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SCS Division of Medicinal Chemistry: What does the DMCCB do?

Y. Auberson[1,2]

[1]President of the Division of Medicinal Chemistry and Chemical Biology, [2]Novartis Pharma AG

The DMCCB comprises about 750 scientists interested in medicinal chemistry, chemical biology and related fields of research. It organizes scientific events such as the Basel mini-symposiums, the Medicinal Chemistry and Chemical Biology session of the SCS annual meeting, and every second year co-organizes the Frontiers in Medicinal Chemistry congress together with the German GDCh. It also offers a high-quality, bi-annual Medicinal Chemistry Course which takes place in Leysin. Beyond Switzerland, the DMCCB interacts with other country organizations to represent the swiss medicinal chemistry and chemical biology community.

Objectives
The aims of the DMCCB are

- to foster a worldwide network of medicinal chemists, chemical biologists and scientists working in related fields
- to facilitate contacts with leading experts in our field
- to organize symposia, seminars and advanced training courses
- to network and encourage the exchange of ideas

DMCCB is a member of the European Federation of Medicinal Chemistry (EFMC)

Scope

- Dedicated scientific sessions at the SCS Fall Meetings
- A bi-annual minisymposium on a cutting edge topic
- Joint conferences with the medicinal chemistry and chemical biology divisions of chemical societies in neighboring countries
- The bi-annual Swiss Course on Medicinal Chemistry, held in a superb Alpine setting. SCS members benefit from reduced fees.

Upcoming Events

- FMC 2015 - Frontiers in Medicinal Chemistry
  Sep 14-16, 2015,Antwerp, Belgium
- The expanding Toolbox of Medicinal Chemistry;From Chemical Biology to Clinical Applications
  October 16, 2015,Parc des expositions et congres, Dijon, France
- Lift Basel Conference 2015
  October 29-30, 2015,MarkthalleBasel
- Changing Paradigms in Drug Development
  February 3, March 24, May 27, September 15 and November 17, 2015, Bern

Website: http://scg.ch/dmccb

Discovery and optimisation of a CREBBP Bromodomain ligand.

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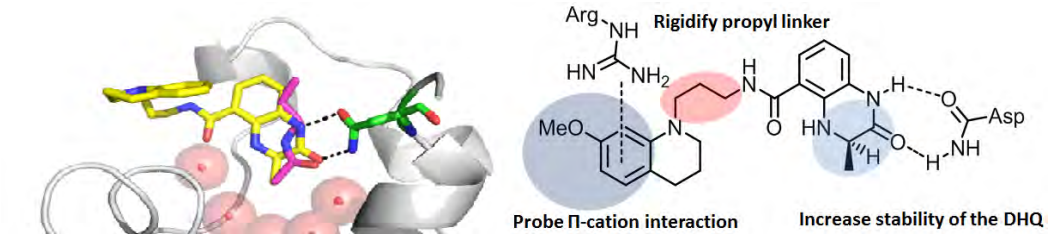
Epigenetic transfer of information is linked to dynamic DNA methylation and post-translational modifications on histones, the small, positively-charged proteins, around which DNA is stored. Specific combinations of these marks, and their crosstalk, can mediate context-dependent effects on transcription, a concept known as the “histone code”. Bromodomains are acetyl-lysine “readers” of the histone code, which interact with acetylated lysine residues. This protein-protein interaction results in changes in gene expression levels and leads to specific downstream effects. [1-3]

The human bromodomain family consists of 61unique proteins, which are divided into eight different subfamilies, according to sequence similarity. Most research has been focused on the bromodomain and extra C- terminal (BET) family, which has yielded probe compounds such as I-BET762, currently in clinical trials. Only a few ligands have been reported for other bromodomain families than BET. Herein we report the discovery [4] and structure-guided development of potent, CREBBP inhibitors. We have focused on the rigidification of the linker between an acetyl lysine mimic and its tail, which fits in an induced cation-π pocket. This cation-π interaction was probed with different electronics of the π-system and showed correlation between the electronic properties and the measured potency. The stability of the acetyl-lysine mimic moiety was also considered in this most recent work by modification of the dihydroquinoline system.



