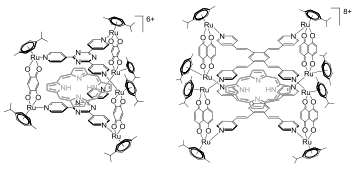
Photodynamic therapy (PDT) is a treatment modality for numerous cancers and certain noncancerous diseases. It utilizes the photoreactions mediated by photosensitizers (PS), light and oxygen to generate reactive oxygen species (ROS), such as singlet oxygen. ROS induced damages ultimately leading to cell death either by apoptosis or necrosis pathways. PDT efficacy is dependent on the selective accumulation of PS such as porphyrins in tumor cells.

PS such as porphyrins and phthalocyanines are in general poorly water-soluble, unless highly substituted with hydrophilic groups. The use of large vehicles to carry PS to cancer cells is one of the strategies. The encapsulation of the PS within the hydrophobic cavity of water-soluble carriers provides an elegant strategy to transport PS in aqueous media, a necessity for biological applications[1]

Moreover, the poor selectivity of commonly used PS frequently leads to the necrosis of surrounding healthy tissues and to a skin photosensitivity during several weeks after treatment.[2] Thus, spatial-controlled release of the PS remains one of the main challenges in photodynamic therapy.



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Medicinal Chemistry **311**

Nanoencapsulation of Antimicrobial Silver-Based Drugs

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Silver compounds and silver nanoparticles are gaining more interest from the scientific society as a replacement to antibiotics. However, these compounds may be too soluble and even toxic for the host. Encapsulation might be advantageous in order to increase the stability and biocompatibility of silver drugs. In this research, ceria nanocapsules were synthesized due to the high stability and low toxicity of this material.[1]

The synthesized nanocapsules were composed of cerium oxide, as determined by powder XRD. From TEM images and from the disappearance of the polystyrene (PS) bands on the IR spectra, it was demonstrated that the PS core was completely removed resulting in empty capsules. CeO_2 capsules were then used to encapsulate the silver compound $Ag(L)NO_3$ illustrated in Figure 1. As determined using TGA, the degradation of $Ag(L)NO_3$ is retarded when it is encapsulated compared to free $Ag(L)NO_3$. Silver release experiments were also performed using ICP-OES and demonstrated that $Ag(L)NO_3$ encapsulated in CeO_2 capsules can release silver over a period of at least one week.

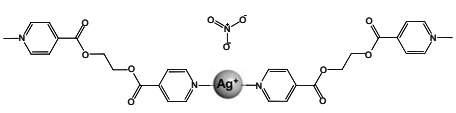

Fig. 1: Representation of an excerpt of $Ag(L)NO_3$.

TGA and release experiments gave promising results for the encapsulation of antimicrobial silver compounds. More experiments and analysis will be performed to study the encapsulation of silver compounds as well as their respective silver release.

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Medicinal Chemistry **312**

High affinity fluorescent probes to study the 5-HT_3 receptor : applications in imaging and flow cytometry

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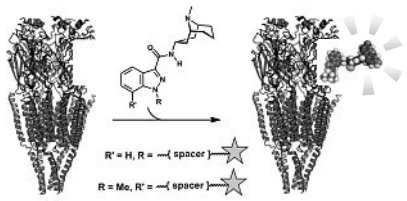
University of Bern, [1]Department of Chemistry and Biochemistry, [2]Institute of Biochemistry and Molecular Medicine, CH-3012 Bern, Switzerland

High affinity fluorescent ligands can be used to study a receptor of interest in cells. The 5-HT_3 receptor is a ligand-gated ion channel (LGIC) and a member of the Cys-loop family of receptors. To date no crystal structure of the protein has been published. Based on our SAR study of granisetron[1], we attached different fluorophores at two different positions of this molecule, with different linkers varying in length and solubility properties. The fluorescent ligands have been characterised by radioligand binding (K_i) and fluorescence spectroscopy. The utility of seven high affinity probes was studied in live cell imaging, resulting in two probes being specific for the 5-HT_3 receptor[2]. Applications in flow cytometry and fluorescence polarization is currently under investigation.



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Medicinal Chemistry **313**

Synthesis and testing of photoaffinity probes for the site-selective chemical modifications of the 5-HT_3 receptor

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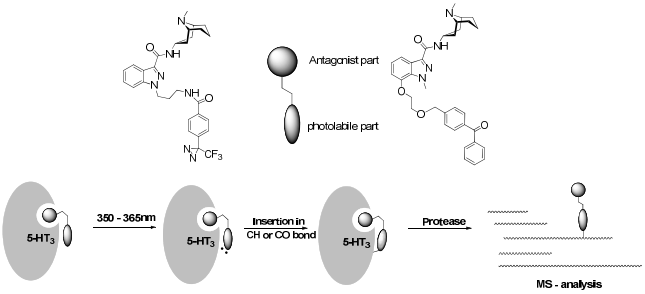
The 5-HT_3 receptor (5-HT_3R) is an important ion channel responsible for the transmission of nerve impulses in the central nervous system.[1] It is difficult to characterize transmembrane dynamic receptors with classical structural biology approaches like crystallization and x-ray. The use of photoaffinity probes is an alternative approach to identify regions in the protein that are important for the binding of small molecules. Therefore we synthesized a small library of photoaffinity probes by conjugating photolabile building blocks via various linkers to granisetron which is a known antagonist of the 5-HT_3R. We were able to obtain several compounds with diverse linker lengths and different photo-labile moieties that show nanomolar binding affinities for the orthosteric binding site. Having a stable 5-HT_3R overexpressing cell line in hand we are currently investigating crosslinking experiments and subsequent MS – analysis.



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Medicinal Chemistry **314**

Synthesis of novel fluorescent agonists, with selectivity for the A_1 adenosine receptor.

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[1]Department of Chemistry and Biochemistry, Universität Bern, Switzerland. [2]School of Life Sciences, University of Warwick, Coventry, CV4 7AL, UK.

The adenosine receptors are members of the GPCR family and there are four sub-types, A_1, A_{2A}, A_{2B} and A_3. The A_1 receptor is involved in a range of processes in the CNS, including epilepsy and ischaemia. Despite its important role, relatively little is known about the trafficking of this receptor in neurons. Studies with fluorescent fusion proteins, such as A_1R-GFP (Green Fluorescent Protein) have so far been limited.[1] An agonist conjugated to a fluorophore may provide further insight.

In collaboration with Professor Bruno Frenguelli at the University of Warwick we have started a research project, with the aim of designing and synthesising selective fluorescent compounds to aid investigations into the trafficking of these receptors. We have selected novel target compounds derived from known A_1R agonists (Figure 1).[2] The synthetic strategy is to attach a linker and fluorophore *via* a novel cyclic component at the 6 position of the adenine. The initial results from this program will be presented.

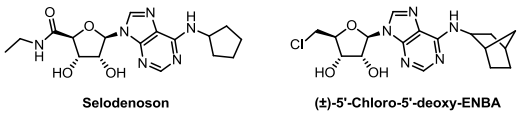

Figure 1 Known agonists with selectivity for the A_1 receptor.

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Medicinal Chemistry **315**

Synthesis of 2-APB analogues as inhibitors of TRPV6-mediated Calcium transport

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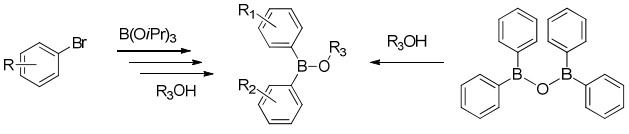
A transport protein responsible for Ca^{2+} uptake in the small intestine was described for the first time in 1999[1]. TRPV6 belongs to the large superfamily of transient receptor potential (TRP) channels, a group of ion channels having diverse modes of activation and different cation selectivity profiles. TRPV6 is mainly expressed in intestine and placenta, and shows high Ca^{2+} selectivity. TRPV6 expression levels were found to be higher in certain cancers of epithelial origin like prostate and breast carcinomas. 2-aminoethyl diphenylborinate (2-APB) was reported to modulate Ca^{2+} transport mechanisms through different modes of action, including the interaction with TRPV6. Different analogs of 2-APB were synthesized in our group in order to investigate the structure-activity relationship. Variations were introduced in the amino-ethanol chain as well as in the phenyl fragments of 2-APB. The small library obtained was tested on TRPV6.