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LC-MS/MS for determination of brain uptake and target mediated differential PK of PDE10A PET tracer candidates

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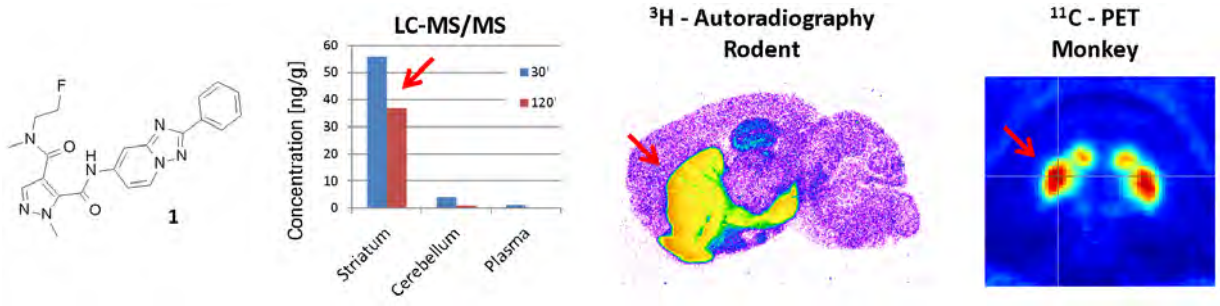
Positron emission tomography (PET) is a non-invasive imaging technique routinely used to support the development of novel drugs to treat neurological and psychiatric disorders. A prerequisite for any PET study is the availability of a radiotracer for the biological target of interest.

At the onset of an internal program to identify inhibitors for the phosphodiesterase PDE10A, no such PET tracer was accessible. We thus started a discovery program, to ensure a validated PET tracer would be available in time for the early development phases of the drug molecule. A LC-MS/MS bio-analytical method [1] was used to rapidly profile 38 unlabeled high affinity PDE10A inhibitors. Rats were intravenously injected with a 'tracer dose' of 10µg/kg of unlabeled compound and samples of plasma, striatum (high PDE10A expression) and cerebellum (low PDE10A expression) were collected after 30 and 120 min. This method allowed identification of tracer candidates with i) high brain uptake, ii) favorable target mediated differential PK (striatum *vs.* cerebellum concentration ratio) and iii) appropriate washout kinetics within the typical time-window of a PET scan (*i.e.* concentration ratio at 120 and 30 min below 1).

Promising candidate structures were radiolabeled with tritium and carbon-11 or fluorine-18 and profiled in autoradiography experiments in rodents as well as PET studies in the non-human primate. A retrospective analysis of the results confirmed good agreement between the LC-MS/MS results and the outcome of the autoradiography and PET experiments.

The LC-MS/MS method was further used to assess and exclude the presence of brain penetrant radiometabolites for the advanced tracer candidate [^{11}C]RO5548119 (**1**).

This work finally lead to the discovery of [^{11}C]RO5548119 as a PET tracer for the visualization and quantification of PDE10A in rodents and non-human primates.



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Synthetic Nucleotides Reduce Human DNA Polymerase η-mediated Synthesis Over a Cisplatin DNA Cross-link Adduct

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[1]ETH Zurich, [2]University of Zurich

DNA cross-link adducts from the chemotherapeutic drug cisplatin block replicative DNA polymerases and induce apoptosis. However, these adducts are bypassed by human DNA polymerase η (hPol η) in the process of translesion DNA synthesis. Therefore, inhibiting hPol η has been suggested as a strategy for improving the efficacy of platinum drugs. We hypothesized that synthetic nucleotides with a propensity to be inserted opposite a DNA adduct but block extension could impede DNA synthesis past the platinum cross-link adduct. In this study, we characterized the influence of synthetic nucleoside triphosphates on hPol η-mediated DNA synthesis. An over ten-fold variation in the incorporation efficiency was observed when varying the hydrogen bonding potential of the synthetic base. Comparing reaction rates with molecular models suggested that incorporation appeared to be promoted by the potential to form an additional hydrogen bond between templating base and incoming dNTP. Additionally, increasing concentrations of synthetic nucleotides reduced the amount of DNA product independent of the template under full-length DNA synthesis conditions. This process is a unique example of inhibiting the progress of hPol η on a platinated DNA template. These data indicate how chemical changes to nucleotide triphosphates impact platinum-DNA adduct bypass by hPol η[1].

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Discovery of G Protein-Coupled Bile Acid Receptor 1 (GPBAR1, TGR5) Agonists as Antiinflammatory Agents

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[1]Novartis Pharma AG

Many inflammatory mediated diseases can be treated today, yet for many of them there is still an unmet need for alternative therapies that offer a benefit in terms of overall efficacy, ease of administration and an improved side-effect profile. To this end, significant research is being conducted towards identifying and dissecting selective biological pathways that are key drivers for human disease.

GPBAR1 (also known as TGR5) is a G protein-coupled receptor (GPCR), which triggers intracellular signals upon ligation by various bile acids. The receptor has been studied mainly for its function in energy expenditure and glucose homeostasis, and there is little information on the role of GPBAR1 in the context of inflammation. After a high-throughput screening campaign, we identified a series of isonicotinamides as non-steroidal GPBAR1 agonists. We optimized this series to potent derivatives that are active on both human and murine GPBAR1. These agonists inhibited the secretion of the pro-inflammatory cytokines TNF-alpha and IL-12, but not the anti-inflammatory IL-10 in primary human monocytes. These effects translate in vivo, and we show with one compound that LPS induced TNF-alpha and IL-12 release in mice is inhibited. The response was GPBAR1 dependent, as demonstrated using knockout mice. Furthermore, agonism of GPBAR1 stabilized the phenotype of the alternative, non-inflammatory, M2-like type cells during differentiation of monocytes into macrophages.

Overall, our results illustrate an important regulatory role for GPBAR1 agonists as controllers of inflammation and highlight the potential benefit of GPBAR1 agonists for the treatment of Th1 driven autoimmune diseases.

From pre-miRNA labeling to the identification of small molecule modulators of microRNA biogenesis: application to the cancer associated pre-let-7/lin28 interaction.

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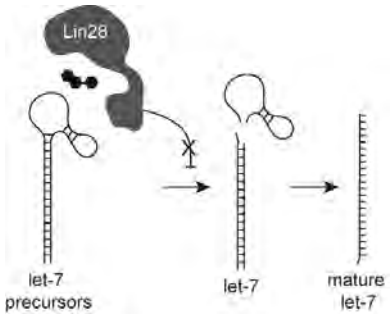
[1]ETH Zurich

MiRNA are a large class of non-coding regulatory RNAs repressing the expression of target messenger RNAs.[1] Post-transcriptional regulation of miRNA biogenesis by RNA Binding Proteins (RBPs) such as Lin28, hnRNP A1, Smad, KHSRP and p53 binding miRNA precursors (pri- and pre-miRNA) is increasingly recognized as an important element controlling miRNA maturation.[2] Malfunctioning of this mechanism causes miRNA misexpression which is significant in some human cancers, and therefore represents a promising novel target for drug development.

We present as part of an on-going program addressing RNA drugability, the development of a novel, carefully optimized Fluorescence Resonance Energy Transfer (FRET) based method which allowed the identification of small molecule inhibitors of the let-7 – Lin28 interaction[3] involved in cancer. A flexible labeling strategy of pre-miRNAs[4] allowed the preparation of multiple RNA FRET acceptors. By varying the position on the pre-miRNA, the number (mono-, bis-) and the nature (Cy3, BHQ-1) of the chromophore acceptor, significant improvement of the energy transfer led to a prominent FRET window. Assay miniaturization to 384 wells format allowed the screen of a library of 16000 small molecule compounds. From the 14 best hits, follow-up cellular assays including RT-qPCR and luciferase reporter assay identified one compound as a potent inhibitor of the pre-miRNA – RBP interaction able to restore let-7 levels in cancer cells. Mechanistic investigation using a biotinylated derivative revealed it as protein-targeting antagonist. Treatment of stem cells with the compound led to a change in morphology of murine embryonic stem cells consistent with its proposed mechanism of action.



We believe this approach will be broadly applicable to other RNA – RBP partners involved in (patho)physiological mechanisms offering the opportunity to identify inhibitors of such interactions. Moreover, compounds emerging from such screens represent valuable tools for further biological investigation of the target and possible lead structures for future drug development.