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Medicinal Chemistry **316**

Towards the site-specific chemical modification of the hERG channel

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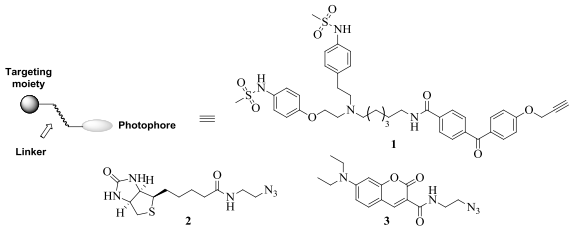
The hERG (***H***uman ***E***ther-a-go-go ***R***elated ***G***ene) encodes a potassium ion channel in several parts of the body, including the heart muscle where it is found to be critical for repolarization of cardiac tissue during the heart beat cycle[1]. The detailed molecular structure of the channel based on x-ray crystallography is not yet available and thus derived from other potassium ion channels such as Shaker (Kv1.1)[2], computer models and mutagenesis studies. The use of photoaffinity probes such as **1** based on a known high-affinity hERG channel blocker, Dofetilide[3], would allow covalent modification of hERG close to the channel pore. Further post-photoaffinity labeling modifications with read-out molecules such as **2-3** via click reaction would offer the possibility for visualization or purification of the modified protein. Ultimately, a fluorescently-labelled hERG could also provide a means for sensitive and rapid detection of potential channel blockers.



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[3] G.J. Diaz et al., *J. Pharmacol. Toxicol. Methods.* **2004**, *50*, 187.

Medicinal Chemistry **317**

VMAT2 – Synthesis of Reserpine Analogs

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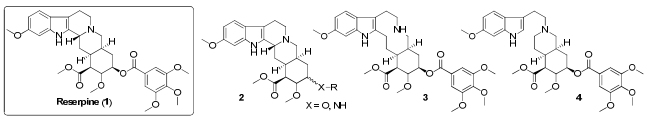
The vesicular monoamine transporter type 2 (VMAT2) is a membrane protein that transports monoamines from the cytoplasm into synaptic vesicles. The discovery of small and brain-penetrable molecules that are effective and selective regulators of either dopamine or serotonin release without affecting the transport of other monoamines could be of value in the treatment of neurological diseases such as Parkinson, Alzheimer or Huntington. In fact, the VMAT2 inhibitor tetrabenazine is approved for the treatment of chorea Huntington, although the compound does not only act on VMAT2 and it is associated with significant side effects.[1]

The plant natural product reserpine is the most potent VMAT inhibitor known.[2]



This contribution will discuss the synthesis of a series of reserpine analogs and their evaluation as potential VMAT2 ligands. The focus of this work was on the modification of the trimethoxybenzoyloxy moiety in reserpine (structures of type **2**), but we have also investigated the ring-opened products **3** and **4**.

[1] Zheng, G.; Dwoskin, L.P.; Crooks, P.A.; *AAPS Journal* **2006**, *8*, 682.
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Medicinal Chemistry **318**

Synthesis and Biological Evaluation of a *trans* Lactam Analog of Resorcylic Acid Lactone L-783277

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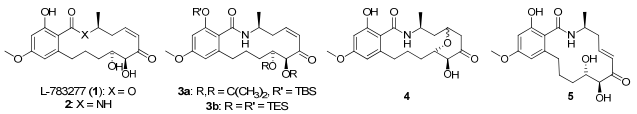
Wolfgang-Pauli-Str. 10, CH-8093 Zürich, Switzerland

Resorcylic acid lactones (RALs) are fungal mycotoxins that are associated with a range of biological activities. RALs containing a *cis*-enone moiety, such as L-783277 (**1**),[1] have been found to be potent irreversible kinase inhibitors.[2] The *cis*-enone moiety is essential for kinase inhibition, which involves 1,4-addition of a Cys residue present in the ATP-binding pocket of a subset of kinases to the α,β-unsaturated carbonyl system.



We have previously reported the first total synthesis of **1**.[3] As part of our ongoing SAR studies around this RAL,[4] we have also pursued lactam analog **2**, which might be metabolically more stable than the parent macrolactone **1**. However, analog **2** so far has remained elusive. Thus, the sequential treatment of intermediate **3a** with sulfonic acid resin and HF•pyridine in THF produced only bicylic analog **4**; treatment of tris-TES derivative **3b** with 70% HF•pyridine in THF gave *trans* analog **5** exclusively. This contribution will discuss the details of the syntheses of **4** and **5** and their biological activities.

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[4] Liniger, M.; *et al*., *ACS Med. Chem. Lett*. **2011**, *2*, 22.

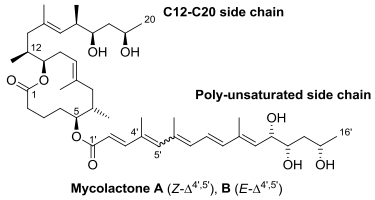
Medicinal Chemistry **319**

Exploring Mycolactone Structure-Toxicity Relationships

Philipp Gersbach,[1] Nicole Scherr,[2] Jean-Pierre Dangy,[2] Gerd Pluschke,[2] Karl-Heinz Altmann[1]*

[1]Departement of Chemistry and Applied Biosciences, ETH Zürich, Zürich
[2]Swiss Tropical and Public Health Institute, Basel

Mycolactones are immunosuppressive and cytotoxic macrolides of mycobacterial origin. Particularly important are mycolactones A/B which are produced by *Mycobacterium ulcerans* and are involved in the pathogenesis of the skin disease Buruli ulcer (BU). Although animal experiments have provided clear evidence for the crucial role of mycolactones A/B in the onset of BU, the underlying molecular mechanisms are poorly understood.[1]



In order to design mycolactone conjugates that could serve as tools for the identification of the cellular target(s) of mycolactones, we were interested in obtaining a better understanding of mycolactone structure-toxicity relationships. To this end, we have synthesized a set of non-natural mycolactones which display modifications either in the poly-unsaturated side chain or the C12-C20 side chain. These mycolactone analogs were tested for their *in vitro* cytotoxicity and apoptosis-inducing properties. Based on these results we were able to identify distinct trends in mycolactone structure-toxicity relationships, which will be presented in this contribution along with information on the syntheses of these mycolactone analogs.

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Medicinal Chemistry **320**

Total Synthesis of New Functionalized Epothilone Analogs for Prodrug Design and Tumor Targeting

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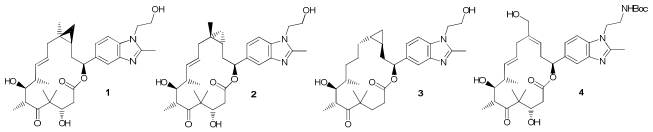
[1]ETH Zürich, Institute of Pharmaceutical Sciences, Wolfgang-Pauli-Strasse 10, 8093 Zürich

Epothilones are microtubule-stabilizing natural products which exhibit strong antiproliferative effects *in vitro* and potent antitumor activity *in vivo*, including tumor growth inhibition in multidrug- resistant human tumor models.[1] Several epothilones have entered clinical trials in humans and ixabepilone was approved by the FDA in 2007. However, the therapeutic utility of epothilones would benefit greatly from an increase in their selectivity for tumor cells, which would reduce side effects and widen their therapeutic window. In this context we have designed novel epothilone analogs **1-4**, with the goal of using the methylbenzimidazole side-chain as an attachment site for various tumor-targeting moieties.



One of the above epothilone analogs was selected for the synthesis of conjugates. Numerous proteases are overexpressed by tumors.[2, 3] Substrates of those proteases have been attached to the epothilone analog. The epothilone is to be released only in the vicinity of the tumor thereby increasing the specificity of the drug.