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Fluoroquinolone containing inhibitors of bacterial topoisomerases with a novel mode of action

C. Zumbrunn[1], S. Enderlin-Paput[1], D. Ritz[1], T. Bruyère[1], G. Rüedi[1]

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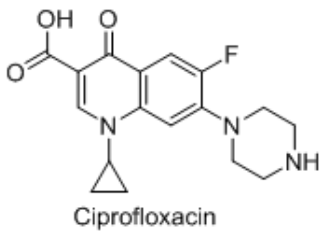
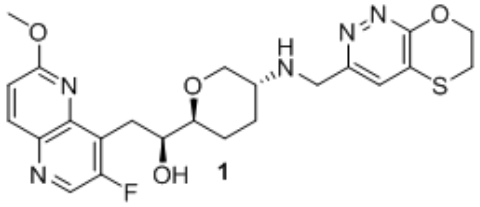
The bacterial topoisomerases Gyrase and TopoisomeraseIV are well validated targets in antibiotic research and discovery. The Fluoroquinolones (FQ, eg. Ciprofloxacin) are potent inhibitors of these targets and are an important weapon in the battle against infections. Unfortunately their utility is lately being limited due to emerging resistance. Over the last years several companies have discovered molecules that inhibit topoisomerases by a novel mode of action and are therefore devoid of cross-resistance with clinically used antibiotics. Especially the *novel bacterial topoisomerase inhibitors* (NBTI) such as **1** have shown promising properties.[1]

We report here the synthesis of compounds (**A**) containing a quinolone moiety as well as a pharmacophore present in NBTI's. Depending on the substitution, these FQ-NBTI hybrids have different modes of action. Very interesting is the improved activity on Gram negative bacteria. The presentation will focus on the characterization of the compounds in terms of enzymatic and cellularactivities.



Ciprofloxacin



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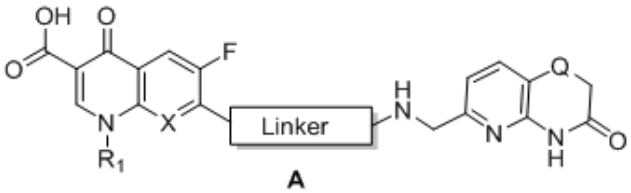

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Siglec-8 – A Novel target For Asthma.

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Sialic acid-binding immunoglobulin-like lectins (siglecs) are members of the immunoglobulin family. They are predominantly found on cells of the immune system. Up to now, 15 siglecs have been identified.[1] Among them is Siglec-8, which is selectively expressed on human eosinophils and regulates their survival.[2-4] Crosslinking Siglec-8 with specific glycan ligands or antibodies induces apoptosis.[5] In some diseases, such as asthma or chronic rhinosinusitis, an excessive amount of eosinophils is produced, causing an inflammatory reaction. Thus, targeting Siglec-8 provides a unique opportunity to control such allergic reactions.

Using a glycan array, the tetrasaccharide 6'-sulfo-sLe^x was identified as a ligand of Siglec-8.[6] However, it exhibits poor drug-like properties and its synthesis is laborious and of high complexity. Therefore, we synthesized a number of mono- and oligosaccharides derived from the scaffold of 6'-sulfo-sLe^x and determined their affinities for Siglec-8.

Herewith, the potent disaccharide Neu5Acα2-3(6-*O*-sulfo)Gal was identified, displaying a relative IC_{50} of 2.2 with respect to the natural 6'-sulfo-sLe^x. Moreover, the affinity of the disaccharide ligand was significantly reduced when small modifications to this structure were made. For example, when the *O*-glycosidic bond was changed from α2-3 to a α2-6 linkage, the sulfate-group was removed or only the corresponding monosaccharide fragments were evaluated, almost no binding to Siglec-8 was observed.

These results suggest that the scaffold of Neu5Acα2-3(6-*O*-sulfo)Gal contains the essential epitope of 6'-sulfo-sLe^x required for Siglec-8 binding. Based on this information, a new family of Siglec-8 ligands is currently synthesized.

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SMN2 splicing modifier for the treatment of Spinal Muscular Atrophy (SMA)

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[1]F. Hoffmann-La Roche AG

Spinal muscular atrophy (SMA) is the leading genetic cause of mortality in infants and toddler and currently only palliative treatments are available. It is caused by the reduced expression of the survival of motor neuron (SMN) protein due to loss of functional SMN1 gene and alternative splicing of exon 7 in the SMN2 gene.