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Medicinal Chemistry **321**

Self-Assembling DNA-Peptide Hybrids

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Department of Inorganic and Analytical Chemistry, University of Geneva-Sciences II; 30, quai Ernest-Ansermet, CH-1211 Geneva 4, Switzerland

Aside from being the universal carrier of the genetic information, DNA and short nucleotide sequences thereof are involved in a plethora of vital biological mechanisms like gene silencing for instance. However, the main obstacles of using nucleotide sequences as such are their limited plasma half-life as well as cellular penetrability and uptake. To overcome these issues, their conjugation with biocompatible ligands has thus increasingly become a topic of intense research. One may also envisage to design nucleic acid decorated structures or supramolecular assemblies which may serve as delivery cargo molecules. Peptides due to their inherent property of self-assembly in solution may be used as one of such ligands. We demonstrate in here for the very first time that conjugation of a peptide ligand with a ss-DNA sequence results in a DNA-peptide hybrid which self-assembles to give rise to vesicular structures as assessed by various microscopic techniques.[1] Vesicular structures efficiently encapsulate a hydrophilic dye and pH triggered release reveals their potential for application as carriers for drug delivery for instance. Moreover, nucleotide decorated self-assembled structure specifically hybridizes with its corresponding complementary nucleotide sequence opening avenues for design of targetted delivery vehicles. The design of this fully biocompatible self-assembling material paves the way of many possible future uses e.g., as targeted drug delivery vehicle for sustained drug release and/ gene therapy just to cite few examples.

[1] N. Gour, D. Kedracki, I. Safir, K. X. Ngo and C. Vebert-Nardin *Chem.Commun.* **2012** (in press)

Medicinal Chemistry **322**

Single-cell analysis vs. traditional MALDI-MS: Who can better describe the effects of a glycolytic inhibitor on *S. Cerevisiae*.

Alfredo J. Ibáñez[1], Stephan R. Fagerer,[1] Matthias Heinemann,[2] and Renato Zenobi[1]

[1]ETH Zurich, Department of Chemistry and Applied Biosciences, CH-8093 Zurich, Switzerland.
[e] University of Groningen, Groningen Biomolecular Sciences and Biotechnology Institute, 9747 AG Groningen, The Netherlands

Based on recent discoveries in the field of cell biology, single-cell level measurements are necessary to better monitor, analyze, and characterize the intrinsic biological variability observed in cell populations.[1] During the past two years, our group has introduced a novel analytical platform called Microarrays for mass spectrometry (MAMS).[2] A MAMS platform is capable of boosting the performance of commercial matrix-assisted laser desorption/ionization (MALDI) mass spectrometers in order to achieve single-cell sensitivity.
Here, we present the first in depth comparison between two MS-based metabolome approaches: (i) a population-level and (ii) single-cell level, for describing the individual biological response of each cell within a clonal cell culture of Saccharomyces cerevisiae (budding yeast) when applying the glycolytic inhibitor, 2-deoxy-d-glucose (2-DG).
Our results show that the efficiency of 2-DG as a drug depends on the individual biological make-up of each individual cell within the isogenic cell culture. For example, yeast cells that express higher amounts of glucose transporter proteins and/or glucose hexokinase enzymes are more susceptible to the presence of 2-DG.

References:
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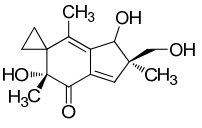
Medicinal Chemistry **323**

Illudin S and Acylfulvene DNA Adducts in Tumor Cells and Relationship with Altered Cytotoxicity

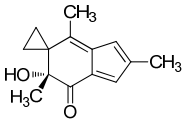
Kathryn E. Pietsch, Paul M. van Midwoud, Shana J. Sturla

ETH Zürich, Schmelzbergstrasse 9, CH-8092 Zürich, Switzerland

Acylfulvene (AF) is a bioreductive alkylating agent and semi-synthetic analogue of illudin S, a highly toxic mycotoxin, which exhibits selective toxicity for cancer cells over normal cells. AF-DNA adducts have been previously identified, but damage to cellular DNA caused by these compounds has not been investigated, nor have differences between the DNA reactivity of AF and illudin S been addressed as a potential contributor to altered cytotoxicity. In this study we have identified and quantified both AF-DNA adducts and novel illudin-DNA adducts in colon cancer cells by LC-MS. These data are compared with relative cytotoxicity data for both compounds, and are expected to improve our understanding of how chemical structure relates to DNA damage and how that contributes to cytotoxicity.



Illudin S



Acylfulvene (AF)

Medicinal Chemistry **324**

Penetration of Topically Applied Actives on Human Skin Tracked by Confocal Raman Microscopy

Franziska D. Fleischli, Christian Adlhart

Zurich University of Applied Science ZHAW, Institute of Chemistry and Biological Chemistry, Einsiedlerstrasse 31, 8820 Wädenswil

Many cosmetic and pharmaceutical products are applied directly to the skin. The effect of these products depends on the penetration behavior of the actives and the formulation of the product. While sunscreens should stay on the skin's surface, anti-inflammatory agents should penetrate easily into skin. Consequently, knowledge about the penetration behavior of the involved actives is need for designing effective products.

Raman microscopy is a powerful tool for characterizing skin penetration because it allows the monitoring of the active's path through the skin and, at the same time, the detection of variations in the skin composition [1, 2]. Depth profiles and distribution maps of the components can be extracted.

We compared the penetration of lipophilic and hydrophilic actives into human skin *in vivo* and skin models using confocal Raman microscopy. *In vivo* studies were performed at the volar forearm, while skin models consisting of reconstructed human epidermis (RHE) were used for *in vitro* experiments. Such skin models are of increasing importance as substitute for human or animal studies. The investigated actives had octanol/water partition coefficients ranging from 10^{-2} (hydrophilic) to 10^{6} (lipophilic).

We develop a standard procedure for skin penetration by confocal Raman microscopy. Penetration occurred differently in human skin *in vivo* and skin models. The polarity of the studied actives and differences in the skin composition (e.g. water content) were the major factor controlling penetration of the actives through the S*tratum corneum*.

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[2] Mélot M et al, *J Controlled Release* **2009**, *138*, 32.

Medicinal Chemistry **325**

PEG-chelators to stabilize siRNA-loaded calcium phosphate nanoparticles

Elisabeth V. Giger[1], Bastien Castagner[1], Jean-Christophe Leroux[1]

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More than 10 years after the discovery of RNA interference [1], its use for medical applications is still challenging [2]. However, this technology holds great potential to treat a wide variety of diseases. Delivery of siRNA is facing many hurdles. We present here a new approach to formulate siRNA that is based on PEG-chelators-coated calcium phosphate nanoparticles.

PEG-inositolpentakisphosphate and PEG-alendronate (Fig. 1) were synthesized and used to coat calcium phosphate particles loaded with siRNA. The calcium phosphate particles displayed high physical stability over a month. The silencing efficiency of the formulated siRNA against the Bcl2-oncogene was determined by transfecting PC-3 cells, and was shown to be above 80%. The uptake pathway of these particles was found to be mostly clathrin-dependent endocytosis. Finally, the PEG-bisphosphonate-coated nanoparticles were found to interact with the mevalonate pathway.

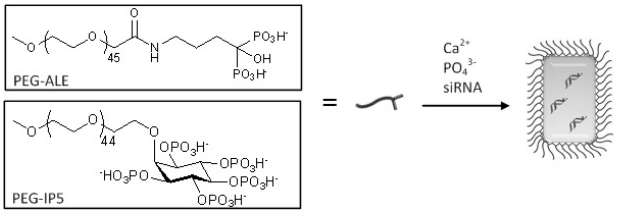

Fig.1: Preparation of calcium phosphate nanoparticles stabilized with either PEG-alendronate (PEG-ALE) or PEG-inositolpentakisphosphate (PEG-IP5)

[1] A. Fire, S.Xu, et al., *Nature* **1998**, *391*, 806

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Medicinal Chemistry **326**

Library-based Discovery and Characterization of Daphnane Diterpenes as Potent and Selective HIV Inhibitors in *Daphne gnidium*

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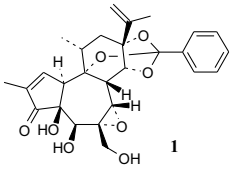
A library of close to one thousand plant and fungal extracts was screened for antiretroviral activity. A dichloromethane extract of the aerial parts of *Daphne gnidium* exhibited strong antiretroviral activity and absence of cytotoxicity. With the aid of HPLC-based activity profiling, the antiviral activity could be tracked to four daphnane derivatives, namely, daphnetoxin (**1**), gnidicin, gniditrin, and excoecariatoxin. Detailed anti-HIV profiling revealed that the pure compounds were active against multidrug resistant viruses irrespective of their cellular tropism. They inhibited equally well the replication of both CXCR4- and CCR5-tropic HIV-1, but differed in their potency, with daphnetoxin and gnidicin being the most potent, and excoecariatoxin the least active compound against both viruses. Importantly, none of the purified compounds displayed any cytotoxic activity at the doses assayed, thus yielding a high selectivity index in each case. Mode of action studies that narrowed the site of activity to viral entry events suggested a direct interference with the expression of the two main HIV co-receptors CCR5 and CXCR4 at the cell surface by daphnetoxin (**1**).



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Medicinal Chemistry **327**

Antiprotozoal isoflavanquinones isolated from *Abrus precatorius*

Yoshie Hata Uribe[1,4], Melanie Raith[1], Samad Ebrahimi[1,5], Stefanie Zimmermann[1,2], Tsholofelo Mokoka[3], Dashnie Naidoo[3], Vinesh Maharaj[3], Reto Brun[2], Marcel Kaiser[2], Matthias Hamburger[1]

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[2]Swiss Tropical and Public Health Institute, Socinstrasse 57, 4002 Basel, Switzerland
[3]Council for Scientific and Industrial Research, P.O. Box 395, Pretoria, 0002, South Africa
[4]National University of Colombia, Carrera 30 45-03, Bogotá, Colombia
[5]Shahid Beheshti University G.C., Evin, Tehran, Iran

A library of 309 extracts from selected South African plants was screened *in vitro* against a panel of protozoan parasites. A CH_2Cl_2/MeOH (1:1) extract of *Abrus precatorius* L. *ssp. africanus* Verdc. (Fabaceae) strongly inhibited *Plasmodium falciparum* (97.8%), *Trypanosoma brucei rhodesiense* (100%), and *Leishmania donovani* (75.5%) when tested at a concentration of 4.8 mg/mL. The active constituents were tracked by HPLC-based activity profiling [1] and isolated by preparative RP-HPLC. NMR spectroscopy (^{1}H, ^{13}C, COSY, HMBC, HSQC, NOE difference) was used to elucidate the structures and establish the relative configuration. The absolute configuration was determined by comparison of electronic circular dichroism (ECD) spectra with calculated ECD data. Five compounds were obtained and identified as isoflavanquinones and hydroquinones, among them two new natural products. (3*S*)-8-hydroxy-7,3',5'-trimethoxyisoflavan-1',4'-quinone and (3*S*)-6,7,8,2',3'-penta-methoxyisoflavan-1',4'-quinone showed strong activity against *T. b. rhodesiense* (IC_{50}s of 0.30 µM ± 0.1 and 0.16 µM ± 0.1, respectively). Selectivity indices (SI) as calculated from cytotoxicity data in L-6 cells were 78.3 and 61.3. (3*R*)-7,8,3',5'-tetramethoxyisoflavan-1',4'-quinone was also very active, but not selective (IC_{50} 0.88 µM ± 0.1; SI 4.5).

[1] M. Adams, S. Zimmermann, M. Kaiser, R. Brun, M. Hamburger, *Nat. Prod. Commun.* **2009**, *4*, 1.

Medicinal Chemistry **328**

Peptide Microarrays by Click Chemistry for Applications in Cancer Diagnostics

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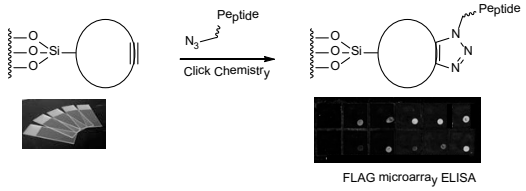
Peptide microarrays are an emerging technology useful for the detection of tumor antigen directed auto-antibodies. Their miniaturization and possibilities for multiplex analysis as well as automation also made them a powerful tool for high-throughput epitope screening.

With the FLAG peptide as model, we tested and compared different surface chemistries for immobilization of peptides such as peptide aldehyde / hydrazine slides, fluorous-tagged peptides / fluorous slides, and click chemistry [1].



For the most promising approach, the no-copper click chemistry with the ADIBO alcyne, we report our results on the optimization of the chemistry and the spotting as well as assay development. The detection limits, reproducibility, ease of handling and costs are comparable to classical methods.

We are currently exploring our microarray technology for the potential use in ovarian cancer diagnostics.

[1] J.C.M. van Hest et al., *Angew. Chem.* **2011**, 123, 8968.

Medicinal Chemistry **329**

Preparation and Biological Evaluation of Novel Antiproliferative Ru(II) Complexes

Vanessa Pierroz,[1,2] Tanmaya Joshi,[3] Anna Leonidova,[2] Cristina Mari,[2] Leone Spiccia,[3] Stefano Ferrari[1] and Gilles Gasser[2]

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[3]School of Chemistry, Monash University, Melbourne, Australia

The phenomenal success of the chemotherapeutic drug cisplatin has boosted the research towards the discovery of novel metal-based drugs, especially because severe side-effects are encountered by patients during their treatments.[1] Among all potential metal complexes candidates, ruthenium complexes have emerged as one of the leading players in this field by showing extremely promising results.[2,3] In this study, four Ru(II) complexes were synthesized, characterized and their cytotoxicity investigated. One particular complex shows an antiproliferative activity in the same range to that of cisplatin. Furthermore, the mechanism of action of this compound was studied highlighting that the Ru complex exerts its cytotoxicity by triggering a mitochondria-mediated apoptosis.

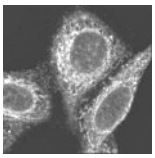

Figure 1. Fluorescence confocal microscopy image of HeLa cells incubated with a cytotoxic Ruthenium complex.

[1] Lippert, B., *Cisplatin, Chemistry and Biochemistry of a Leading Anticancer Drug*. Verlag Helvetica Chimica Acta: Zürich, **1999**
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Medicinal Chemistry **330**

Design, synthesis and biological testing of novel MMP-Inhibitors

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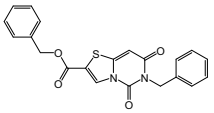
Matrix Metalloprotease-13 (MMP-13) or collagenase-3 is one of the enzymes belonging to the zinc-depending endopeptidase family and is involved in angiogenesis as well as in tissue remodeling. An over activity of MMPs can lead to various pathological processes such as rheumatoid arthritis or tumor growth and metastasis for example [1].

In our present work, we have generated new inhibitors against MMP-13 based on compound **1a** published by *Johnson* [2]. Usage of a scaffold replacement process with our in house fragment database and the MOE software, yielded several promising scaffolds. Those compounds were further investigated *in silico* and synthesized in a library format. Thereby, submicromolar inhibitors could be identified. Further steps of this iterative process will be carried out to improve the properties of the most active compounds to generate lead structures.



1a

[1] M.G. Natchus, *J.Med.Chem.* **2001**, *44*, 1060-1071.
[2] A. R. Johnson, *J.Biol.Chem.* **2007**, *282*, 27781-27791.

Medicinal Chemistry **331**

Enhancing CyBy^2: Visualization of Structure Activity Relationships of large Datasets

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Medicinal chemistry projects are very complex with respect to the chemical and biological data content. For successful medicinal chemistry projects, it is mandatory to have access to key correlations between chemical structures and their biological data such as potency, selectivity and pharmacological data to highlight and easily extrude structure activity relationships (SAR). The professional information management of a multitude of medicinal chemistry projects in a given organization such as pharmaceutical companies requires intelligent IT-tools to fully utilize the organization's global data.

We present new data-analyzing capabilities of CyBy^2, our information management tool for chemical and biological data [1]. Besides advanced searching and filtering functions for biological data we present new visualization methods such as rainbow formatting that can be used to facilitate analysis of structure activity relationships (SAR) of large datasets. We also show how these new functionalities could easily be implemented in a type-safe manner making use of the advanced type system and functional programming support of the *Scala* programming language [2].