At the end of 2011, PTC Therapeutics, the SMA Foundation and F. Hoffmann-La Roche, Ltd entered into a unique three party collaboration to develop urgently a life changing treatment for children with SMA.

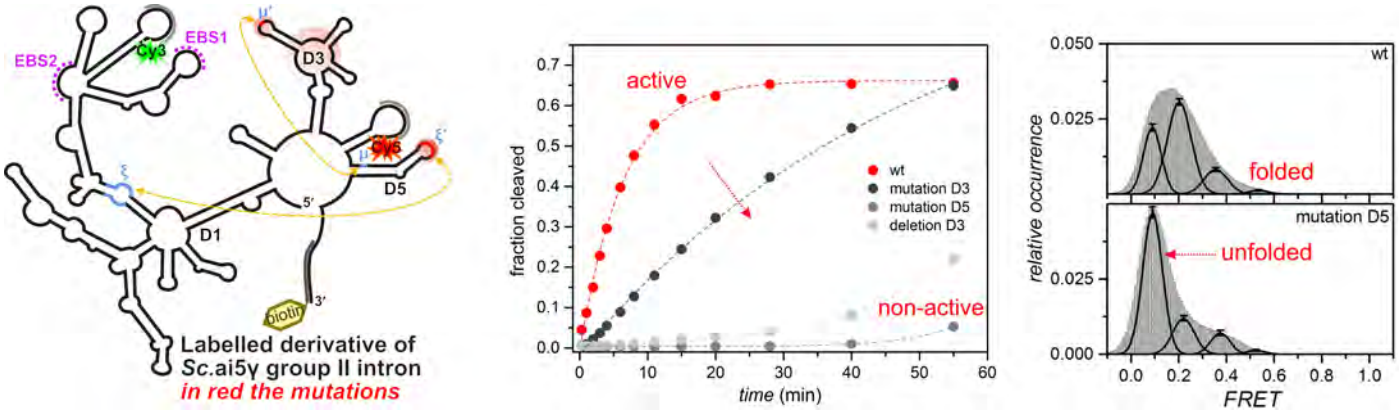
The strategy was to identify orally available novel small molecules that specifically modify SMN2 splicing in SMA patient-derived cells, increasing the production of full length SMN2 mRNA and consequently functional SMN protein production. Upon oral administration, the SMN protein level was restored in two mouse models of SMA, and subsequently, a dramatic increase in the life-span of delta 7 mice, a model of severe SMA, was achieved. This program is currently in clinical trials.

From bulk to single molecule - Point mutations reveal specific intra domain interactions essential for group II intron ribozyme folding

E. Fiorini[1], L. Cardo[2], R. Börner[1], D. Kowerko[1], R. K. O. Sigel[1]*

[1]University of Zurich, [2]University of Birmingham

Group II introns are among the largest ribozymes known. Their structural analysis suggests that they have evolved into ribonucleoproteins generating the eukaryotic nuclear spliceosome. They are found in the genome of bacteria, plants and lower eukaryotes [1]. These self-splicing ribozymes are active upon formation of specific long-range tertiary interactions that define a precise conformation influenced by co-factors such as Mg^{2+} [2,3]. We study the folding pathway of a truncated but active Sc.ai5γ group II intron through point mutations in the RNA sequence in positions essential for inter-domain docking. Combining bulk activity assays and single molecule Fluorescent Resonance Energy Transfer (smFRET) experiments we test the effect of these mutations on the catalytic activity and the folding pathway of this ribozyme. In both, bulk and single molecule experiments, different mutations have distinct effects on both activity and folding. In particular smFRET allowed us to quantify the differences in the relative population of a certain conformation attributed for splicing activity, especially a clear shift towards the unfolded conformations when the catalytic domain (D5) is mutated (Figure, right) [4]. Although even a drastic mutation still allows for the folding into the most compact state, addressed to be the active one, activity assays show that no activity is present if the interaction D5-D1 is disturbed. We introduced high Mg^{2+} concentration and crowding environment, however, the mutation cannot be compensated and the catalytic activity restored [5]. From the obtained results, we can assign a change in conformation/FRET state to a particular event in the folding, providing us with a deeper understanding of the actual active state. Targeting specific domains, in particular single motifs, drastically decreases the activity making group II introns a specific target for drugs. Furthermore, their capability to reinsert into the genome may ultimately be applicable for gene therapy.