[1] Stefan Höck, Rainer Riedl: Cyby^2: A Structure-based Data Management Tool for Chemical and Biological Data, *Chimia*, **2012,** *66***,** 132 – 134**.**
[2] Martin Odersky, *The Scala Language Specification,* Version 2.8; Programming Methods Laboratory EPFL, Lausanne **2010.**

Medicinal Chemistry **332**

Functionalized Oligoprolines As Multivalent Scaffolds in Tumor Targeting

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Azidoproline containing oligoprolines are conformationally well-defined, helical molecular scaffolds that can be functionalized for example by copper-catalyzed azide-alkyne cycloaddition (CuAAC) or Staudinger reduction and subsequent acylation.[1] The structural integrity of the oligoproline scaffold allows for conjugating targeting vectors in defined distances towards each other. Recent studies on radiolabeled oligoproline-bombesin conjugates that target the gastrin-releasing peptide receptor (GRP-R showed *in vitro* and *in vivo* superior internalization in prostate cancer cells compared to established monovalent ligands.[2]

We are currently expanding this concept to the integrin-ligand c(RGDyK) as well as to [Tyr^3]-Octreotide. The latter is successfully used in radiopharmaceuticals targeting somatostatin-receptors, which are overexpressed in somatostatin-positive tumors such as neuroendocrine tumors.[3] A facile route to synthesize these alkynylated ligands has been developed successfully.

[1] (a) Y.A. Nagel, M. Kuemin, H. Wennemers, *CHIMIA*. **2011**, *65,* 264. (b) M. Kuemin, L.-S. Sonntag, H. Wennemers *J. Am. Chem. Soc*. **2007**, *129*, 466.
[2] C. Kroll, R. Mansi, F. Braun, H.R. Maecke, H. Wennemers, **2012**, *submitted*.
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Medicinal Chemistry **333**

Sequence-Activity Relationships of Antimicrobial Peptides

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Antimicrobial peptides (AMPs) represent a class of bioactive agents that can be used to target multidrug resistant bacteria [1]. However, we still lack profound understanding of the underlying structure-selectivity relationships that could guide the rational design of membrane-selective AMPs. In this study we selected two potent AMPs, protonectin and decoralin, as seed peptides and synthesized randomly scrambled derivatives based on these two templates. We also synthesized peptides with deleted or mutated C-terminal residues. Membrane disruption was tested using large unilamellar vesicles (LUVs). Protonectin induced more dye leakage from LUVs composed of POPC (zwitterionic) than from LUVs composed of POPE:POPG=7:3 (anionic), while decoralin induced the same level of dye leakage from both LUVs. The nature of the C-terminal residues critically affected peptide activity. Some of the scrambled peptides that were derived from the seed peptides exhibited different effects on LUVs and even changed the preference between zwitterionic vesicles and anionic vesicles. These scrambled AMPs showed altered membrane selectivity although they have identical amino acid composition, net charge and amphipathicity as their respective seed peptide.

[1] Fjell, C. D., Hiss, J. A., Hancock, R. E. W. and Schneider, G. (2012) Designing antimicrobial peptides: Form follows function. *Nat. Rev. Drug Discov*. 11, 37-51.

Medicinal Chemistry **334**

From membrane rupturing to membrane targeting: feature swapping between antimicrobial peptides and mitochondrial transit peptides

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Public healthcare is increasingly threatened by multidrug resistant pathogens requiring fundamentally new antibiotics. Certain classes of antimicrobial peptides (AMPs) selectively destroy pathogens without inducing major resistances [1]. Such AMPs apparently evade resistance mechanisms by targeting and destroying lipid membranes instead of binding to a specific target protein. We aim to identify the structural basis of membrane selectivity by a systematic approach combining computational predictions and *in vitro* assays. Here, we compared mitochondrial transit peptides (mTPs) with antimicrobial peptides (AMPs). Both types of peptides have features in common that are important for their respective activity such as net cationic charge, alpha-helical secondary structure, and amino acid composition [2]. Despite these apparent structural similarities they exhibit distinct activities, namely membrane rupturing by AMPs, and membrane targeting by mTPs (respectively Tom20 interaction). Using computational methods, such as self-organizing maps and nearest neighbor analysis, we identified pairs of physicochemically closely related AMP and mTP sequences. Selected peptide pairs were synthesized and subjected to *in vitro* testing for their membrane rupturing capability.

[1] CD Fjell, JA Hiss, RE Hancock, G Schneider, *Nat. Rev. Drug Discov*. **2011**, *11*, 37.
[2] G Heijne, *EMBO J*. **1986**, *5*, 1335.

Medicinal Chemistry **335**

Development and validation of a multi-model cascaded machine-learning approach to designing MHC-I stabilizing peptides

Christian P. Koch[1], Anna Perna,[1] Michael Reutlinger,[1] Renato Baleeiro,[2] Max Pillong,[1] Jan A. Hiss,[1] Gerd Folkers,[1] Paul Wrede,[3] Peter Walden,[2] Gisbert Schneider[1*]

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Deep as well as cascaded architectures of machine-learning models have recently gained much scientific interest.[1] We present the development and application of multi-model predictions to finding novel MHC class I (murine H-2K^b allele; influenza A H3N8 Hokkaido 1980) stabilizing peptides. In contrast to earlier cascaded neural network approaches[2], we utilized not only known and newly derived peptide descriptors, but also employed different learning algorithms. Peptide descriptors were associated in a combinatorial manner bearing 4096 cascaded models. The best-performing model was selected by retrospective evaluation revealing a significant performance increase in comparison to individual first stage models. Subsequently, the selected cascaded model was applied to slice-and-diced host and pathogen proteomes as well as the complete octapeptide space. Top-ranking predictions were robotically synthesized and tested by cell-based stabilization[3] and thermal shift assays. Experimental measurements concur with the results of the machine learning model, further dissipate the crumbling canonical motif[4] dogma and unveil novel peptides exhibiting nanomolar EC_{50} constants.

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Medicinal Chemistry **336**

Boosting Sensitivity of Ligand-Protein Screening by NMR of Long-Lived States

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[1] Ecole Polytechnique Fédérale de Lausanne, Institut des Sciences et Ingénierie Chimiques, 1015 Lausanne, Switzerland

The binding affinity of a ligand to a protein is a key parameter in pharmaceutical research and drug development. NMR has shown to be a technique of choice to measure dissociation constants K_D. This constant can be extracted by titration of the ligand for any observed relaxation rate (A) described by:

$$R_A^{obs} = \frac{[P]_0}{K_D + [L]_0}\left(R_A^{bound} - R_A^{free}\right) + R_A^{free}$$

We have developed a new method that exploits the unusual lifetime $T_{LLS} > T_1$ of Long Lived States (LLS) [1]. The LLS method permits to dramatically lower the protein-ligand ratio needed to measure the dissociation constant K_D (1:100 in Fig. 1). This opens the way either to a decrease in protein concentration, to a gain in experimental time, or to a better contrast.

Either direct titration of the ligand under investigation or competition experiments can be monitored by LLS relaxation. LLS can readily be excited and sustained in virtually any peptide containing at least one glycine, thus offering a broad choice of inexpensive weak 'test' ligands without requiring any isotopic labeling.

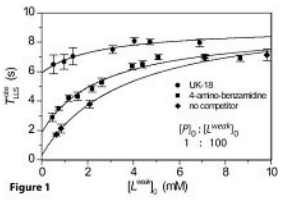

Figure 1

Our method is illustrated by screening of inhibitors of a prototypical target for cancer therapy, the urokinase-type plasminogen activator (uPA) [2].

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Medicinal Chemistry **337**

Polyproline Based Cell Penetrating Peptides - A Tool for Intracellular Delivery?

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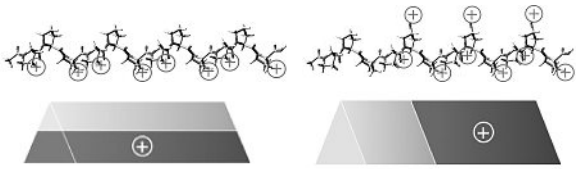
[2]Laboratory of Organic Chemistry, ETH Zürich, Wolfgang-Pauli-Str. 10, 8093 Zürich, Switzerland

The effective delivery of drugs and other biomolecules into cells still holds challenges, since poor translocation across the plasma membrane is a major limitation. Cell penetrating peptides (CPPs) based on cationic amphiphilic polyproline structures might have the potential to address this issue. Exploiting the unique properties of oligoproline as a well-defined molecular scaffold[1] we designed CPPs that bear guanidinylated moieties in various positions along the backbone of a polyproline II (PPII) helix (see figure). Oligoprolines with different chain lengths as well as different charge densities were prepared and their uptake into human cancer cells was evaluated by fluorescence activated cell sorting (FACS), showing higher uptakes relatively to established CPPs (e.g. Tat, Octaarginine). Additionally we observed that our studied peptides do not only enter successfully cells, but also show specific accumulation in the nuclei, which holds promise for future intracellular delivery applications.