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Photoaffinity labeling in Chemoproteomic: Cyanopindolol and a small molecule mediated reprogramming of mESCs as successful case study.

M. Patoor[1], C. Hebach[1], M. Schirle[2], V. Beck[1], F. Bassilana[1], H. Lee[1], M. Mueller[1], C. Spanka[1], L. C. Bouchez[1]*

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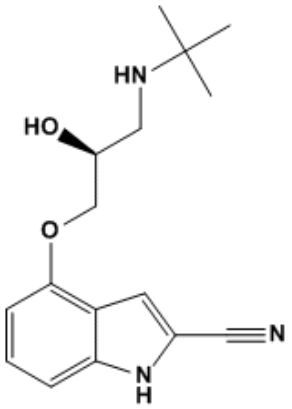
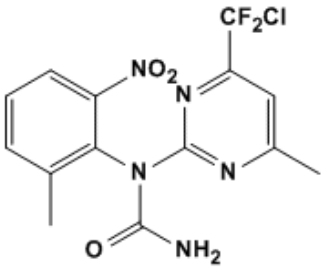
Knowing the cellular targets of drugs is crucial if the process of drug discovery is to be made more efficient. Identifying the full spectrum of targets associated with a bioactive small molecule can lead to faster optimization, understanding of off-target side effects and the ability to minimize possible toxicities early on in the process. We have developed a robust and unbiased method of probing the proteins that bind to the small molecule of interest in a biologically relevant setting.

We propose to present two show cases for which we are able to successfully unravel the target and/or the MoA of the molecule of interest in two separated context: one being the well-known Cyanopindolol and the other being a small molecule modulator of mESC reprogramming.



Cyanopindolol



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[1] Laure Bouchez*et al.Article in preparation.*

Refining the understanding of the catalytic mechanism of DNAzymes

M. H. Räz[1], M. Hollenstein[2]*

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DNAzymes (or DNA enzymes) are single-stranded DNA molecules that are capable of catalyzing chemical reactions.[1] Unlike their natural counterparts, the ribozymes and proteinaceous enzymes, DNAzymes have no precedent in nature and are all identified by SELEX and related combinatorial methods of *in vitro* selection.[2] In this context, DNAzymes 8-17 and 10-23 are two well-known and widely used ribonucleases that are capable of cleaving a broad variety of mRNA substrates with high catalytic efficiencies (k_{cat}/K_M › 10^8 $min^{-1}M^{-1}$).[3] In the absence of any X-ray structures, numerous studies have been dedicated to investigate on the folding and catalytic mechanism of these DNAzymes, underscoring the importance of conserved residues and the M^{2+} cofactors.[4, 5] Here, we show that minor grove interactions might play a significant role in the catalytic mechanisms of DNAzymes.[6] Indeed, substitution of dA units of the catalytic core of these DNAzymes by an analog were the capacity at forming interactions in the minor groove was suppressed, revealed to be an adequate tool for investigating these fragile interactions.

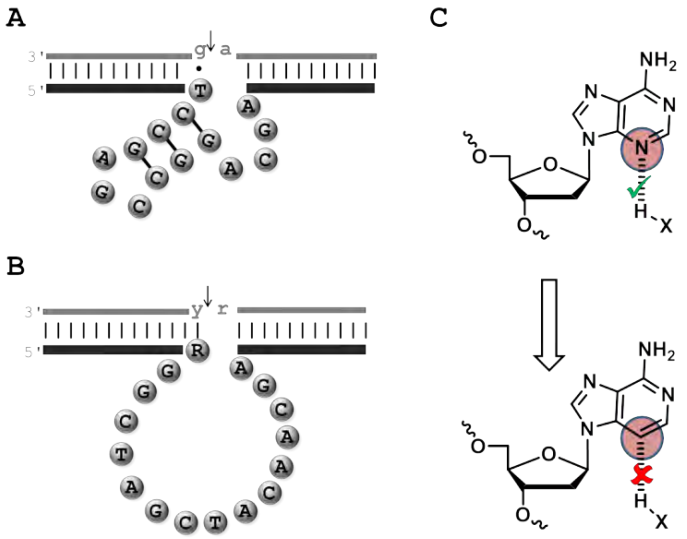

Figure 1. Hypothetical secondary structures of DNAzymes 8-17 (A) and 10-23 (B); substitution of the *N*3-atoms in the catalytic cores (C).