[1] a) Y. A. Nagel, M. Kuemin, H. Wennemers, *Chimia* **2011**, *65*, 264; b) M. Kuemin, Y. A. Nagel, S. Schweizer, F. W. Monnard, C. Ochsenfeld, H. Wennemers, *Angew. Chem. Int. Ed.* **2010**, *49*, 6324; c) M. Kümin, L.-S. Sonntag, H. Wennemers, *J. Am. Chem. Soc.* **2007**, *129*, 566.

Medicinal Chemistry **338**

CELL PERMEABILITY OF STEREOISOMERIC POLYCATIONIC OLIGOPROLINES

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[1]Laboratory of Organic Chemistry, ETH Zürich, Wolfgang-Pauli-Str. 10, 8093 Zürich, Switzerland.

A common limitation of active drugs and imaging agents is their limited ability to penetrate into eukaryotic cells. Cationic and amphiphilic peptides are promising tools to address this challenge.[1] We envision steroisomeric polycationic oligoprolines as molecular carriers with high potency and proteolytic stability to have improved uptake properties. The well-defined polyproline II helix (PPII) and the functionalizability of the backbone[2] allowed us to design polycationic cell penetrating peptides (CPP's).

The influence of the left- and right-handed helix of the synthesized oligoprolines on the cellular uptake into human cervical cancer cells (HeLa) was investigated by fluorescence activated cell sorting (FACS) and compared to the uptake of the Tat peptide. The intracellular localization of the peptides was analysed by confocal microscopy using the nucleus Hoechst marker 33342. The stability of the L- and D- oligoproline analogues in trypsin and human blood serum was evaluated for 48 hours.

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Medicinal Chemistry **339**

Postsynthetic ligation of spermine to 2'-*O*-Me RNA *via* click chemistry and evaluation of their affinity towards RNA targets

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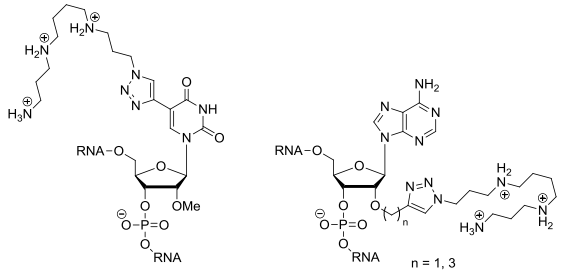
Although tremendous effort has been made to target DNA and mRNA with modified oligonucleotides during the antisense area in the last 20 years, there is still a need for modified oligonucleotides with better binding properties; not least because of the emerging field of microRNAs and their inhibition with antagomirs [1]. One strategy to enhance duplex stability is the introduction of polycationic moieties which act by neutralizing the polyanionic charges inherent to oligonucleotides. Here we report the ligation of spermine to RNA oligonucleotides in the major and in the minor groove (**1** and **2**, respectively) by the postsynthetic CuAAC click chemistry approach [2]. The modified oligonucleotides were evaluated for their influence on RNA duplex stability and thermodynamic properties.



1 2

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[2] Yamada, T. *et al.*, *J. Org. Chem.* **2011**, *76*, 1198.

Medicinal Chemistry **340**

Inhibition of microRNA biogenesis

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MicroRNAs are a class of small non-coding RNAs which modulate protein translation and are involved in cell differentiation, development and metabolism[1][2][3], as well as in cancer and other diseases.[4][5]

The loop region found in the microRNA primary transcript (pri-microRNA) and in the microRNA precursor (pre-microRNA) has been identified as an important regulatory binding site for a number of proteins[6], and is therefore an accessible and versatile target for drugs.

In anticipation that microRNA biogenesis will be a significant pharmacological target, we devised different strategies for its inhibition and characterization.

[1] Authors Names, *Journal Abbr*. **2000**, *30*, 1111.
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[3] Bartel, D. P.., *et al*., *Cell*, **2004**, *116*, 281.
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[6] Krol, J., Loedige, I., Filipowicz, W., *Nat. Rev. Genet*., **2010**, *11*, 597.

Medicinal Chemistry **341**

In Silico Based Actin Inhibitors

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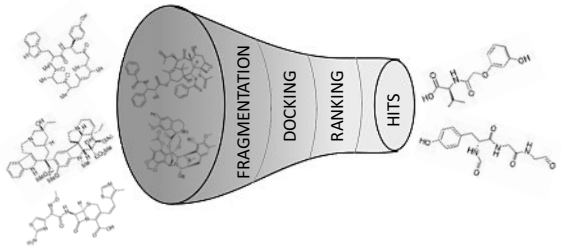
The importance of actin cytoskeleton in pathogenic cellular processes has made it an attractive target for the development of new anticancer drugs. Only complex natural products such as latrunculins and cytochalsins among others are known to interact with actin [1]. By *in silico* methods we aim to design small actin binding molecules that will allow us to gain a deeper understanding of the actin polymerization process at a molecular level.



The final molecules obtained from an *in silico* discovery campaign of novel actin binding molecules inspired by natural products have been succesfully synthesized and biologically tested. Our present efforts are concentrated on the design of more potent actin binding small molecules that show comparable potency to complex actin binding natural products.

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Medicinal Chemistry **342**

Tuberculosis drug development: targeting the unusual chorismate mutase – DAHP synthase complex

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Tuberculosis remains one of the deadliest infectious diseases for humans. Due to an ever-growing spread of multi-drug resistant *Mycobacterium tuberculosis* strains, the discovery of novel drug targets are of particular interest. Intracellular chorismate mutase and DAHP synthase are involved in the shikimate biosynthesis pathway, which is essential in bacteria, fungi and plants but is absent in mammals, thus representing promising targets for drugs. It has been show that the interaction between the two enzymes increases catalytic efficiency of chorismate mutase >100 fold [1]. Therefore, ligands that interfere with complex formation will potencially have a dramatic effect on the viability of the pathogen. The results from high-throughput compound screening and *in vitro* validation of potential inhibitors of the complex will be presented.

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Medicinal Chemistry **343**

Amino Acid Peroxyl Radicals: Reaction with Ascorbate and Urate

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Proteins are significant targets of partly reduced oxygen species *in vivo*. Protein oxidation results in the formation of amino acid radicals ($AA^{\bullet}$) randomly on the protein surface; further reaction may yield protein peroxyl radicals ($AAOO^{\bullet}$) and protein hydroperoxides (AAOOH). All these species are likely to propagate damage. Ascorbate and urate are able to repair tyrosine and tryptophan radicals in various proteins *in vitro*.[1-3]

We have studied the reactions of ascorbate and urate with the peroxyl radicals of *N*-Ac-Gly-amide, *N*-Ac-Ala-amide and *N*-Ac-Pro-amide. Both antioxidants reduce amino acid peroxyl radicals. The rate of radical repair by ascorbate is concentration-dependent and the rate constants are close to 10^7 M^{-1} s^{-1}. In contrast, repair by urate is independent of the urate concentration with rate constants of ca. 10^3 s^{-1}, which suggests initial formation of an adduct between $AAOO^{\bullet}$ and urate that then further decays to form urate radicals.

It is to be stressed that reaction of $AAOO^{\bullet}$ with ascorbate or urate gives rise to hydroperoxides (AAOOH) that are also reactive molecules. Ascorbate and urate could "repair" protein radicals ($AA^{\bullet}$) and prevent biological damage *in vivo*, given the relatively high concentration of these antioxidants in living organisms. The urate radical produced upon repair of protein radicals is, in turn, reduced by ascorbate. The net result is loss of ascorbate with conservation of urate.

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Medicinal Chemistry **344**

Hohenbuehelia reniformis extract is active against human pathogenic *Fusarium* sp.

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The prevalence of *Fusarium* spp. as causative agent of onychomycoses is rising and *Fusarium* spp. as well as other non-dermatophyte fungi appear to be insensitive to systemic standard treatment [1]. Hence, new antifungal agents active against *Fusarium* spp. are needed.

In a large screening, different plant and human pathogenic fungi were co-cultured with *Fusarium* spp. in Petri dishes. Few fungi were able to keep *Fusarium* at bay, among them the Basidiomycete *Hohenbuehelia reniformis*. An extract of the mycelium of *H. reniformis* grown in Petri dishes contained mainly saccharides as confirmed by NMR of the total extract. Prefractionation with HP20SS was successfully applied to separate the secondary metabolites from the saccharides. The concentrated prefraction containing aromatic compounds was strongly active against human pathogenic *Fusarium solani* on a 96-well plate Agar test [2].