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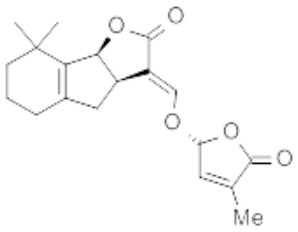
Strigolactones and their potential role in modern agriculture

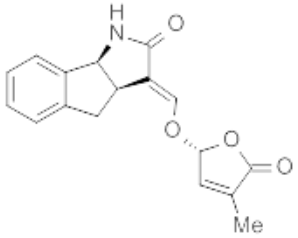
M. Lachia[1], A. Lumbroso[1], P.-Y. Dakas[1], A. de Mesmaeker[1], C. Screpanti[1]

[1]Syngenta Crop Protection AG

Nowadays, the importance of abiotic stresses has been strongly recognized as threat for crop production both in public and industrial research organizations. New technologies able to mitigate the stress caused by the main abiotic stresses (i.e. drought, salinity, cold and heat) represent a substantial opportunity to contribute to a sustainable increase of agricultural production. Very recently, strigolactones have been conclusively identified as phytohormones and their role in controlling plant architecture and germination has been unveiled. The progresses achieved in this field are culminating in the identification of the molecular receptors involved in the signal transduction mechanism. The exact mechanism of the mode of action of strigolactones still remains to be fully elucidated and we were interested to gain some insight into the mechanism of action of strigolactones by selectively modifying the reactivity of the lactone C-ring. Therefore, we will present the synthesis of 5-deoxystrigol and synthetic analogue strigolactam and their surprisingly good activity on the germination of *Orobanche cumana* parasitic weed seeds.



5-deoxystrigol



strigolactam

M.Lachia, P.-Y. Dakas, A. De Mesmaeker, *Tetrahedron Lett.* **2014**, *55*, 6577-6581
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Guineensine as a Novel Inhibitor of Endocannabinoid Reuptake

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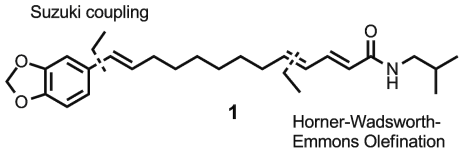
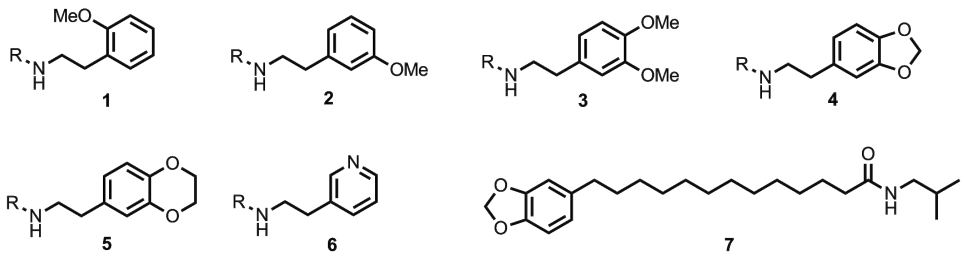
Guineensine (**1**) is a plant-derived natural product that can be isolated from *Piper nigrum* and was recently shown to be a novel nanomolar inhibitor (EC_{50} = 290 nM) of the cellular reuptake of the endocannabinoid anandamide.[1]



Scheme 1: Structure of guineensine (**1**) and key retrosynthetic disconnections.

In order to gain insight into the structure-activity-relationships for guineensine(**1**) we first developed an efficient total synthesis of the natural product itself. Key steps were a Suzuki coupling and a Horner-Wadsworth-Emmons Olefination (Scheme 1). Based on this chemistry, we then prepared a number of analogs of **1** (such as compounds **2**-**7**) and we assessed their capacity to inhibit anandamide upuptake *in vitro*.

In this contribution we will discuss the details of the synthesis of **1** and guineensine analogs and we will disclose the first SAR data for this new type of endocannabinoid uptake inhibitors.



Scheme 2: Amide part analogs of guineensine (**1** - **6**) and saturated guineensine (**7**).

[1] Simon Nicolussi et al., *Pharmacological Research***2014**, *80*,52-65.