The analytical strategy and first results towards the isolation and identification of anti-*Fusarium* compounds at the microgram level are presented.

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Medicinal Chemistry **345**

High resolution HPLC biological profiling for the rapid identification of antifungal compounds in plants from French Polynesia

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In order to rapidly localize antifungal compounds in crude plant extracts, micro dilution assays with the opportunistic yeast *Candida albicans* were used jointly with semi preparative HPLC micro-fractionation. The method was optimized in order to unambiguously highlight antifungal activity of given LC-peaks in complex mixtures.

Using this approach, the antifungal biological profiles of selected active crude extracts of plants from French Polynesia were recorded. The biological assays were performed in one step directly on the 96 well plates obtained by HPLC micro-fractionation of 50 mg of the crude extracts. The leaf extract of the tree *Alphitonia zizyphoides*, a plant traditionally used to treat dermatomycoses [1], appeared to be the most active.

The combination of HPLC antifungal profiling together with dereplication by LC-MS and CapNMR micro-fractionation leaded to the rapid identification of the bioactive compound known as betulinic acid. The method presented is generic and applicable for the screening of extracts containing polar to medium polar natural products.

Acknowledgements: This work was supported by Swiss National Science Foundation Sinergia Grant CRSII3_127187 (to J.-L. W. and M. M.)

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Medicinal Chemistry **346**

NAD^+ dependant deacetylases as promising biotargets to fight against Chagas disease and Leishmaniasis

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Trypanosoma cruzi and *Leishmania spp.* are protozoan pathogens responsible of Chagas disease and Leishmaniasis, respectively. Current therapies rely only on a very small number of drugs, most of them inadequate because of their severe host toxicity or due to drug-resistance mechanisms. In order to find therapeutic alternatives, the identification of new biotargets is highly desired. SIR2, a NAD^+ dependant deacetylase belonging to the sirtuin family, is known to be essential for the life cycle of both parasites and, for this reason, widely used in anti-parasitic drug design [1]. Recent studies also highlighted the therapeutic potential of other NAD^+ dependant deacetylases found in both parasites [2]. In this work, the structure of such enzymes has been retrieved by homology modeling techniques. A restricted number of chemical scaffolds, potentially active on both parasites, have then been identified through a virtual screening approach and energies of binding estimated through MM-PBSA calculations. Such promising *in silico* hits are now submitted to biological evaluation.

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Medicinal Chemistry **347**

Enhancement of chemodiversity in crude plant extracts by generic chemical transformation

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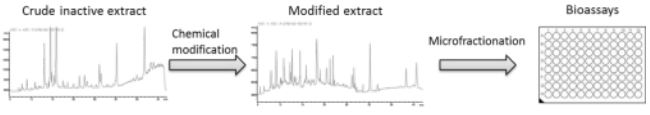
Natural products have been utilized successfully for drug discovery. Plant extracts represent natural libraries that usually contain a high number of molecules with different scaffolds and functionalities. In order to further enhance chemodiversity of such extracts, chemical transformation may be applied [1,2]. This work presents a strategy to generate bioactive compounds through chemical reaction applied to an initial inactive plant extract. Considering that the average nitrogen content per molecule in natural products is lower than in drug molecules, functional group containing nitrogen atoms were introduced by generic chemical modification. In this study enriched extracts containing flavonoid were converted in pyrazoles which are known for their large diversity of bioactivity. Modified extracts were analyzed by HPLC-UV-ELSD-MS to evaluate the extent of chemical transformation and then submitted to HPLC based biological profiling to localize new bioactive compounds. *De novo* structure determination of the new unnatural products was made by microflow NMR analysis of the corresponding HPLC peaks.



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Medicinal Chemistry **348**

Efficient identification of antifungal compounds from the stem bark of *Diospyros bipendensis* Gürke

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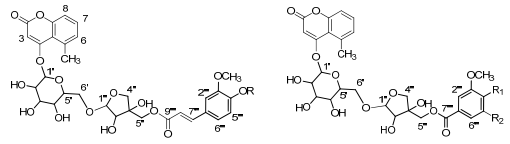
The stem bark of *Diospyros bipindensis* (Ebenaceae) is used in Cameroon by pygmies Baka for the treatment of infectious diseases caused by fungus and bacteria [1]. The MeOH and CH_2Cl_2 extracts presented an antifungal activity against *Candida albicans*. The bioguided isolation was undertaken using the HPLC-microfractionation in 96 well plates and bioautography to localize the active compounds in the HPLC chromatogram. In a second step, medium pressure chromatography was used to isolate the active compounds. Using this approach seventeen compounds were isolated, nine of them are new natural products. The structures of the isolated compounds were elucidated by classical spectroscopic methods including UV, NMR and HR-MS.



10 R=H
11 R=CH_3

8 R_1=OH R_2=OCH_3
9 R_1=OCH_3 R_2=H

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Medicinal Chemistry **349**

HPLC-microfractionation and bioautography with a hypersusceptible strain of *C. albicans* for an efficient detection of antifungal natural products in complex crude plant extracts

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The increase of invasive fungal infections and the appearance of multidrug-resistant strains represent a threat for human health. In the developed world, these infections predominantly occur in the context of increasingly aggressive immunosuppressive therapies [1]. There is thus an urgent need for new antifungal drugs with new modes of action to improve the therapeutic outcomes associated with fungal infections. In this context we have developed an efficient strategy for profiling antifungal activity in crude plant extracts from higher-plants. The method combines the HPLC-microfractionation in 96-well plates and subsequent bioautography for tracking the bioactive compounds. In order to improve the sensibility of the assay for the detection of potentially interesting minor natural products, a sensitive engineered strain of *C. albicans* (DSY2621) hypersusceptible to known drugs was used [2]. This procedure enables a precise localization of the antifungal agents in the HPLC chromatograms and additional detection by PDA-ELSD-MS enables dereplication. For a complete *de novo* structure elucidation of the compound of interest at the microgram level, micro-flow NMR (CapNMR) analysis of the microfractions of interest was performed in parallel to this process. The approach allowed a rapid and efficient identification of potential antifungal agents with restricted amounts of crude plant extract.

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Medicinal Chemistry **350**

Dynamics of Analogue of c-di-GMP (endo-S-c-di-GMP) in Solution

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Cyclic diguanosine-monophosphate (c-di-GMP) is a bacterial signaling molecule that triggers a switch from motile to sessile bacterial lifestyles [1,2]. Analogues of c-di-GMP, which can selectively modulate the activities of c-di-GMP processing proteins, will be useful chemical tools for studying and altering bacterial behavior. Recent studies [3,4] revealed that c-di-GMP is a monomeric state at low micromolar concentration (1mM) in the absence of metal ions and dimerization may occurs only on the proteins (i.e., diguanylate cyclase, PilZ). Higher oligomer formation occurs only in the presence of monovalent (particularly K^+) metal ions. Another report[5] showed that a conservative modification of one of the phosphate groups in c-di-GMP with a bridging sulfur in the phosphodiester linkage affords an analogue called endo-S-c-di-GMP does not readily form higher aggregates. Local c-di-GMP pools with higher concentrations have been discussed [1], but so far remain hypothetical. In our work, we presented Molecular Dynamic Simulation on endo-S-c-di-GMP in aqueous solution with a concentration of 80 mMol. The result shows the dimerization free energy of endo-S-c-di-GMP is −12.5 kcal/mol comparing to −22 kcal/mol for c-di-GMP dimer, which indicates that the former is less favoured in dimeric form. This finding suggests that the phosphate in c-di-GMP is important in aggregate formation and may also in the binding of c-di-GMP to proteins.

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Medicinal Chemistry **351**

Molecular Dynamics Investigation of the Dimerization and Activation in PleD Protein

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Cyclic dinucleotides have been recognized as important signaling molecules in bacterial cells. In particular, bis-(3'→5')-cyclic diGMP (c-diGMP) is a globaly active second messenger controlling motility and adhesion of bacterial cells. c-diGMP is involved in regulation cell surface-associated features and community behavior (biofilm formation), and is catalyzed by diguanylate cyclases (DGC) [1]. In particular, PleD protein is one of the DGC's responsible for the condensation reaction 2 GTP → c-di-GMP + 2 PPi. PleD is a dimeric response regulator whose monomers contain three different domains: the DGC domain (catalytic domain) and two CheY-like receiver domains (D1/D2) [2, 3]. To activate PleD, the D1 domain needs to be phosphorylated. The phosphorylation results in dimerization and structural changes in the D2 receiver domain and further, in the catalytic domain (DGC), allowing the condensation of the substrates. It has been found that PleD is allosterically regulated by c-diGMP (negative regulation).

Here, we use Molecular Dynamics simulation on the nanoseconds time scale to investigate the effect of phosphorylation on the dynamics in the D1/D2 domains. Understanding the dynamics of PleD activation will allow to design strategies to control the DGC dimerization and thereby, to prevent the c-diGMP production which is involved in bacterial proliferation.

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Medicinal Chemistry **352**

Enzymatic Reaction Mechanism of Dengue Methyltransferase

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Dengue fever is a mosquito-borne viral infectious disease predominantly prevalent in tropical regions with annually 50−100 million cases and around 25000 death worldwide. The decease, which is caused by a positive-sense RNA virus, is one of the most important emerging infectious diseases in many areas of the world. Currently, neither vaccines nor specific drug treatments are available.[1]
The dengue virus genome contains a type 1 cap structure at its 5' end which is essential for viral replication.[2] The viral NS5 RNA methyltransferase is critical for the formation of the RNA cap structure and is thus an attractive target for drug discovery.[3-5]
The enzyme is known to catalyze two distinct reactions on an RNA cap structure with a specific sequence,[4] but so far neither the structure nor the mechanism of the two methylation reactions is known at an atomistic level. Thus, we have built structural models of the protein in complex with the RNA and applied molecular dynamics simulations to identify protein residues critical for RNA sequence specificity of the enzyme. Furthermore, we investigated model reaction pathways, using high level ab initio calculations. We found that the protein environment substantially lowers the reaction barrier, mediated by an active site lysine residue.

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Medicinal Chemistry **353**

ACTIVATION ANTI-INFLAMMATORY & FERMENTATVE ACTIVITY OF MUSHROOMS CULTURES EXTRACTS BY EHF EMI

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The mushroom is rich by β-glycosidase and various peroxidases, necessary for synthesis and cleavage of lignin and polysaccharides and their derivatives.We have shown that at certain frequencies of extremely high frequencies electromagnetic irradiation (EHF EMI) in diapason 45-53 GHZ, some of the enzymes of mushroom rapidly activated in replay to the outer stress: increasing protein content, level of fermentative activity of peroxidase and β–glucosidase up to 60%. Obtained differences have diversity directed character and depend from frequency and time of exposition by mm-waves [1, 2].

We have study on determination of anti-inflammatory activity of the above mentioned extracts of mushroom on model of rat ear acute inflammation, induced by xylol. Intraperitoneal injection of an extracts both from not irradiated and the irradiated by mm-waves culture of a mushroom reduces an inflammatory acute by 85 %. Such effective influence of this extracts may be explain by increase of peroxidase activity in culture of a mushroom on 3 day after an irradiation. By HPLC analyze have been revealed increasing of glutamine in 25 time in composition of acid-soluble protein in treated mushroom`s culture, which is probable responsible for such immune replay of organism.

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Medicinal Chemistry **354**

Covalently Linked Photoactive Cisplatin Conjugates: Synergistic Chemo- and Photodynamic Therapy?

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We have selected cationic porphyrins due to their excellent water solubility and cellular uptake as the photosensitizer (PS) of choice.[1] In addition, the central metal within the porphyrin allows tuning the visible absorption bands of the PS. Three human cancer cell lines (MCF7, A2780 and A2780cis) were treated with novel covalently linked platinum-porphyrin conjugates in the presence and absence of red light ($\lambda > 600$nm) or at a precise wavelength of 627nm[2]. IC_{50} values were determined with the help of cell viability assays (using MTT). The lowest IC_{50} value for 2 human cancer cell lines was 0.08 μM in the presence of red light. The light irradiation increased the toxicity of the conjugates by a factor up to 57 compared with toxicity in the dark. On the other hand, the toxicity was ten-fold higher than cisplatin alone in the absence of light. Furthermore, we have studied the cell uptake of these compounds.

In summary, photosensitizer consisting of novel porphyrins have been covalently linked with cisplatin. The conjugates adsorb red light and show an increased toxicity against human cancer cell lines compared with photosensitizer or cisplatin alone. These promising results suggest to further investigate similar systems with fine-tuned absorption properties, other cancer lines, and explore the cell uptake of these conjugates.

Financial support by the University of Zürich and its Forschungskredit are acknowledged.

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Medicinal Chemistry **355**

Terminally modified Mannosides as high-affinity Inhibitors of *Pseudomonas aeruginosa* Lectin LecB

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The pathogenic bacterium *Pseudomonas aeruginosa* can form biofilms on host tissue or implant material and thereby establishes chronic infections. The lectin LecB is a virulence factor and necessary for the formation of the biofilm; its inhibition with L-fucose or D-mannose glycoconjugates results in a reduction of biofilm formation [1,2]. Fucose-derived molecules with substitutions at the anomeric center were studied in great detail [3]. As a consequence of the terminal fucoside motif, these molecules may be simultaneously recognized by a variety of fucose-binding lectins in the host. This could lead to a reduced efficacy and possible side effects. Here we present a set of novel mannose-based small molecules, that may serve as selective inhibitors of LecB over other lectins of the host's immune system as a consequence of their terminal substitution pattern. The compounds were characterized by microcalorimetry and hemagglutination, a model of host cell binding. $^{1}H,^{15}N$-HSQC NMR experiments of LecB indicate major changes of the protein upon binding to the inhibitor. Based on molecular dynamics simulations we propose a binding mode that is consistent with the thermodynamic data and may explain the drastic changes in the NMR spectrum.

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Medicinal Chemistry **356**

Non-Carbohydrate Inhibitors of *Pseudomonas aeruginosa* Lectin LecB

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The rise of resistance against antibiotics in bacteria is a major threat and demands the development of novel antibacterial therapies. Infections with the opportunistic pathogen *Pseudomonas aeruginosa* are a severe problem as they can form biofilms and thereby increase their resistance towards antibiotics through the physical barrier of the biofilm matrix. The *Pseudomonas* lectin LecB was shown to be necessary for biofilm formation and the inhibition of LecB with its carbohydrate ligands resulted in reduced biofilm formation [1]. The natural ligands for LecB are glycosides of D-mannose and L-fucose, the latter displaying an unusual strong affinity to its lectin receptor. This fact was explained by the interaction of the carbohydrate with two calcium ions bound by the receptor and an additional lipophilic interaction of the terminal methyl group in fucose [2]. Interestingly, although mannosides are much weaker ligands for LecB, they do form an additional hydrogen bond with the protein in the crystal structure [3].To analyze the individual contributions of the methyl group in fucosides and the hydroxylmethyl group in mannosides, we designed and synthesized derivatives of these saccharides. Here we describe molecules lacking carbohydrate properties, that address the individual interactions of their saccharide precursors with LecB. These molecules may lead the way towards non-carbohydrate anti-adhesion therapeutics.

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NK3$^+$-approach: Discovery of dual NK3/NK2 Antagonists for the Treatment of Schizophrenia

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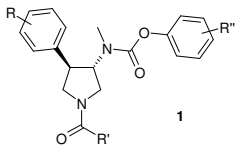
The neurokinin (also called tachykinin) peptide family is composed of substance P, neurokinin A and neurokinin B. These peptides act as neurotransmitters/neuromodulators and elicit their effects through three types of neurokinin receptors: NK1, NK2 and NK3. The NK receptors belong to the class A family of G-protein-coupled receptors (GPCRs) and have been implicated in the pathology of psychiatric diseases such as depression, anxiety and schizophrenia.[1] While the NK3 receptor is clinically validated by improving significantly positive symptoms in schizophrenic patients,[2] additional NK2 activity might be of interest for depression or mood disorders[3].

The discovery of the pyrrolidine carbamate chemical series **1** as highly potent dual NK3/NK2 antagonists will be presented including SAR, detailed molecular property and pharmacokinetic profiles as well as rodent in-vivo activity data.



1

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